Mechanochemical activation of latent 
$N$-heterocyclic carbene catalysts

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de 
Technische Universiteit Eindhoven, op gezag van de 
rector magnificus, prof.dr.ir. C.J. van Duijn, voor een 
commissie aangewezen door het College voor 
Promoties in het openbaar te verdedigen 
op dinsdag 29 januari 2013 om 16.00 uur

door

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geboren te Almelo
Dit proefschrift is goedgekeurd door de promotor:

prof.dr. R.P. Sijbesma

Cover: Project “Windgrafiek” (by Ralph Brodruck), GLOW 2011, Eindhoven.

Printed by: Gildeprint Drukkerijen, Enschede

A catalogue record is available from the Eindhoven University of Technology Library.

ISBN: 978-90-386-3319-0

This work has been financially supported by the National Research School Combination Catalysis Controlled by Chemical Design (NRSC-Catalysis).
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In this chapter, the concept of “mechano catalysis” is introduced: using mechanical forces to activate polymer-functionalized, latent organometallic catalyst complexes. The history and fundamental aspects of polymer mechanochemistry are discussed, as well as some examples of current applications of mechanochemistry in mechanoresponsive functional materials, including mechanocatalysts. Subsequently, experimental methods for mechanochemical polymer scission are reviewed, with a strong focus on ultrasound, which is the most common technique for scission of polymers in solution. The silver(I)–NHC latent catalyst complex (NHC = N-heterocyclic carbene) is of main interest throughout this thesis, so a short overview of the chemistry and catalysis of free (NHCs) as well as some of their metal complexes is given. We conclude this chapter with an overview of the aims and outline of this thesis.
Chapter 1

1.1 Mechanochemistry

1.1.1 Mechanochemistry: using force to activate chemical bonds and reactions

The use of mechanical forces to activate chemical bonds is called mechanochemistry.¹ Mechanochemistry is an alternative, but less well-known method for initiating chemical reactions, next to thermal activation and activation by (photo)chemical stimuli. The first documented example of a mechanochemical reaction used by humans dates back to before 300 BC when Theophrastus of Ephesus—student of the well-known Greek philosopher Aristotle—reported the formation of liquid mercury when rubbing cinnabar (mercury(II) sulfide) in the presence of vinegar in a brass mortar.¹ The same principle of activating chemical reactions by vigorously rubbing compounds is still used today.¹⁻³ Polymer mechanochemistry started in the early 1930s when the German scientist Hermann Staudinger observed the degradation of rubber under mastication.⁴ He attributed the decrease in molecular weight to scission of the polymer chains under the influence of mechanical stress. This statement was confirmed in later studies⁵⁻⁷ and the mechanochemical degradation of polymers became a subject of intense study in the decades that followed. Solid state degradation was studied using mastication and milling, whereas degradation of polymer melts was studied in a variety of hydrodynamic flows. These studies were of particular interest for the application of polymers as lubricants and drag-reducing agents. The rapid developments in the field of ultrasound allowed the study of polymer degradation in (dilute) solutions. Even today, polymer mechanochemistry is of particular interest in the development of stress-responsive functional materials.

Examples of the use of mechanochemistry by nature are found in the regulation of the activity of some enzymes and proteins by force-induced structural changes. Since the activity of enzymes and proteins strongly depends on their exact conformation, small distortions in their structure lead to a change or even complete inhibition of their activity.⁸ A very elegant example of this is found in the Von Willebrand Factor (VWF).⁹ This vascular protein regulates blood clotting through platelet formation. An important regulatory mechanism is the cleavage of the VWF by the enzyme ADAMTS13 which occurs in the A2 domain of the VWF.⁹ In the native state, the A2 domain is shielded, but when a blood vessel is cut or damaged, the flow profile of the blood is altered. Elongational forces arise when blood flows in the hemorrhage (see Figure 1), leading to unfolding of the VWF and exposure of the A2 domain that is now accessible to ADAMTS13. In a similar way, mechanochemical transformations play an important role in the Notch signaling pathway, which is crucial for tissue...
development and regeneration.\textsuperscript{11} Mechanochemical unfolding of the Notch receptor negative regulatory region (NRR), leads to exposure of the active site for proteolysis (S2), a the key step in regulation of protein activity.

1.1.2 Bonds under stress: fundamental aspects of polymer mechanochemistry

In recent years, the focus of studying mechanochemical degradation of polymers has shifted from optimization of processing properties to understanding the mechanochemical scission process in more detail and trying to tailor mechanochemical scission of bonds in polymers for the development of functional, mechanoresponsive materials. The use of force to activate chemical bonds and to initiate chemical reactions is of interest because the reaction pathways and outcome of mechanochemical reactions can be completely different than for their thermal analogues.\textsuperscript{12–16} One illustrative example is the ring-opening reaction of cyclobutanes (CBs), an orbital-controlled reaction, that has been studied computationally and experimentally.\textsuperscript{12–14} Thermal ring-opening is only allowed via a conrotatory pathway, yielding a different isomer of the ring-opened product (\textit{E,Z} or \textit{E,E}) for each starting isomer (\textit{cis-} or \textit{trans}-CB, respectively). However, when activated by mechanical force, the ring-opening always yields the \textit{E,E} isomer as a product, irrespective of the starting material. Theoretical analysis has shown that lowering of the energy barrier under the influence of mechanical energy allows the disrotatory ring-opening pathway for \textit{cis}-CB (see Figure 2a).

The discrepancy between the outcome of thermal and mechanochemical reactions is a direct consequence of the fact that mechanical work involved with force, in contrast to thermal energy, is anisotropic (“force has a direction”). The potential
energy landscape of a chemical bond under force is deformed with respect to its rest state (i.e., at zero external force) as described by Kauzmann and Eyring. At rest, the potential energy of a chemical bond is given by the Morse potential, as shown in Figure 2b. When the bond is stretched from its equilibrium length $r_0$ to a new position $r'$ as a result of an external force $F_{\text{ext}}$, the potential energy of the bond is lowered with the amount of mechanical work that is put into the system, which equals $W = F_{\text{ext}}(r' - r_0)$ by definition. As a result of the deformation, the energy barrier for bond dissociation $D$ is lowered to a value $D'$. The thermally activated barrier to scission (TABS) theory states that mechanochemical scission becomes possible when this reduced energy barrier is low enough for thermal fluctuations of molecules to be sufficient to overcome the energy barrier. In practice, this means that $D' \approx k_B T$ ($k_B T \approx 2.5$ kJ mol$^{-1}$ at 25 °C). The Bell–Evans theory gives the force-dependence of the rate of mechanochemical dissociation:

$$v_{\text{off}}(F_{\text{ext}}) = v_0 \exp \left( -\frac{D'}{k_B T} \right) \approx v_0 \exp \left( -\frac{D - F_{\text{ext}}(r' - r_0)}{k_B T} \right) \quad (1)$$

In this equation, the rate of dissociation is measured by the “off-rate”, $v_{\text{off}}$. The off-rate is equal to the inverse lifetime of the chemical bond under stress. It is evident that for mechanochemical scission to occur, bond lifetime should be approximately equal to the experimental timescale. From this it follows that, with respect to the TABS theory, the required reduction in bond dissociation energy depends on the experimental timescale (which can vary over several orders of magnitude, from microseconds in ultrasound to seconds in AFM experiments).
Stretching of polymer chains as a result of strain imposed by external force is a first and prerequisite step for mechanochemical chain scission. At high chain extension, individual bonds along the polymer backbone will be stretched and may eventually break when the force is high enough. Accumulation of force along an (isolated) extended polymer chain can be calculated using the bead–rod model:7,20–22

\[ F_{\text{max}} = \frac{3\pi}{4} \eta ab\delta SN^2 \]  

(2)

In this model, the extended polymer chain is described by a series of \( N \) “beads”, each with a radius \( a \) that are connected to each other by \( N - 1 \) rigid “rods” of length \( b \). The beads account for the hydrodynamic interactions through viscous coupling with the solvent. Other important parameters in this equation are solvent viscosity \( \eta \), and the shielding factor \( S \), which is a measure for the extent of hydrodynamic shielding of one chain segment by others. For a fully extended chain, there is no shielding and \( S = 1 \). Since the number of chain segments is directly proportional to the molecular weight (\( N \propto M \)), it follows that the maximum force that can be accumulated along the polymer chain scales as \( F_{\text{max}} \propto M^2 \). Two important additional aspects of polymer mechanochemistry derive directly from this quadratic scaling relation: (i) There is a limiting molecular weight (\( M_{\text{lim}} \)) below which mechanochemical chain scission is not possible because the polymer chain is too short to accumulate enough force to overcome the rupture force of the individual chemical bonds.20–25 (ii) Mechanochemical scission of polymer chains is a non-random process: it always occurs near the midpoint of the polymer chain because there, the accumulated force reaches a maximum value.10,11,20–24

Until now, we have not explicitly considered the role of polymer structure and composition of the polymer chain. The above description of polymer chains under external force applies to polymers consisting of identical bonds, or bonds with equal bond strength along the polymer backbone. It has been shown that incorporation of a single weaker bond within the polymer chain can alter the mechanochemical scission behavior. For example, Paulusse in our group showed that \( M_{\text{lim}} \) of a polymer could be significantly reduced when a covalent C–C bond near the center of the polymer backbone was replaced by a weak metal–ligand coordination bond.26 Similar observations were made by Encina et al.27 and Berkowski et al.28 when incorporating peroxide (O–O) and azo groups (N=N) in the polymer backbone, respectively. The incorporation of such a weak bond within the polymer chain increases the selectivity of mechanochemical bond scission even further: since a polymer chain under stress breaks at its weakest link, only this bond is broken upon applying mechanical force.
A weak bond that is put within the polymer chain for targeted bond scission is commonly referred to as being a “mechanophore”. Berkowski et al. additionally demonstrated that the precise location of mechanochemical scission could be programmed to some extent by placing the mechanophore in an “off-center” position along the polymer chain. Even though this bond does not experience the highest force, its weaker nature still ensures selective scission.

1.1.3 Polymer mechanochemistry today: stress-responsive and self-healing materials

The field of polymer mechanochemistry has recently experienced a strong revival following the rapid developments made in the field of synthetic polymers. With new methods for synthesis of well-defined polymers (both in terms of chemical structure and composition as well as molecular weight distribution), great progress has been made over the past decade in the field of development of functional materials. Particularly, research on mechanoresponsive materials strongly benefits from the advances made in the field of polymer mechanochemistry over the past century. Mechanoresponsive materials constitute a class of functional materials that display a desired response upon deformation by force. The desired responses are diverse and include, but are not limited to, mechanochemically induced color changes (“mechanochromism”), chemiluminescence (“mechanoluminescence”) or change of material properties. In the initial studies on mechanochromic polymers, fluorescent dyes were dispersed into the polymer matrix or bound covalently to polymer chains. Fluorescence spectroscopy has been used for probing strain-induced changes in fluorescence because of excimer break-up or reduction of FRET intensity upon elongation of these materials.

More recent examples of mechanoresponsive materials, however, make use of the concept of selective mechanochemical bond scission in polymers by incorporation of a mechanophore within the polymer chains. The mechanophore is designed in such a way that it displays the desired responsive behavior under stress. A beautiful example of this approach was reported by Moore and co-workers in 2009. They developed a mechanochromic material by incorporation of spyropyran (SP) within a polymethylacrylate (PMA) polymer matrix. SP is colorless by itself, but it was shown that upon deformation of this material (either by tensile or compressive forces), isomerization of SP to the red merocyanine dye (MC) took place in the solid state. As a result of this force-induced rearrangement, the polymer sample colored intensely red, effectively indicating that the material had been subjected to mechanical loadings close to material failure (see Figure 3a). In follow-up
reports, the researchers show that the application of this mechanochromic force sensor is not limited to elastic polymers such as PMA, but can be prepared from polyurethane elastomers and glassy polymers as well.\textsuperscript{34} O’Bryen \textit{et al.} have use the mechanochemical ring-opening of SP to MC followed by the reverse ring-closing reaction under irradiation with UV light to probe stress relaxation in glassy poly(\(\varepsilon\)-caprolactone).\textsuperscript{35} Mechanistic studies of polymer failure are of particular interest to the materials science community. To this end, our group recently reported the development of a mechanoluminescent material based on a polymer-functionalized 1,2-dioxetane moiety.\textsuperscript{36} 1,2-Dioxetanes are molecules that consist of a four-membered ring having two adjacent oxygen atoms. Depending on the nature of the substituents, the 1,2-dioxetane group is thermally labile and generates two ketones upon dissociation.\textsuperscript{37} 1,2-Dioxetanes are chemiluminescent because one of these ketones is in the excited state immediately after dissociation and emits a photon upon relaxation. The bis(adamantyl)-substituted 1,2-dioxetane used by Chen \textit{et al.} in our group is thermally stable up to 190 °C, but the four-membered ring can be opened by mechanical forces when functionalized with PMA chains. This way, they were able to visualize failure of a polymer sample in tensile tests by looking at the position and intensity of its force-induced luminescence (Figure 3b).

Force-induced enhancement of the strength and/or toughness of materials is a very attractive feature when achieved for materials that are about to fail under mechanical loading.\textsuperscript{38} Craig and co-worker showed the use of perfluorinated cyclobutanes (PFCBs) for this purpose.\textsuperscript{39} Mechanochemical scission of the PFCB mechanophores resulted in the formation of polymer fragments possessing terminal trifluorovinyl aryl ether groups (Figure 3c). These groups are reactive enough to allow remending of the polymer while heating the material to 180 °C for 16 h. However, this polymer does not yet constitute an ideal self-healing material because a completely autonomous self-healing material should be capable of reinforcing or even repairing itself directly as a consequence of the mechanical stimulus, without any external interference, \textit{e.g.} heating or exposure to solvent vapor.\textsuperscript{40}

Bond formation in solid state polymers under stress was shown by Craig and co-workers for \textit{gem}-dibromocyclopropanated polybutadiene (gDBC–PB).\textsuperscript{16} Nucleophilic substitution of the allylic bromide with chloride was observed when carrying out mechanochemical gDBC ring-opening experiments in extrusion in the presence of a quaternary ammonium chloride salt (see Figure 3d). Multiple nucleophilic substitutions along the partially ring-opened polymer backbone occurred as the result of a single chain scission event; this, in turn, makes this scheme viable for carrying out mechanochemically induced cross-linking reactions when using
Chapter 1

Figure 3 Several examples of polymer mechanochemistry in recent literature: (a) mechanochromism in PMA polymers by force-induced ring-opening of spiropyran to merocyanine; (b) polymers containing bis(adamantyl)-1,2-dioxetane mechanophores emit light upon stretching (“mechanoluminescence”); (c) mechanochemical scission and subsequent thermal remending of PFCB-containing polymers; (d) single chain scission events during extrusion of gDBC-functionalized PB leads to multiple formations of covalent chemical bonds along the stretched polymer backbone,16 and (e) cyanoacrylates are generated during ultrasound irradiation of 1,2-dicyano-substituted CB-functionalized polymers. The figures were adapted and reprinted with permission from Refs. 33,36 (Copyright © 2009 and © 2012 Nature Publishing Group) and Refs. 39,41 (Copyright © 2011 and © 2010 American Chemical Society)
an appropriate bifunctional nucleophile. Without mechanochemical ring-opening of the dibromocyclopropane ring, substitution of the bromides was not possible. An alternative approach to autonomous self-healing materials is the generation of free reactive groups upon mechanochemical chain scission. These reactive groups should be passivated (masked), but after generation they can initiate the actual remending reaction. A first example of a mechanophore that was capable of doing this was the masked cyanoacrylate reported by Kryger et al.41 This mechanophore consisted of a 1,2-dicyano-substituted cyclobutane moiety incorporated in a polymer chain. Upon force-induced ring-opening, a highly reactive cyanoacrylate was formed which is a very reactive monomer in free radical polymerization, similar to monomer used in “super glue” (Figure 3e). However, only preliminary studies using ultrasound-induced scission of the polymers in dilute solution were reported and, to the best of our knowledge, no follow-up studies in solid state have appeared since.

1.1.4 Mechanochemical activation of latent catalysts (“mechanocatalysis”)

We have used the concepts discussed above to develop polymer-functionalized latent catalyst complexes that can be activated by mechanochemical bond scission (“mechanocatalysis”).42 The mechanocatalysts are based on organometallic coordination complexes involving N-heterocyclic carbenes (NHCs) which are coordinated to either silver(I) or ruthenium(II) (see Figure 4). In their complexed form, the catalysts are latent (or dormant), but upon dissociation of one of the two NHC ligands, they become active. Usually, metal–NHC catalyst complexes are activated by heating; however, we have shown that by functionalization of the NHC ligands with a polymer chain, the catalyst complexes become susceptible towards...
activation by mechanical forces. Two distinct cases can be classified: either the ligand or the metal center become the active catalytic species after activation. The polymer silver(I)–NHC complex is an example of the first case, where the highly nucleophilic free NHC is a good catalyst for transesterification reactions.\textsuperscript{42–44} In contrast, after activation of the polymer ruthenium(II)–NHC complex, alkene metathesis reactions are catalyzed by the ruthenium(II) metal center itself.\textsuperscript{42,44,45} More recently, Bielawski and co-workers developed a polymer mechanocatalyst based on the palladium(II)–pyridine coordination complex. This mechanocatalyst was able to catalyze anionic polymerizations, albeit that highly activated perfluorinated acrylates had to be used as monomers in order to allow initiation with the weakly nucleophilic pyridine ligand.\textsuperscript{46} Soon after, the first example of a metal-free mechanocatalyst was reported by the same group. This mechanocatalyst was similar to the previous examples, but used a boronium–pyridine instead of a palladium(II)–pyridine complex with similar catalytic activity.\textsuperscript{47} Of course, mechanocatalysis is not limited to these examples. Ongoing attempts in our group focus on the development of other (supramolecular) catalyst complexes that can be activated by mechanical force.

1.2 Ultrasound

1.2.1 The physical aspects of ultrasound in solutions

In solution, ultrasound is the most widely used technique for carrying out polymer mechanochemistry. It has been recognized as being the most efficient way of creating mechanical forces in solution.\textsuperscript{48} The first observations of the often destructive effects of ultrasound were made in 1895 when acoustic shockwaves severely damaged the propellers of the H.M.S. Daring.\textsuperscript{49} Soon after, Lord Rayleigh was the first to derive a mathematical description of this phenomenon\textsuperscript{50} and, when Richards and Loomis discovered the first chemical and biological effects of ultrasound several years later,\textsuperscript{51} ultrasound was definitively established as an prominent research subject, both fundamental as well as applied. Ultrasound can be roughly divided into two types: (i) high-intensity (min. 10 W cm\textsuperscript{-2}), low-frequency (20 kHz–2 MHz) and (ii) low-intensity (max. 0.5 W cm\textsuperscript{-2}), high-frequency (2–10 MHz) ultrasound.\textsuperscript{48,52} The latter type of ultrasound is called non-invasive and is used for medical diagnostics applications. The more extreme and destructive conditions associated with the first type of ultrasound makes this type suitable for performing sonochemistry.\textsuperscript{48}

In ultrasound, acoustic pressure waves pass through a liquid as longitudinal sound waves that locally compress and expand the fluid. As a result of this, small gas bubbles form on the spots where the rarefaction takes place. These cavitation
bubbles nucleate around gas molecules that are dissolved in the liquid; they subsequently grow by migration of volatile compounds from the solution into the bubbles (see Figure 5). At a certain moment, the size of the bubble becomes so large that the interplay between forces (e.g., surface tension, vapor pressure and hydrostatic pressure) becomes unfavorable and destabilizes the growing cavitation bubble. Consequently, the cavitation bubble rapidly implodes on a timescale of microseconds. This timescale of collapse is shorter than the effective timescale required for heat transfer so that the collapse is essentially adiabatic. Temperatures and pressures in the resulting hotspots can reach up to 5000 K and 500 bar. Under these extreme conditions, the contents of the cavitation bubbles will pyrolyze, leading to the formation of highly reactive radical species, that may give rise to a variety of sonochemical reactions within the hotspot. In fact, the hotspot temperatures can become so high that a plasma is formed in the cavitation, giving rise to a phenomenon called sonoluminescence. Next to the thermal effects, sonochemical effects also comprise of mechanical effects, caused by the high strain rates in the liquid associated with the collapse of cavitation bubbles. Mechanical effects are the predominant driving forces in polymer mechanochemistry and will be treated in more detail in the next section.

**Figure 5** (a) Ultrasound experimental set-up, similar to the one used in the research for this thesis for carrying out polymer mechanochemistry experiments in solutions. (b) Schematic overview of the evolution of the cavitation bubble radius under the influence of an acoustic pressure wave in ultrasound.

1.2.2 The behavior of polymer chains in the presence of cavitation bubbles

Provided that their molecular weight is sufficiently high, polymer chains degrade upon the action of ultrasound in solution. The main responsible factor for this is a hydrodynamic force field that is generated surrounding the collapsing cavitation bubbles. The hydrodynamic force field is a result of a velocity gradient caused by the rapid retraction of the bubble wall, leading to high strain rates in its proximity,
that decay to zero at a distance far from the cavitation bubble (as $r \to \infty$). The strain rate (symbol: $\dot{\varepsilon}$, in $s^{-1}$) at any radial distance $d$ from the bubble wall is equivalent to the value of the velocity gradient at that position:

$$\dot{\varepsilon}(d) = \left. \frac{dv}{dr} \right|_{r=R+d}$$

(3)

Here, $R$ is the instantaneous bubble radius. When neglecting solvent compressibility, the radial strain rate distribution can be calculated by:

$$\dot{\varepsilon}(d) = -2 \frac{uR^2}{(R+d)^3}$$

(4)

With $u$ being the bubble wall velocity.\cite{52,58} When a polymer chain is present close to the collapsing cavitation bubble, the velocity gradient will cause it to unfold from its (random) coil conformation into a (partially) extended polymer chain. In order for the coil-to-stretch transition to occur, the timescale of the extension event (as given by $1/\dot{\varepsilon}$) should be shorter than the timescale required for recoiling of the polymer chain.\cite{7,21} In other words: one should pull faster on the polymer chain than it can retract itself into a coiled conformation. The timescale of recoiling is determined by the longest characteristic relaxation time (symbol: $\lambda_0$) of the polymer chain. The importance of both parameters is quantitatively captured using the dimensionless Deborah number ($De$) which gives the ratio between the two characteristic timescales that govern the coil-to-stretch transition:\cite{21,59}

$$De = \dot{\varepsilon} \times \lambda_0$$

(5)

The coil-to-stretch criterion states that, for extension of the coiled polymer chains to occur, it is required that the value of $De \geq \frac{1}{2}$;\cite{21,59} this value is called the critical Deborah number and its corresponding strain rate is the critical strain rate for coil-to-stretch transition. Sometimes, the Weisenberg number ($Wi$) is used instead of $De$, however, this is a matter of convention and both dimensionless numbers represent the exact same phenomenon. We have chosen to use $De$ throughout this thesis.

Actual strain rates obtained in ultrasound experiments can be as high as $10^7$–$10^8$ s$^{-1}$, with the exact values depending on the cavitation behavior which is governed by the exact physical conditions used such as irradiation power, solvent vapor pressure and viscosity and (external) temperature.\cite{53,58,60,61}
1.3 Alternative techniques for mechanochemical polymer scission

1.3.1 Flow-induced mechanochemical polymer scission

Flow-induced scission of polymers, either in solutions or melt state, has been a parallel subject of study for decades, next to ultrasound-induced scission. The use of hydrodynamic forces in (laminar) flows is considered to be more controlled and better quantifiable than the mechanical effects of ultrasound, mainly because of the absence of thermal effects due to cavitation and the higher uniformity of the force field. However, the variety of flow devices and experimental conditions used in the early studies and the poor interpretation of data due to lack of a complete understanding of the scission mechanism limits the possibility of making a good comparison of these studies. Experiments by Porter and Johnson confirmed that the mechanical degradation of polymers originates from hydrodynamic forces in fluids and are not due to what they call “local effects” such as viscous heating or cavitation. These researchers studied semi-dilute polyisobutene solutions in cetane using a Couette-type viscometer. This way, a uniform and well-defined laminar shear flow was created, while excluding the occurrence of local effects. Under these well-defined hydrodynamic conditions, they observed efficient mechanical chain scission with rates that were dependent on the initial molecular weight of the polymer.

There is ongoing debate about the relative contributions of shear and elongational forces to polymer chain stretching and scission in these flows. Pure shear flow is a superposition of an elongational and a rotational component, and it has been argued that, because of the presence of the rotational component, it is not possible to stretch polymer chains in shear flow. Instead, the shear forces makes them tumble around until they align with the flow direction where the net force on the polymer chain becomes zero. Clay and Koelling corroborated this statement by comparing the flow of polymer solutions through an orifice (which leads to a strong elongational component of the force field) with flow through a tube of the same diameter (pure shear flow). They found that elongational force was required for polymer degradation and that there was no significant polymer degradation under pure shear flow. By monitoring FRET using in situ fluorescence spectroscopy in combination with rheometry, Chan et al. recently showed that in concentrated polymer solutions in Couette flow, the forces that act on the polymer chains are compressive, rather than elongational due to restricted chain mobility. All the experiments described so far have been performed under strictly well-defined laminar flow regimes. Successful drag reduction experiments in turbulent flows have also been performed however, the mechanism of chain scission in turbulent flows is poorly understood even today.
With respect to the characteristics of elongational hydrodynamic flows, they can be divided into two types.\textsuperscript{7,66,67} The first one is \textit{fast transient flow} (FTF), where the residence time of the polymer chain in the high-strain region is shorter than, or equal to, the longest characteristic relaxation time of the polymer chain ($\tau \leq \lambda_0$). The second one is \textit{quasi steady-state flow} (QSSF), which possesses a stagnation point as a result of the flow device geometry. In this point, the local flow velocity is zero, giving rise to very long residence times of polymer chains ($\tau \gg \lambda_0$). In this point, high strain rates are obtained as a result of the high velocity gradient. Therefore, any polymer chain present in the stagnation point will fully uncoil. Typical devices for creating QSSF are the four-roll mill, opposite jets and cross-slot (Figure 6a–b, the stagnation point marked by “x”) devices. In the 1980s, Odell, Keller and co-workers in Bristol used these devices for studying polymer dynamics and scission under QSSF conditions.\textsuperscript{20,23,68} In the case of FTF, only partial uncoiling of the chains is possible which results in a “yo-yo”\textsuperscript{69} or “dumbbell” shaped conformation. This type of hydrodynamic flows is typically observed in flow channels having a contraction zone (Figure 6c) or when a fluid in injected or sprayed through an orifice. Polymer degradation in this type of flow was intensively investigated in the 1990s in the Lausanne laboratories of Nguyen and Kausch.\textsuperscript{7,58}

Rabin used the two classifications to discriminate between different scaling relations for the strain, or elongational rate of bond rupture, $\dot{\varepsilon}_{\text{rup}} \propto M^x$ in FTF and QSSF. He derived that the value of $x$ should be 1.1 and 2 for FTF and QSSF, respectively.\textsuperscript{67} The scaling exponent for QSSF flows agrees quantitatively with solving Equation (2) for a fixed $F_{\text{max}}$ (indeed, the bead–rod model of Equation (2) assumes full chain extension), whereas the scaling exponent for FTF is in good agreement with experimental observations.\textsuperscript{7} In addition to this, Islam \textit{et al}. found that the transition between both scaling laws is not only dependent on the residence time of the polymer chain in a high-strain region, but that it is also governed by the flow regime.\textsuperscript{70} They

![Figure 6](image-url)
observed an excellent scaling of \( \dot{\varepsilon}_{rup} \) with the Reynolds number \( (Re) \) in both their own data and data from literature with a transition of \( x = 2 \) to \( x = 1 \) at \( Re > 1000 \).

The rapid developments in the field of micro-electromechanical systems (MEMS) over the past two decades have led to miniaturization of laboratory equipment into so-called lab-on-a-chip devices.\(^7\) Several examples of microfluidic devices for macromolecule characterization have appeared in literature. Next to “conventional” microfluidic rheometers,\(^7\) a variety of microfluidic devices was developed to study polymer unfolding, stretching and mechanochemical scission on small scales.\(^70\),\(^73\),\(^74\) For the purpose of studying fundamental aspects of mechanochemistry, miniaturization has proven to be very valuable. Several papers report the use of microfluidics in combination with fluorescence microscopy to study the behavior of single DNA molecules under the influence of hydrodynamic stresses.\(^59\),\(^63\),\(^75\)

1.3.2 Single molecule mechanochemistry using atomic force microscopy

The term single molecule force spectroscopy (SMFS) comprises all techniques that are able to investigate molecules and their response to external forces on a single molecule level. The two most prominent SMFS techniques are atomic force microscopy (AFM) and the use of optical tweezers.\(^9\),\(^76\) In the latter technique, the molecule of interest (mostly synthetic polymers or biological macromolecules such as DNA and proteins\(^9\),\(^77\)) is immobilized between two glass beads that are held in a laser trap. The same laser trap is used to displace the beads relative to each other, thereby imposing stress on the molecule.

The other technique, AFM, is of interest within the scope of this thesis. In AFM, a macromolecule is immobilized on a solid (glass/mica/gold) surface. A connection is established between AFM cantilever and substrate by “phishing” off the macromolecules from the surface with the cantilever. These connections can be based on non-specific adhesion (physisorption) of the macromolecule on the cantilever or by covalent attachment of the macromolecule on a chemically functionalized cantilever.\(^78\),\(^79\) Upon retraction of the cantilever away from the surface, the molecule is elongated and stretched. Eventually, when forces become high enough, the tether connection between cantilever and surface will be broken, either when one of the bonds within the tether molecule breaks; or when the bonds connecting the tether to surface or cantilever break (“surface detachment”). The forces involved with this process are monitored by measuring the deflection of the cantilever, which is essentially a Hookean spring. A typical force–displacement curve for approach, retraction and linker scission is shown in Figure 7.
Bond rupture forces are extracted from the obtained force–displacement curves by fitting them to conventional models for polymer chain extension, like the freely jointed chain (FJC) or worm-like chain (WLC) model for more rigid polymer chains. As mentioned before, the probability of bond rupture of a stressed bond depends on both the experimental timescale and the magnitude of the external force. In AFM experiments, the experimental timescale is linked to the applied force loading rate, \( \dot{F} = \frac{dF}{dt} \), which is directly proportional to the speed of retraction through the stiffness of the cantilever, as given by its spring constant: \( \dot{F} = C \dot{x} \). The rupture force probability function scales as:

\[
p(F, \dot{F}) \propto F \times \exp(\dot{F})
\]

The actual rupture force \( F_{\text{rup}} \) is the most probable force required for bond rupture to occur given a certain experimental timescale and external force, \( dp/dF = 0 \). Solving this equation gives a logarithmic dependence of \( F_{\text{rup}} \) on loading rates for sufficiently large external forces: \( F_{\text{rup}} \propto \log(\dot{F}) \). The first successful and systematic attempt to determine bond strengths by AFM were reported by Grandbois et al., who used polysaccharide molecules as tethers between cantilever and surface. By carefully analyzing the force–displacement curves, they were not only able to distinguish multiple rupture events of stress-induced ring-opening along the polysaccharide backbone during elongation, but they also successfully determined the location of tether scission. In the years after, many related studies have been reported where AFM was used to study the stretching and breaking of synthetic polymers as
well the behavior of biomacromolecules \cite{77,81} under stress. Single molecule force spectroscopy has also proven to be a powerful technique to study bond dynamics of various receptor–ligand interactions \cite{81} and supramolecular complexes, based on hydrogen bonding motifs and metal–ligand coordination complexes. \cite{82}

1.4 Chemistry and catalysis of N-heterocyclic carbenes

1.4.1 N-heterocyclic carbenes and their complexes with metals

In the work described in this thesis we use N-heterocyclic carbene (NHC, imidazolylidene; see Figure 8 for the general structure) as transesterification reaction catalysts. Free NHCs are highly nucleophilic species owing to the free electron pair on one of the carbon atoms. Their existence as transient intermediate species was already speculated in the first decades of last century, but it was not until the 1960s that Wanzlick and co-workers were able to provide definitive proof of their existence by trapping experiments. \cite{83,84} It lasted another thirty years before Arduengo and co-workers succeeded in isolating free NHC 1. \cite{85} They were able to isolate the free NHC by crystallization after deprotonation of 1,3-diadamantylimidazolium chloride salt using a strong base and confirmed its structure by X-ray crystallography. The bulky adamantyl substituents on the N1 and N3 nitrogen provide steric stabilization of the highly nucleophilic C2 carbon. In the meantime, NHCs have advanced to systems that are studied by a large number of research groups in the world, for applications in (organo)catalysis. \cite{86-88} Other free NHCs have been isolated in the meantime, \cite{89} including the so-called “abnormal” NHC 2 that was recently isolated by Bertrand and co-workers. \cite{87,90} “Abnormal” NHCs have their free electron pair located on the C5 position instead of on the C2 carbon. An even larger number of NHCs have been used in organometallic complexes with a variety of transition metals (silver, \cite{91-93} gold, \cite{94} copper, \cite{95} nickel, \cite{96} and palladium, \cite{96,97} just to name a few) or main group

![Chemical structure for NHCs 1, 3–6 and “abnormal” NHC 2.](image-url)
elements. Here, we will limit the discussion to the imidazolylidene species as shown in Figure 8 and other, closely related, five-membered ring NHCs such as (saturated) imidazolinylidene, triazolylidene (C4 = N in Figure 8) and thiazolylidene (N3 = S).

The relatively high stability of free NHCs compared to that of other carbenes is a direct result of the neighboring heteroatoms. The carbene carbon has a six-electron structure and is \( sp^2 \) hybridized. Coordination of NHC ligands to metal centers is often compared with phosphine coordination. Like phosphines, NHCs are strong \( \sigma \)-donors giving very stable metal–NHC complexes. Owing to the weak \( \pi \)-accepting properties, back bonding from the metal center to the NHC ligand is minimal, even though it can certainly not be neglected in some cases. Especially in the case of complexes with Group 11 metals (copper, silver, gold), the effect of \( \pi \) back-bonding becomes significant, although the metal–NHC bonds in these complexes still have predominantly \( \sigma \) character.

The first examples of coordination complexes of NHCs with metal centers were reported independently by Wanzlick and Öfele in 1968. Wanzlick and Schönherr observed the formation of the \( \text{Hg(3)}_2\text{ClO}_4 \) complex after addition of mercury(II) acetate to the corresponding imidazolium perchlorate of NHC 3. Similar results were obtained a couple of years later when adding mercury(II) chloride to a solution containing 3 which was generated in situ by deprotonation of the corresponding imidazolium chloride salt by potassium tert-butoxide. After these pioneering studies, a large number of metal–NHC complexes was prepared, mostly for catalytic purposes. A full review of these metal–NHC complexes would be an enormous task and goes beyond the scope of this thesis. For now, it suffices to say that complexation of free NHCs to metal centers serves two purposes in general. The first, and probably most widely desired, purpose is the development of organometallic catalyst complexes where the steric and electronic properties of the NHC ligand(s) can be used to tailor the catalytic activity of the complex.

The second purpose, which is the one that is of interest for the work described in this thesis, is the stabilization of the highly reactive free NHC species. Coordination of NHC ligands to e.g. silver(I) ions results in an air- and moisture-stable complex that is, in principle, inactive as a catalyst. In their complexed form, the NHCs can be stored for a prolonged period outside a glovebox. Only upon (thermal) dissociation of the silver(I)–NHC complex, the NHC ligand(s) are liberated and they become active catalysts. Silver(I)–NHC complexes are very easy to synthesize by reaction of the corresponding imidazolium salt with a silver base, like silver(I) oxide, acetate...
or carbonate. The advantage of this method is that the reaction need not be carried out under dry conditions and inert atmosphere because, once formed, the NHCs are immediately coordinated to silver(I) ions. The ability of these complexes to generate free NHCs by thermal dissociation of the obtained silver(I)–NHC complexes is frequently exploited in organometallic synthesis, such as transmetallation reactions where the silver(I) metal center is exchanged for other metal centers. This way, a number of organometallic catalyst complexes have been synthesized that would have been very difficult to achieve using conventional complexation methods, such as in situ generation of free NHCs by deprotonation with strong bases. Gold(I)–NHC and copper(I)–NHC complexes are used for the same purpose, although copper(I) itself also has catalytic activity. Non-metals have also been used for stabilization of free NHCs. Numerous adducts of NHCs have been reported, such as NHC–boranes, NHC–phosphines, NHC–azides, and the (zwitterionic) adducts of NHCs with isothiocyanates, carbon dioxide, or carbon disulfide.

1.4.2 Structure and dynamics of ligand exchange in silver(I)–NHC complexes

Silver(I)–NHC complexes display a high structural diversity (especially when bearing halide counterions) and are highly dynamic. In solution, silver(I)–NHC complexes with coordinating (typically halide) counterions can adopt three types of structures that are in equilibrium with each other (Figure 9). They can be present as a mono-coordinated complex (denoted by Ag(NHC)X, where X = halide anion), as a bis-coordinated complex (Ag(NHC)₂[AgX₂]) or as a bridged dimer ((Ag(NHC)X)₃). Wang and Lin reported an associative mechanism for the structural exchange from dimeric to monomeric complex and vice versa; in this mechanism, the rate-determining step is the association of two dimeric complexes to form a bridged intermediate which subsequently dissociates into two monomeric complexes.

![Figure 9](image-url) Equilibrium structures of the silver(I)–NHC complex with chloride counterion.
NMR studies on $^{13}$C2-enriched NHC 4 (with various halogen counterions), carried out by Su et al. showed that the kinetics of the structural exchange are dependent on the counterion and concentration. Experimental values for the free activation energy for exchange between monomeric and dimeric complex were found to be around 12 kcal mol$^{-1}$ (ca. 50 kJ mol$^{-1}$). Studies in our own group showed that the relative amount of each species was strongly dependent on solvent polarity, but independent of the total concentration of the silver(I)–NHC complex. It was observed that a more polar solvent favored the formation of the monomeric complex, whereas in a non-polar solvent, or when the non-coordinating counterion PF$_6^-$ was used, the complex could be forced into its bis-coordinated form. For the use of silver(I)–NHC complexes as mechanocatalysts, the presence of the bis-coordinated complex is essential as only this type of complex will be susceptible to activation by mechanical forces when incorporated in a polymer chain. However, even when the silver(I)–NHC complex is synthesized having a non-coordinating counterion (like BF$_4^-$, PF$_6^-$ or CF$_3$SO$_3^-$), the true latency of the complex is compromised by the highly dynamic nature of ligand exchange. In a preliminary study in our group, 2D-NMR exchange spectroscopy (EXSY) was used to determine the kinetics of ligand exchange between homocomplexes Ag(5)$_2$PF$_6$ and Ag(6)$_2$PF$_6$. The formation of heterocomplex was observed and the ligand exchange rate was determined to be on the order of seconds at room temperature. As a result of this highly dynamic nature of the silver(I)–NHC complexes, some background reactivity may be expected in catalytic tests using these catalyst complexes.

### 1.4.3 N-heterocyclic carbenes as nucleophilic catalysts

The first example of an NHC-catalyzed reaction was demonstrated by Breslow in 1958. He observed that benzoin condensation could be catalyzed by thiazolium and imidazolium salts. Today, NHCs are most frequently used as catalysts for transesterification reactions and ring-opening polymerization of lactones and lactides. Although the exact reaction mechanism of NHC-catalyzed transesterification reactions is still subject of debate, two mechanisms have been proposed:

- A **nucleophilic mechanism** (Figure 10a) where the reaction proceeds via the formation of NHC–acyl adducts as intermediates through a nucleophilic attack of the NHC onto the carbonyl group of the ester;

- An **alcohol activated mechanism** (Figure 10b) where the alcohol is activated towards a nucleophilic attack as a result of H-bonding between the NHC and alcohol group. In addition to this, the H-bonding stabilizes the tetrahedral intermediate that is formed.
Indirect evidence has been found for the first mechanism,\textsuperscript{89} whereas the plausibility of the second mechanism was shown by direct evidence of NHC–alcohol adduct.\textsuperscript{115,117,119} The alcohol activated mechanism was also supported by Lai \textit{et al.} using DFT calculations on the proposed transition states of both mechanisms;\textsuperscript{120} it was found that the energy of the transition state involving the NHC–acyl adduct was considerably higher than for the case of an NHC-stabilized tetrahedral intermediate. Trends in reactivity and activation energies could be very well predicted by assuming the formation of the tetrahedral intermediate. Some final remarks considering the activity of NHC in transesterification reaction should be made here. In the extensive studies performed by Waymouth, Hedrick and co-workers,\textsuperscript{89} it was observed that $N$-alkyl substituted NHCs (e.g. \textbf{5} in Figure 8) are more active catalysts in transesterification reaction than $N$-aryl substituted NHCs (e.g. \textbf{6}), especially for secondary alcohols.

Stable NHC–alcohol adducts have been exploited more recently in NHC-catalyzed ring-opening polymerization (ROP) of lactones.\textsuperscript{117,121} The NHC–alcohol adducts were added to the reaction mixture as a single-component latent catalyst/initiator system. Not only was the free NHC formed \textit{in situ} upon dissociation of the adduct in solution, the liberated alcohol could act as initiator at the same time.

Being a special case of transesterification, NHC-catalyzed (ROP) of a variety of lactones and $\epsilon$-lactide was first demonstrated by Hedrick and co-workers in 2001.\textsuperscript{113,122} They used $N,N'$-dimesityl substituted NHC (\textbf{6}) as catalyst; however, in later work a

\textbf{Figure 10} Proposed catalytic cycles for NHC-catalyzed transesterification of vinyl acetate with benzyl alcohol: (a) nucleophilic mechanism and (b) alcohol activated mechanism.
large variety of NHCs was found to possess catalytic activity in ROP, including “abnormal” NHCs.123 NHC-catalyzed ROP, using a primary alcohol as initiator was found to have living character and to proceed to high degrees of polymerization within minutes to hours.89 As with NHC-catalyzed transesterifications in general, little is known about the details of the mechanism. Either a monomer activated mechanism was proposed, which involves NHC–acyl adduct formation similar to the nucleophilic mechanism discussed earlier, or a chain-end activated mechanism, which is essentially the same as the alcohol activated mechanism. These mechanisms will not be discussed in more detail here, but for a more detailed discussion of ROP and its proposed mechanisms, one is referred to Ref. 89. Attempts in our group to carry out mechanocatalyzed ROP of β-butyrolactone (β-BL) were not successful: no conversion of the monomer was found when a solution of the silver(I)–NHC catalyst and β-BL in toluene was subjected to ultrasound.

1.5 Aim and outline of this thesis

In the years after the first publication from our group that demonstrated scission of palladium(II)–phosphine supramolecular coordination polymers by ultrasound,26 the concept was soon extended to mechanochemical scission of organometallic catalyst complexes and their application in mechanocatalytic transformations.42–45,109 The work in this thesis has two principal aims: (i) gain a better understanding of the fundamental processes and mechanisms underlying mechanochemical activation of (polymer) mechanocatalysts and (ii) use this knowledge for a rational design and development of alternative activation methods for these mechanocatalysts, next to ultrasound-induced polymer scission. Throughout this work, we have used silver(I)–NHC coordination complexes, embedded within PTHF chains, as the latent catalysts; however, we anticipate that all the results for this particular polymer catalyst system hold in a similar way for other catalyst systems and can be extended to them in a straightforward manner.

Mechanochemistry of PTHF has not been widely explored before outside of our research group. In Chapter 2, ultrasound-induced scission of non-functionalized, covalent PTHF is described. Key concepts of polymer mechanochemistry are introduced, the experimental protocols are discussed and methods for evaluation of scission kinetics are compared.

In Chapter 3, it was demonstrated that the activation of the mechanocatalyst has a true mechanochemical nature. This was done by carrying out ultrasound-induced scission experiments under conditions that suppress the formation of
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radicals as sonochemical impurities. It was found that the amount of polymer chain scission remains the same under radical-suppressing conditions, which excludes the contribution of radicals to mechanocatalyst activation. In Chapter 4, the physical aspects of polymer chain unfolding and scission of polymer-functionalized silver(I)–NHC catalysts by external forces was studied in more detail to gain a better understanding of the underlying processes and mechanisms. Experimental work was combined with molecular dynamics simulations to verify that the typical strain rates and forces during ultrasound experiments are sufficient to unfold and stretch the PTHF chains in solution and break the bond between the NHC ligand and the silver(I) metal center. Subsequently in Chapter 5, the efforts to identify the effect of sonochemical impurities on the activity of the silver(I)–NHC mechanocatalyst in transesterification reactions are summarized. It was shown that during sonication, protic impurities are formed, which deactivate the highly basic free NHC catalyst species. This finding could also successfully explain the observed concentration dependence of mechanocatalyst activity. In addition, it was confirmed that mechanocatalyst activity is significantly enhanced when carrying out mechanocatalytic transformations under radical-suppressing conditions.

In Chapter 6, the synthesis and application of a metal-free NHC-based mechanocatalyst, based on the polymer NHC–isothiocyanate adduct is reported. This adduct was successfully synthesized and it showed midpoint scission under the influence of ultrasound irradiation. However, the adduct did not possess any mechanocatalytic activity (whereas it was active in thermal catalysis). When studying the mechanochemical scission process in more detail, it was discovered that the C–C bond of the NHC–isothiocyanate adduct did not dissociate under the influence of external force; instead, scission occurred at another location in the polymer chain, perhaps along the PTHF backbone.

Chapter 7 reports the results of explorative experiments on using atomic force microscopy (AFM) as an alternative method for mechanocatalyst activation are presented. Even though these results are still preliminary and more experiments are definitely required, they are very promising and hint towards the possibility of using AFM for “single molecule mechanocatalysis”. This thesis ends with a short Epilogue, where the most important results obtained in this thesis work are briefly summarized and put in perspective. To conclude, some future directions for research on the use of mechanical forces to activate latent catalysts are discussed here, with a main emphasis on expanding the number of mechanocatalysts and mechanocatalytic reactions and the investigation of alternative activation methods.
Notes and references

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25. Typically, for covalent polymers the value for $M_{\text{lim}}$ is between 40–100 kg mol$^{-1}$, see e.g. Refs. 20, 22, 24, 26, 64 and G.J. Price, P.F. Smith, *Polymer* **1993**, 34, 4111–4117
38. Alternatively, ultrasound-induced break up of rhodium(I)– and iridium(I)–phosphine organogels was demonstrated by Paulusse, see Ref. 26 and J.M.J. Paulusse et al., *J. Am. Chem. Soc.* **2007**, 129, 2392–2397. Upon standing at room temperature, the organogel was reformed, with the timescale of reformation depending on the metal center that was use for phosphine coordination.
57. The picture of the sonication set-up was taken from: http://www.sonics.biz/lp-vibra.htm (last accessed: September 2012).
62. Shear stress is defined as the stress between adjacent fluid layers that flow with different velocity and it consists of an elongational and rotational vector component. The shear stress is proportional to the velocity gradient perpendicular to the flow direction (the shear rate, $\dot{\gamma} = \frac{dv_x}{dz}$).
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Chapter 1


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Chapter 2

Covalent mechanochemistry of poly(tetrahydrofuran) and PTHF-functionalized mechanophores

Abstract

In the first part of this chapter, the mechanochemical scission of poly(tetrahydrofuran) (PTHF) by ultrasound is investigated. Using various analysis methods, kinetic parameters (scission rate constant and limiting molecular weight) for mechanochemical chain scission are extracted. The obtained results constitute a reference data set for all other mechanochemical scission experiments reported in this thesis. In the second part of the chapter, mechanochemical facilitation of the retro [2+2] cycloaddition of cyclobutane-1,3-dione (ketene dimer) is investigated. The ketene dimer was successfully incorporated in the center of a PTHF polymer chain, and mechanochemical near-midpoint scission was demonstrated. However, careful analysis of the scission process revealed that non-selective scission of the PTHF backbone occurred, rather than the desired retro [2+2] cycloaddition. The exact reason for this remains subject of further study.
2.1 Introduction

The use of mechanical forces to change the molecular weight and structure of polymers and, as a consequence, alter their properties is a well-established subject of study since the early 1930s when German scientist Hermann Staudinger discovered the molecular weight reduction of rubber under mastication.\textsuperscript{1–3} He attributed the change in molecular weight to homolytic bond scission along the polymer backbone under the influence of stress. When (isolated) polymer chains are stretched by an external force field, the force will accumulate along the contour length of the chain. At the chain ends, the force is zero and it reaches a maximum value at the chain center.\textsuperscript{4–6} As a consequence of this, the maximum force accumulated along the polymer chain is proportional to the square of its molecular weight ($F_{\text{max}} \propto M^2$) and mechanochemical scission of polymer chains does not occur in a random way, but always occurs statistically around the chain midpoint.

In order to achieve mechanochemical bond scission of polymers, the force that is built-up along the polymer chain must exceed a critical value in order to overcome the bond strength of the individual covalent bonds which make up the polymer chain. Therefore, there is a certain limiting molecular weight ($M_{\text{lim}}$) for each polymer chain, below which mechanochemical chain scission does not take place.\textsuperscript{4,6–9} At molecular weights higher than $M_{\text{lim}}$, mechanochemical chain scission has a scission rate constant $k_{\text{sc}}$ that scales with the molecular weight difference $M - M_{\text{lim}}$.\textsuperscript{4,7,10}

\begin{align*}
   k_{\text{sc}} &= b(M - M_{\text{lim}})^p \quad \text{if } M \geq M_{\text{lim}} \quad (1a) \\
   k_{\text{sc}} &= 0 \quad \text{if } M < M_{\text{lim}} \quad (1b)
\end{align*}

Different scaling exponents $p$ have been reported in literature, but typically, its value varies between 1 and 3,\textsuperscript{3,11} although most often a linear relationship is assumed ($p = 1$).\textsuperscript{10,12,13}

Most of the work reported in older literature deals with mechanochemical degradation of bulk polymers, like PS, PEO, PE, PP and PM(M)A, or biopolymers based on cellulose, polysaccharides or DNA. For most studies, solutions of these polymers are subjected to mechanical force field in fluid flow devices.\textsuperscript{4,5,8} For a more detailed description of these experiments, one is referred to Chapter 1 of this thesis. In addition to the use of flow devices, it is also possible to impose strain onto polymer chain in solution by irradiation with ultrasound.\textsuperscript{3,6–9} The rapid growth and collapse of gas-nucleated cavitation bubbles in solution during ultrasound generates local regions...
Covalent mechanochemistry of poly(tetrahydrofuran)

of high fluid strain in solution surrounding these cavitation bubbles.\(^6,7,9,14\) When a polymer chain is present in this region, the fluid strain will cause it to (partially) unfold and subsequently stretch. When the extension of the polymer chain is high enough, individual chemical bonds within the polymer backbone will be extended as well. When the forces accumulated in the polymer chain center are even higher, bond scission will occur. Finally, mechanochemical bond scission is possible in solid state; however, the mechanism of force transduction is fundamentally different here: like in concentrated polymer solution (above the critical overlap concentration of the polymer) it relies on polymer chain entanglements and (physical) cross-links.\(^3,4\) Although some nice examples of solid state polymer mechanochemistry have been shown in literature,\(^15–17\) we will not discuss this activation method in more detail here.

In more recent literature on mechanochemistry of polymers, the focus has been on the design of functional materials using mechanochemical transformations and/or bond scission in polymers.\(^3\) The concept of near-midpoint scission can be exploited by placing a weaker bond at the polymer chain center.\(^18–21\) Since a polymer chain under force will break at its weakest point, such a weak bond allows for highly selective chain scission only at that particular point of the polymer chain. Such a mechanochemically active domain within a polymer chain is commonly referred to as a “mechanophore”. In the past few years, several interesting mechanophores have been developed and tested in polymers. These examples vary from stress-relief in polymer materials by selective mechanochemical ring-opening reactions\(^22\) and visualization of stress build-up by mechanochemically induced color changes\(^15\) or chemiluminescence\(^17\) to mechanochemically activated catalysis.\(^23,24\)

In this chapter, the mechanochemistry of covalent poly(tetrahydrofuran) (PTHF) under ultrasound is reported in more detail. Outside of our group,\(^20\) PTHF has not been used much in mechanochemical scission experiments and, therefore, no exact data is available on its mechanochemical scission kinetics and \(M_{\text{lim}}\). The results obtained in this chapter will serve as a reference data set for all further experiments in this thesis. The second part of this chapter reports the behavior of a potential new and interesting mechanophore, the cyclobutane-1,3-dione ring, incorporated in the center of PTHF chains. The cyclobutane-1,3-dione is the product of a [\(2+2\)] cycloaddition reaction of two ketenes (C=\(\text{C}=\text{O}\)).\(^25,26\) Upon dissociation (which is very difficult to achieve thermally), the free ketene groups should be reformed. Ketenes are very reactive species that react readily with a large number of nucleophiles.\(^26\) This feature makes the ketene dimer very interesting as a putative mechanophore to study for application in self-healing materials because liberation of free ketenes under
stress would immediately trigger new cross-linking reactions with any nucleophilic substituents along the polymer backbones or simply by redimerization of dangling free ketene groups with each other, although the latter is a rather slow process at room temperature. Here, we have studied the possibility of mechanochemically facilitating the retro [2+2] cycloaddition reaction.

### 2.2 Synthesis of PTHF using cationic ring-opening polymerization

Covalent, non-functionalized PTHF was synthesized by cationic ring-opening polymerization (CROP) of THF using methyl triflate (CH$_3$OTf) as initiator, according to a procedure developed by Goethals and co-workers. CROP can be regarded as a *living polymerization*, resulting in polymers with a controllable molecular weight and narrow molecular weight distributions (PDI < 1.4). PTHF samples with various molecular weights were synthesized by controlling total polymerization time, as shown in Figure 1a. An average growth rate of $8.4 \pm 0.2$ kg mol$^{-1}$ h$^{-1}$ was observed at room temperature (ca. 20 °C). When the desired molecular weight was reached, the polymerization was terminated by the addition of an excess of methanol. Henceforth, the polymers will be denoted as $P_x$, where $x$ is the approximate number-average molecular weight (here, $x = 30k$, 45k, 55k and 65k).

In Figure 1b, the different steps in CROP of THF are schematically depicted. CROP of THF has been studied extensively in the past and the details of its mechanism and reaction rates of different steps within the course of polymerization are well-known. It can be regarded as a living polymerization because termination and irreversible chain transfer can be eliminated, *e.g.*, “back-biting” which leads to (terminated) cyclic species is very slow compared to propagation.

Initiation occurs by the nucleophilic attack of monomer THF on methyl triflate (CH$_3$OTf). Subsequently, the polymerization is propagated by similar nucleophilic attacks of the monomer on the carbon atom of the cyclic oxonium ion (90% of the positive charge density is located on this carbon atom). The TfO$^-$ (CF$_3$SO$_3^-$) counterion, being a weak nucleophile, may result in temporary deactivation of the growing PTHF chain via recombination. Similar ester formation takes place when other noncomplex counterions are used, *e.g.*, mesylate (CH$_3$SO$_3^-$) or perchlorate (ClO$_4^-$). The deactivation step is reversible and the PTHF chain can be reactivated in either an *intra*molecular (nucleophilic attack of the adjacent ether oxygen) or *inter*molecular way (attack of monomer THF). Only the intramolecular case has been shown in Figure 1b and it has been found that this type of reactivation is faster than the intermolecular type. In both cases, TfO$^-$ is eliminated and the active
oxonium ion species is formed again. In the polymerization of THF, the rates of propagation and temporary deactivation are very similar. In addition to this, the rate of propagation does not depend on the relative degree of dissociation of the growing PTHF chain: the reactivity of the separate ions and ion pairs has found to be similar, and independent of the counterion.28

2.3 Mechanochemical scission kinetics of PTHF

Mechanochemical scission experiments of polymers $P_x$ were carried out. Ca. 10 mg mL$^{-1}$ of polymer was dissolved in toluene and subjected to ultrasound irradiation for 90 min (continuous sonication at a power input of ca. 17 W). During sonication, the double-jacketed sonication vessel was cooled continuously with water from a thermostat-controlled bath at 2.0 ± 0.2 °C. Separate temperature measurements have shown that in this case, the bulk temperature of the sonication solution is around 10 °C after an initial stabilization period of a few minutes. During the sonication experiments, samples were withdrawn from the sonication vessel at regular time intervals and analyzed by gel permeation chromatography (GPC) to determine evolution of the molecular weight distribution (MWD).

GPC traces for samples taken during the sonication experiment are shown in Figure 2a–d for $P_{30k}$, $P_{45k}$, $P_{55k}$ and $P_{65k}$. The MWD of the $P_{30k}$ sample (Figure 2a) does
not change significantly during ultrasound treatment. A molecular weight of 30 kg mol\(^{-1}\) is around or even below the \(M_{\text{lim}}\) for mechanochemical chain scission of PTHF under these conditions. Only at the high molecular weight end of the peak (\textit{i.e.}, at lower GPC retention times), the intensity of the signal slightly decreases as a result of mechanochemical scission, while signal intensity increases somewhat at higher GPC retention times. This is in line with midpoint scission of polymer chains at the high molecular weight end of the distribution. In contrast, \(P_{45k}\), \(P_{55k}\) and \(P_{65k}\) do break upon irradiation with ultrasound (Figures 2b–d). Over time, the maximum of the original peak decreases in intensity and a second shoulder of lower molecular weight appears in the GPC trace. Analysis shows that the top molecular weight of this second peak is indeed approximately half of the top molecular weight of the starting material, confirming near-midpoint scission. This is particularly well seen in the GPC traces of \(P_{45k}\); the MWD of \(P_{55k}\) and \(P_{65k}\) appears to shift gradually to lower molecular weights, rather than that a clear bimodal MWD develops upon scission. This is due to the fact that the \(M_n\) of these polymers is well above \(M_{\text{lim}}\) which means that mechanochemical scission takes place continuously over almost the entire molecular weight range. The relatively high PDI of these polymers (which is an intrinsic feature of the polymerization process due to slow termination of the viscous reaction mixture at high molecular weights) further masks the development of a clear bimodal MWD.

A more quantitative analysis of the mechanochemical scission process was performed by deconvolution of the total GPC trace after baseline correction and normalization (to give a total integral peak area \(A_{\text{tot}} = 1\)). In the following discussion, the high molecular peak will be denoted as “peak 1”, whereas the second peak of the low molecular weight scission product is “peak 2”. Deconvolution of the GPC trace was done using the deconvolution method developed by Jakobs in our group.\(^{30}\) A double Gaussian peak equation was used for fitting to the experimental GPC data:

\[
I(x) = \frac{A_1}{w_1\sqrt{\pi}/2} \exp\left(-2\left(\frac{x-x_{c,1}}{w_1}\right)^2\right) + \frac{A_2}{w_2\sqrt{\pi}/2} \exp\left(-2\left(\frac{x-x_{c,2}}{w_2}\right)^2\right) \tag{2}
\]

Where \(A\), \(w\) and \(x_c\) represent the area, width and top retention time of each peak. This is a slightly modified version of the original deconvolution protocol, which was developed to account for selective midpoint scission of a weak metal–ligand coordination bond. In this case, the polydispersity of both starting material and scission product should be identical (\(w_1 = w_2\) in Equation (2)). To account for the increase in polydispersity that is typically observed in mechanochemical scission
experiments, the values of $w_1$ and $w_2$ were fitted independently. The (monomodal) peak of the starting material was first fitted with a single Gaussian function in order to determine $w_1$ and $x_{c,1}$. These values, along with $x_{c,2}$, were fixed in subsequent fitting of the other GPC traces. Representative results of the deconvolution procedure are shown in Figure 3a–b for $P_{45k}$ and $P_{55k}$ where the red line is the result of fitting a double Gaussian to the black GPC traces.

In all deconvolution procedures the total area ($A_1 + A_2$) was between 0.9–1.0 and typically, $R^2$ values between 0.95–0.98 were obtained. Although the deconvolution was not as perfect as for the case of selective midpoint scission, it was possible to extract kinetic data (see e.g. the inset of Figure 2b), particularly for $P_{45k}$ where scission results in a clear bimodal MWD (Figure 3a). However, the results of deconvolution for $P_{55k}$ and $P_{65k}$ were less accurate as seen in Figure 3b. In RI detection, the area of a peak is proportional to the weight fraction of material, thus, from the relative peak areas $A_1$ and $A_2$, the weight fraction of starting material $C_1$ can be calculated at any time $t$ during the sonication:
When assuming first-order mechanochemical scission kinetics, the weight fraction of starting material should decay exponentially with sonication time:

$$C_1(t) = C_1(0) \times \exp(-k_{sc}t)$$  \hspace{1cm} (4)

In Figure 3c, the obtained mechanochemical scission rate constants $k_{sc}$ are shown for different (number-average) molecular weights of the $P_x$ samples used in this study. From this graph, it is clear that the $M_{lim}$ for mechanochemical chain scission of PTHF under these conditions is around 30 kg mol$^{-1}$, which is in close agreement with earlier observations in our group by Paulusse, albeit for more polydisperse PTHF samples.$^{20}$ The standard deviations of the fitted value for $k_{sc}$ are included in this graph. They
reflect the reduced accuracy of the deconvolution procedure at higher molecular weights as noticed earlier. At the highest of the molecular weights, the scission product itself contains a significant fraction of PTHF chains that is still above $M_{\text{lim}}$. Therefore, a second mechanochemical chain scission step is to be expected, leading to a multimodal MWD. Obviously, the present deconvolution protocol does not allow for this to be fitted accurately.

2.4 Analysis of scission kinetics using numerical methods

From the previous section it is clear that there is a need for a more general analysis method of mechanochemical scission kinetics data. This method should provide kinetic data independent of the (starting) molecular weight and MWD/polydispersity of the sample. Different methods have been proposed in literature for this purpose. The best method would be a method that treats the scission kinetics of chains of each particular degree of polymerization (DP) independently instead of considering them as part of a population of chains having an average DP with a certain distribution around it. Such a method was developed by Heymach and Jost in the late 1960s. However, such a method is very elaborate and is too tedious for routine analysis. Analytical expressions for $k_{\text{sc}}$ have been derived and implemented successfully, but their use required the availability of specialized software packages. Less elaborate, numerical models were developed by others. In this work, we will use the numerical analysis which was developed more or less independently by Casassa and Jellinek. They originally derived a kinetic expression for random (thermal) polymer chain degradation, but it was shown by Malhotra and co-workers that this method also works for non-random mechanochemical chain scission processes. This method (henceforth referred to as the Malhotra method) evaluates the development of the number-average molecular weight ($M_n$) of a polymer during polymer chain scission:

$$\frac{M_n(t)}{M_n(0)} = \frac{1}{1 + k_{\text{sc}} t}$$

In this equation, $M_n(0)$ is the number-average molecular weight of the starting material. Since the kinetics are determined from the evolution of the $M_n$, this method takes into account the full MWD of a polymer sample. The Malhotra method was applied to the data sets of the mechanochemical scission experiments of $P_x$ and the results are summarized in Figure 4.

For all polymers $P_x$, the Malhotra method provided much better fits in plots of scission versus sonication time than deconvolution (compare Figure 4a with the
inset of Figure 2b). Fitting Equation (5) to the data sets gave the values of $k_{sc}$ for all samples. The result is shown in Figure 4b. The standard deviations in the fitted value of $k_{sc}$ are much smaller for this method than the values obtained from deconvolution (see error bars in Figure 2d). However, the numerical values of $k_{sc}$ are similar for both methods (for clarity, the $k_{sc}$ values obtained by deconvolution are also shown in Figure 4b). This is somewhat surprising since the fits obtained in deconvolution had relatively large standard deviations. In general, we can say that the Malhotra method is preferred over deconvolution for analysis of scission kinetics data. Similar values of $k_{sc}$ are obtained for both methods, while the first method is easier, much less time-consuming and gives better fits to the experimental data as it takes into account the full MWD of polymers. The deconvolution protocol is most reliable when it is used for analysis of selective mechanochemical scission of polymers having a relatively low molecular weight ($M_n$ between 1 and 2 times $M_{lim}$) and narrow PDI. Only then, single scission events predominate and the MWD does not change because, within the narrow distribution of molecular weights, all scission rates are approximately equal.

![Figure 4](image)

**Figure 4** (a) Results of the kinetic analysis in Equation (5) for PTHF samples $P_x$. (b) Molecular weight dependence of the mechanochemical scission rate constant $k_{sc}$ comparing the results of the Malhotra method with those obtained in deconvolution (see also Figure 3c). The solid line represents the best fit for a quadratic dependence of $k_{sc}$ on $M_n$ ($p = 2$ in Equation (1)).

Finally, it was attempted to determine the scaling relation between $k_{sc}$ and $M_n$ (i.e., the value of the exponent $p$ in Equation (1)). The solid line in Figure 3b represents the best fit for a quadratic dependence, i.e., $p = 2$. In this case, $M_{lim} = 17$ kg mol$^{-1}$ and $b = 8.6 \times 10^{-6}$ mol$^2$ kg$^{-2}$ min$^{-1}$. Although not shown here, linear fitting ($p = 1$) also gave a very satisfactory fit with $M_{lim} = 37$ kg mol$^{-1}$ and $b = 7.3 \times 10^{-4}$ mol kg$^{-1}$ min$^{-1}$ (this is excluding the data point of $P_{30k}$). So, in conclusion, both scaling relations gave satisfactory fits (with $R^2 > 0.99$ in both cases), but the present data set is too small for determination of the scaling exponent $p$. 
2.5 Mechanochemical retro [2+2] cycloaddition of ketene dimers

As a practical example of mechanochemical transformations in PTHF, we have studied the possibility of mechanochemically induced retro [2+2] cycloaddition of ketene dimers. For this purpose, the putative ketene dimer mechanophore was incorporated at the central position of a PTHF chain using a synthetic method that was originally developed by Goethals and co-workers for the synthesis of kentro-functionalized and star-shaped PTHF (see Figure 5). The two isomers of the cyclobutane-1,3-dione ring, having both benzyl groups either cis or trans (henceforth denoted as C and T) were separated after synthesis. Subsequently, they were converted into their triflate esters and used in situ as initiators for THF polymerization.

![Reaction scheme for the syntheses of PTHF-functionalized ketene dimers C and T. Reaction conditions: (i) 2.1 eq. Tf₂O, excess DTBP, Ar, 30–60 min, 0 °C → r.t.; (ii) THF, Ar, 4 h, r.t.; (iii) excess CH₃OH, Ar, 30 min, r.t.](image)

Different polymers \( P_x-C-P_x \) and \( P_x-T-P_x \) were synthesized, with \( x = 20k \) and \( 30k \) for isomer T and \( x = 30k \) only for isomer C. The initial GPC traces of \( P_{30k}-C-P_{30k} \) and \( P_{30k}-T-P_{30k} \) in Figure 6a–b show that the MWD is initially not perfectly monomodal. A small shoulder is visible at approximately half the molecular weight, which shows that some fraction of the material has no or only very short PTHF chains on one of the sides. In \( ^1H \) NMR of the final product, signals corresponding to benzyl alcohol, at 2.3 ppm (t, OH) and 4.6 ppm (d, CH₂OH), respectively, are absent. From this, we concluded that the initiation was complete (at least within the limit of detection of NMR), but that part of the growing chains was terminated early on in the polymerization, likely as a result of trace amounts of water present in the THF. Reliable deconvolution in order to quantify the weight fractions of mono- and bifunctional ketene dimer was not possible.

The behavior of \( P_x-C-P_x \) and \( P_x-T-P_x \) in mechanochemical scission experiments, including possible mechanochemically induced retro [2+2] cycloaddition was investigated by applying ultrasound to a solution of these polymers in toluene in the presence of benzylamine (BnNH₂) or benzyl alcohol (BnOH). Amines and alcohols immediately scavenge free ketene groups (C=O) by nucleophilic attack,
forming amides and esters, respectively. The most important results of these scission experiments are shown in Figure 6a–d.

In Figure 6c the kinetic plots are shown for the mechanochemical scission of $P_{\text{30k}}$–C–$P_{\text{30k}}$, $P_{\text{30k}}$–T–$P_{\text{30k}}$, and $P_{\text{20k}}$–T–$P_{\text{20k}}$. Scission rate constants were determined using Equation (5). Deconvolution of the GPC traces using Equation (1) did not result in satisfactory fits even when $w_1$ and $w_2$ were each defined separately (except at $t = 0$ min). Comparison of the scission kinetics of the cis- and trans-isomers shows that there is no significant difference in scission kinetics between both isomers. From regression analysis, the $k_{\text{sc}}$ values were obtained for all molecular weight samples. It was found that the scission rate constants of PTHF-functionalized ketene dimers were not significantly different from those of non-functionalized PTHF with the same molecular weight (see Figure 6d).

**Figure 6** Results of the mechanochemical scission experiments of (a) $P_{\text{30k}}$–C–$P_{\text{30k}}$ and (b) $P_{\text{30k}}$–T–$P_{\text{30k}}$. First order kinetic plots and rate constants for the mechanochemical scission of (c) $P_{\text{30k}}$–C–$P_{\text{30k}}$ and $P_{\text{30k}}$–T–$P_{\text{30k}}$ (comparing both isomers) and $P_{\text{20k}}$–T–$P_{\text{20k}}$ as determined by Equation (5). (d) Comparison of scission rate constants with those of non-functionalized PTHF (see Figure 4b, the solid line was drawn to guide the eye).
The similarity in mechanochemical scission rates of $\text{P}_x\text{C} - \text{P}_x$ and $\text{P}_x\text{T} - \text{P}_x$ compared to non-functionalized PTHF makes it doubtful that selective scission of the four-membered ring takes place. To investigate at which site scission takes place, the sonication was performed in the presence of 9-anthracenemethanol (AnCH$_2$OH). We anticipated that the incorporation of the anthracene moiety after reaction with the free ketene could be monitored by UV/Vis detection in GPC. However, the characteristic absorption spectrum of anthracene was not visible at the retention time of the scission product. In addition to this, careful inspection of the 1H NMR spectrum of the sample after work-up of the sonication mixture showed no changes in the characteristic chemical shifts of the protons associated with the ketene dimer group, meaning that this group remained intact during the sonication process. From this, we concluded that the retro [2+2] cycloaddition did not take place under the mechanochemical scheme that was imposed. The observed mechanochemical scission, therefore, must be a result of non-selective, near-midpoint scission of bonds within the covalent PTHF backbone. In this case, homolytic bond scission is the most likely scenario. This, in turn, would lead to the formation of two radical chain ends which can be detected by coupling to the radical scavenger DPPH. Analysis of the scission product by UV/Vis detection in GPC showed the characteristic absorption of polymer-bound DPPH at $\lambda_{\text{max}} = 340$ nm.

We can only speculate why the retro [2+2] cycloaddition of ketene dimers did not take place under a mechanochemical scheme, whereas mechanochemically facilitated retro cycloadditions of other four- and five-membered rings do occur. According to the Woodward–Hoffmann rules, [2+2] cycloadditions are photochemically allowed and thermally forbidden. However, the relative ease with which ketenes dimerize (even in the absence of any photochemical stimulus) makes this a non-standard case. Woodward and Hoffmann postulated that, therefore, this cycloaddition must take place via a multistep process. Experimental work by Huisgen confirmed that dimerization is non-concerted and proceeds via a zwitterionic mechanism (Figure 7). Work by Roberts and co-workers further demonstrated that the transition state of ketene dimerizations is most likely to be orthogonal (antarafacial), which means that the ketenes are oriented perpendicular to each other in the dimerization reaction (Figure 7). We hypothesize that, based on the concept of microscopic reversibility, this implies that the reverse thermal reaction must take place via the same orthogonal transition state. When applying force, this geometry is very difficult to obtain. Pulling on the cis-isomer (i.e., applying force on substituents $\text{R}_1$ and $\text{R}_4$ in Figure 7) results in twisting of the four-membered ring so that the oxygen atoms approach each other above the plane of the ring. In contrast, pulling the trans-isomer (substituents $\text{R}_1$
and $R_3$ leads to a flattening of the molecule because these substituents gradually move into the plane of the four-membered ring. It should, however, be added to this that the mechanochemically facilitated ring-opening of cyclobutanes, as reported by Moore and Martínez and co-workers, has also been shown to proceed in a stepwise fashion via radical intermediates.$^{35,37}$

At the moment of writing this thesis, we have started to study this system in more detail with molecular dynamics simulations and COGEF calculations to gain more insight into the energy landscape of ketene dimers under externally applied force. We hope that these theoretical studies provide more insight into the geometry and energy landscape of cyclobutanedione rings under stress. The importance of careful interpretation and considering alternative reaction pathways for mechanochemical bond scission was recently highlighted by Smalø and Uggerud.$^{44}$ They present theoretical calculations on the mechanochemical 1,3-dipolar cycloversion of the 1,2,3-triazole moiety, formed by copper-assisted azide–alkyne click reaction, which was presented before by Brantley et al.$^{38,45}$ In their calculations, Brantley et al. only consider the potential energy landscape of the 1,3-dipolar cycloversion reaction under the influence of an external force.$^{45}$ Smalø and Uggerud were able to perfectly reproduce the results obtained by Brantley et al., but they complemented these by considering homolytic bond scission of C–C polymer backbone bonds as an alternative route to mechanochemical chain scission.$^{44}$ They demonstrated that for small external forces (below ca. 1 nN), the cycloversion is indeed the preferred reaction pathway; however, activation energy is still well above 300 kJ mol$^{-1}$ which is too high for cycloversion to occur spontaneously unless at elevated temperatures. At higher forces there is a cross-over point in potential energy for both processes, and homolytic bond scission becomes the more favorable pathway. Based on these results, the authors question the true mechanochemical nature of the cycloversion that was observed by Brantley et al. and, in fact, propose a mechanochemically facilitated mechanism that is either solvent-assisted or initiated by radicals, since the application of force alone cannot account for chain scission through cycloversion. In conclusion, this example demonstrates the importance of comparing the potential energy landscape of a mechanophore under external force to that of homolytic bond
scission, which—even though it is generally undesired—will be an alternative pathway to mechanochemical chain scission. This is especially the case when the mechanophore bond is not much weaker than the chemical bonds making up the polymer backbone.

2.6 Conclusions

The synthesis and mechanochemical scission of non-functionalized PTHF was studied. The polymers were synthesized by CROP of THF using standard literature procedures. Mechanochemical scission of the polymers was carried out by subjecting a solution of PTHF in toluene to ultrasound and the scission kinetics were monitored by GPC analysis. For analysis of the mechanochemical scission kinetics two methods were compared: (i) deconvolution of the MWDs during scission as obtained by GPC and (ii) numerical analysis using the expression derived by Casassa and Jellinek, and further developed by Malhotra to account for non-random, near-midpoint scission. It was found that deconvolution of the MWDs with a double Gaussian fitting function leads to systematic deviations. This is especially the case at high number-average molecular weights when a significant fraction of the MWD consists of very high molecular weight polymer (higher than 2 times $M_{\text{lim}}$). In these cases, multiple scission events take place which cannot be accounted for by the double Gaussian deconvolution protocol which was originally developed to analyze selective midpoint scission of polymers containing a weak bond.

The numerical Malhotra method provided much more accurate results as this method takes in account the full MWD during evaluation of scission kinetics. However, when comparing the results of both methods, it turned out that the obtained scission rate constants $k_{\text{sc}}$ were similar for each PTHF sample that was investigated, even though deconvolution gave very unsatisfactory fits. Owing to its ease of implementation and higher accuracy, however, the Malhotra method would be the preferred analysis method, especially when the scission is non-selective near-midpoint scission of polymer chains. A molecular weight dependence of $k_{\text{sc}}$ for non-functionalized PTHF was established and it was found that $M_{\text{lim}}$ for PTHF is between 17–30 kg mol$^{-1}$ although, intuitively, it is most likely closer to the latter value. The present data set could not discern the exact scaling relation for $k_{\text{sc}}$ with $M_n$.

Subsequently, the mechanochemical response of ketene dimers was investigated. Bifunctional hydroxyl-functionalized ketene dimers were incorporated within the PTHF backbone and solutions of these polymers were subjected to ultrasound. However, it was found that retro [2+2] cycloaddition of the ketene dimers could not
be achieved mechanochemically. A more detailed study of the mechanochemical scission process showed that scission of these ketene-functionalized PTHF proceeds via homolytic bond scission of the PTHF backbone, leaving the four-membered ketene dimer ring intact. It was hypothesized that mechanochemical retro [2+2] cycloaddition cannot take place because of the geometry that is required in the transition state. Both individual ketenes should adopt an orthogonal geometry which is not achieved by applying force on the 2- and 4-positions of the four-membered ring. We have no direct evidence proving this statement, but currently, we are pursuing a theoretical study on the response of the ketene dimer group to external stress.

Acknowledgements

We thank F.A. Leibfarth and Prof. Dr. C.J. Hawker (Materials Research Laboratory, University of California, Santa Barbara (CA), United States) for the synthesis and characterization of the ketene dimer cis- and trans-isomers and for the fruitful discussions on the possible mechanisms of (retro) [2+2] cycloaddition reactions.

Experimental section

General. All reagents and solvents were used as received unless stated otherwise. Methyl trifluoromethane sulfonate (methyl triflate; purity 96%), trifluoromethane sulfonic anhydride (triflic anhydride; ≥99%) and di-tert-butylpyridine (DTBP; 97%) were purchased from Sigma-Aldrich (Germany). All solvents were obtained from BioSolve (The Netherlands) and of at least AR grade quality. Deuterated solvents for recording NMR spectra were obtained from Cambridge Isotope Laboratories, Inc. (United States). For the mechanochemical scission experiments, benzylamine (BnNH₂; 99%), benzyl alcohol (BnOH; anhydrous, 99.8% in a Sure/Seal™ bottle), 9-anthracenemethanol (AnCHOH; 97%) and 2,2-diphenyl-1-picrylhydrazyl (DPPH; 95%) were purchased from Sigma-Aldrich (Germany).

All polymerizations were carried out under inert argon atmosphere using Schlenk line techniques. After synthesis and work-up, the polymers were characterized by 1H NMR and gel permeation chromatography (GPC). 1H NMR spectra were recorded on a Varian 400MR spectrometer. GPC was carried out on a Shimadzu LC-10AD chromatograph equipped with refractive index and UV/Vis detectors (Shimadzu RID-10A and Shimadzu SPD-M10A photodiode array detector), using either THF or chloroform as eluens and polystyrene (PS) as calibration standards. Molecular weights of PTHF were corrected by using a PTHF sample of known \( M_n \) (21.4 kg mol⁻¹) and low PDI (<1.2) as external standard.

All sonication experiments were carried out using a Sonics VC750 sonication set-up operating at 20 kHz and 30% of maximum amplitude using continuous sonication protocol.
**Synthesis of α,ω-dimethoxy poly(tetrahydrofuran).** Covalent, non-functionalized $P_x$ ($x = 30k, 45k, 55k, 65k$, being the approximate $M_n$) were synthesized via cationic ring-opening polymerization of THF, using the method adapted from Ref. 27. THF (80–100 mL) and DTBP (100 µL, 0.46 mmol) were placed inside a Schlenk round-bottom flask, placed under inert argon atmosphere. Prior to use, THF was dried and purified over an alumina-packed column. Subsequently, methyl triflate (50 µL, 0.45 mmol) was added to initiate the polymerization. After stirring for the required amount of time to achieve the target molecular weight (4–7.5 h), the polymerization was terminated by adding a large excess of methanol (ca. 1 mL). After an additional 30 min, the polymer was precipitated in water which resulted in the formation of a white polymer film overnight. The film was dissolved in diethyl ether, dried over MgSO$_4$ and precipitated overnight at −30 °C which yielded the polymer ligand as a white powder in good yields.

GPC (in CHCl$_3$, versus PS and corrected for PTHF): $P_{30k}$: $M_n = 29.1$ kg mol$^{-1}$, PDI = 1.32; $P_{45k}$: $M_n = 45.7$ kg mol$^{-1}$, PDI = 1.14; $P_{55k}$: $M_n = 53.9$ kg mol$^{-1}$, PDI = 1.30; $P_{65k}$: $M_n = 63.9$ kg mol$^{-1}$, PDI = 1.34.

**Synthesis of cis- and trans-2,4-bis(4-(hydroxymethyl)-benzyl)-2,4-dimethyl-cyclobutane-1,3-dione (C and T).** These compounds were synthesized, separated and analyzed by F.A. Leibfarth (Materials Research Laboratory, University of California, Santa Barbara (CA), United States) and kindly donated to us for use as initiator in THF polymerization. The synthetic procedure was similar to that reported earlier for analogous ketene dimers.$^{26}$

**Synthesis of $P_x$–C–P$_x$ and $P_x$–T–P$_x$ ($x = 20k$ or $30k$).** Kentro-functionalized PTHF containing the cis or trans ketene dimer group were synthesized via cationic ring-opening polymerization of THF, using the method from Ref. 33. For a typical polymerization, $C$ or $T$ (44 mg, 0.25 mmol) was suspended in dichloromethane (1.8 mL; dried and purified by passage over an alumina-packed column). DTBP (100 µL, 0.45 mmol, 1.8 equiv.) was added and the suspension was cooled in an ice/water bath while stirring. Subsequently, triflic anhydride (45 µL, 0.53 mmol, 2.1 equiv.) was added and the reaction mixture was allowed to stir for 30–60 min at 0 °C. During this time, the suspension turned into a clear light orange solution which is indicative of the formation of the bis(triflate ester) initiator. The ice/water bath was then removed and the initiator solution was allowed to warm up to ambient temperature. THF (ca. 70 mL; dried and purified over an alumina-packed column) was placed inside a Schlenk round-bottom flask, placed under inert argon atmosphere and cooled in an ice/water bath. The initiator solution was added swiftly to the THF and the ice bath was removed to allow the reaction mixture to warm up to ambient temperature. After stirring for 180 or 240 min, excess methanol (1 mL) was added to terminate the polymerization. After an additional 30 min, the polymer was precipitated in water which resulted in the formation of a white polymer film overnight. The film was dissolved in diethyl ether, dried over MgSO$_4$ and precipitated overnight at −30 °C which yielded the polymer ligand as a white powder in good yields. Sometimes a second precipitation in diethyl ether was required to remove all DTBP.
The resulting polymers $P_x$–$C$–$P_x$ and $P_x$–$T$–$P_x$ ($x = 20k$ or $30k$) were analyzed by $^1$H NMR to confirm that the ketene dimer remained intact during the polymerization. Analysis by GPC showed that the molecular weight distribution was bimodal for all polymers, indicating partial deactivation of the initiator during the polymerization.

**$P_x$–$C$–$P_x$:** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.23 (d, Ar–H), 7.04 (d, Ar–H), 4.41 (s, Ar–CH$_2$OCH$_2$), 3.2–3.6 (br, C$_2$H$_5$OCH$_2$), 2.35 (s, Ar–CH$_2$), 1.4–1.8 (br, CH$_2$CH$_2$), 1.25 (s, CCH$_3$). GPC (THF, *versus* PS, corrected for PTHF): $x = 30k$: $M_n = 60$ kg mol$^{-1}$, PDI = 1.24.

**$P_x$–$T$–$P_x$:** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.21 (d, Ar–H), 7.08 (d, Ar–H), 4.44 (s, Ar–CH$_2$OCH$_2$), 3.2–3.6 (br, CH$_2$OCH$_2$), 2.83 (s, Ar–CH$_2$), 1.4–1.8 (br, CH$_2$CH$_2$), 0.47 (s, CCH$_3$). GPC (THF, *versus* PS, corrected for PTHF): $x = 20k$: $M_n = 31$ kg mol$^{-1}$ ($M_{top,1} = 35$ kg mol$^{-1}$, ca. 82%; $M_{top,2} = 20$ kg mol$^{-1}$), PDI = 1.18; $x = 30k$: $M_n = 63$ kg mol$^{-1}$, PDI = 1.36.

**Mechanochemical scission experiments of $P_x$.** $P_x$ (ca. 50 mg) was dissolved in toluene (ca. 5 mL, dried over 4Å molecular sieves prior to use). After complete dissolution the solution was transferred into a 10 mL double-jacketed sonication vessel and cooled to 10.0 ± 0.2 °C using water from a recirculation thermostat bath. After saturation with argon, the solution was sonicated for 60 min at 30% of the maximum amplitude. Samples (ca. 0.2 mL) were taken at regular time intervals. Solvent was evaporated in vacuo and the residual solid was dissolved in chloroform (ca. 0.8 mL) for analysis by GPC. Deconvolution of the resulting GPC traces was done using the Origin® 8.5 software package (OriginLab Co.),

**Mechanochemical scission experiments of $P_x$–$C$–$P_x$ and $P_x$–$T$–$P_x$.** For a typical sonication experiment, $P_x$–$C$–$P_x$ or $P_x$–$T$–$P_x$ (50–60 mg) was dissolved in toluene (ca. 5 mL, dried over 4Å molecular sieves prior to use). BnNH$_2$, BnOH (ca. 100 µL), AnCH$_2$OH (ca. 10 mg) or DPPH (ca. 40 mg) was added to the sonication solution. A small fraction of this solution was set aside at ambient temperature as a control for thermal dissociation. The remaining solution was transferred into a 10 mL double-jacketed sonication vessel and cooled to 2.0 ± 0.2 °C using water from a recirculation thermostat bath. After saturation with argon, the solution was sonicated for 60 min at 30% of the maximum amplitude. Samples (ca. 0.2 mL) were taken at regular time intervals. Solvent was evaporated *in vacuo* and the residual solid was dissolved in THF (ca. 0.8 mL) for analysis by GPC. Deconvolution of the resulting GPC traces was done using the Origin® 8.5 software package (OriginLab Co.).

**Notes and references**

Covalent mechanochemistry of poly(tetrahydrofuran)

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Chapter 2

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Chapter 3

The mechanism of ultrasound-induced scission of silver(I)–NHC supramolecular polymer complexes

Abstract

The mechanochemical scission of a supramolecular polymer complex containing a silver(I)–N-heterocyclic (NHC) coordination complex by ultrasound in solution was investigated. By carrying out the ultrasound scission experiments using different saturation gases (argon, nitrogen, methane and isobutane), radical production during the sonication process could be controlled. The efficiency of polymer scission did not change under radical-suppressing conditions, provided that the hydrodynamic conditions of cavitation bubble collapse were kept similar. These results further confirm that scission of the supramolecular silver(I)–NHC polymer complexes under ultrasound occurs via a true mechanochemical mechanism and not through thermal scission or scission induced by radicals.

Parts of this chapter have been published:
3.1 Introduction

Chemical bonds can be activated by mechanical forces, instead of conventional means such as thermal or photochemical activation.\(^1\)–\(^3\) The energy landscape of mechanically and thermally activated reactions can be substantially different sometimes, resulting in different reaction pathways for each activation method.\(^3\)–\(^7\) For efficient transduction of (external) mechanical forces onto the chemical bond or moiety (“mechanophore”) that needs to be activated, a handle is required. Polymer chains have shown to be very effective for this purpose.\(^1,\)\(^5\)–\(^10\) The use of mechanical forces to carry out chemical transformations within molecules has recently gained interest because it opens the way to the development of mecanoresponsive materials (e.g., materials that give a color change upon strain\(^10\) or self-healing materials\(^11\)). In this respect, it is especially interesting to look at activation of catalytic processes induced by mechanical forces (mechanocatalysis). Recent work has shown the promising prospects of using mechanical forces for activation of latent transition metal complexes,\(^12,\)\(^13\) which can subsequently be used as catalysts. In our group, transesterification and alkene or ring-opening polymerization metathesis reactions have been successfully performed by subjecting a solution of the polymer mechanocatalyst complexes to ultrasound irradiation in the presence of reactants. Activation of these organometallic complexes is achieved by scission of the coordination bond between the metal center and the \(N\)-heterocyclic carbene (NHC) ligand. This leads to either an active ruthenium(II)–NHC catalyst, which can be used as an olefin metathesis catalyst,\(^14\) or a free NHC, a catalyst that is commonly used in, e.g., ring-opening polymerization reactions of cyclic esters,\(^15,\)\(^16\) and transesterification reactions.\(^17,\)\(^18\) The silver(I)–NHC complex has a low critical molecular weight for scission with ultrasound.\(^19\) Therefore, this complex is very useful for studying the mechanochemical scission process. The polymer chains attached to the complex can be relatively short, and scission can therefore be monitored directly by end-group analysis in \(^1\)H NMR spectroscopy. A free NHC is formed in solution when scission of the silver(I)–NHC bond occurs (see Figure 1). The free NHC can recoordinate to the silver(I) metal center since the complex and free NHCs are in a dynamic equilibrium.\(^19\) However, if a source of protons (such as water) is present, the strongly basic NHC is converted to the corresponding imidazolium salt, and reformation of the complex is prevented.

Ultrasound in solution can create the forces needed for mechanochemical scission, by inducing growth of gaseous nuclei, which subsequently collapse.\(^20\) This process is called cavitation, and it may lead to radical formation,\(^21\) high heating and cooling rates,\(^20\) and polymer scission.\(^22,\)\(^23,\)\(^25\) Radical formation results from the dissociation of gas molecules because of the high temperatures and pressures inside the bubble due
The mechanism of ultrasound-induced scission to the adiabatic compression during the collapse.\textsuperscript{20} High temperatures are reached because the collapse time is shorter than the relevant times for mass and heat transfer. Polymer scission is caused by the high strain rates generated at the bubble wall. The obtained strain rates can be as high as $10^7$ s\textsuperscript{-1} or more. The resulting forces are high enough to induce stretching and breaking of a covalent bond in a polymer above a critical molecular weight.\textsuperscript{8,22,23,25} There is a strong influence of gas solubility on the efficiency of an ultrasonic scission process as was demonstrated in the work by Price et al. on scission of covalent polymers.\textsuperscript{25} They found that ultrasonic scission was less efficient under gases with a high solubility.

In this work, we investigate the relative contributions of mechanical, thermal, and radical-induced dissociation mechanisms to the overall observed ultrasound-induced scission of a silver(I)–NHC coordination bond in a supramolecular polymer. The internal temperatures of the cavitation bubbles and the radical production rate are varied by using a number of saturation gases with heat capacities that increase in the sequence argon, nitrogen, methane and isobutane. It has been demonstrated that gases with a higher heat capacity lead to lower maximum internal temperatures during (adiabatic) collapse of cavitation bubbles.\textsuperscript{25} Using this principle, the formation of radicals as thermal sonochemical byproducts during sonication can be effectively suppressed. The negligible contribution of thermal chain scission was already established in previous work by Karthikeyan et al.\textsuperscript{19} In the present study we further demonstrate the true mechanical nature of chain scission by showing that the contribution of radicals to chain scission is also negligible.

### 3.2 Synthesis of silver(I)–NHC polymer complexes

The supramolecular polymer which is of interest in this work is based on the organometallic complex of two (polymer-functionalized) $N$-heterocyclic carbene...
(NHC) ligands coordinated to a silver(I) metal center. Mechanochemical ligand dissociation in this complex was already studied before in our group,\textsuperscript{12,19} this scission is of particular interest since the resulting free NHC ligand is an active catalyst for transesterification reactions. Similar to our previous work, the polymer ligand $\text{NHC}_{7k}$ was synthesized via cationic ring-opening polymerization of THF, following a procedure by Dubreuil et al.\textsuperscript{26} Full end-functionalization of the polymer with imidazolium groups was achieved by terminating the growing polymer chain with an excess of $N$-ethylimidazole, cf. the reaction scheme in Figure 2.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{reaction_scheme.png}
\caption{Synthesis of supramolecular polymer complex $\text{Ag}(\text{NHC}_{7k})_2\text{PF}_6$ by cationic ring-opening polymerization of THF. Reaction conditions: (i) methyl triflate, di-tert-butylpyridine, Ar, 3 h, 0 °C; (ii) 2 eq. $N$-ethylimidazole, Ar, 30 min, 0 °C; (iii) Dowex\textsuperscript{®} ion exchange resin, CH$_3$OH, 2 h, r.t.; (iv) NH$_4$PF$_6$, CH$_3$OH, 2 h, r.t.; (v) excess Ag$_2$O, CH$_2$Cl$_2$/1 M NaOH solution, 2 d, r.t.}
\end{figure}

For the synthesis of the silver(I)–NHC complex, the “silver base route” was used.\textsuperscript{27} This procedure consists of direct complexation with silver(I) ions after \textit{in situ} generation of the free NHC by deprotonation with the oxide anion of the silver(I) salt. The advantage of this route is that it does not require the addition of an additional strong base for deprotonation of the imidazolium salt. In addition, in the presence of silver(I) ions, the deprotonated NHCs are directly complexed, so the reaction does not necessarily have to be performed under protective atmosphere (in fact, the reaction is done in aqueous medium). Complexation of the non-polymeric 1-ethyl-3-methylimidazolium hexafluorophosphate salt with silver(I) was carried out using a modified version of the synthetic procedure of Wang and Lin:\textsuperscript{28} excess silver(I) oxide (Ag$_2$O) was suspended in a solution of the imidazolium salt in a 5:1 to 10:1 (v/v) mixture of dichloromethane and aqueous 1 M NaOH. The addition of phase transfer catalyst to this heterogeneous system, as advocated by Wang and Lin, was not required and full complexation was obtained within 24 h. However, despite being an easy and straightforward synthetic procedure, its implementation for complexation of polymer imidazolium ligands was not a routine. Owing to the low (molar) concentrations, the
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complexation reaction with polymer ligand was found to be slow. A reaction time of two days or more was typically required to achieve full complexation. It was necessary to carry out the reaction with a large excess of Ag$_2$O and at high polymer ligand concentrations (ca. 100 mg mL$^{-1}$). In fact, the highest yield of product was sometimes obtained when the dichloromethane had accidentally evaporated over the course of several days and the reaction mixture had become a very viscous slurry of polymer, water and Ag$_2$O (as a suspended solid). Work-up of the reaction mixture was done by dilution of the crude mixture with dichloromethane and water, followed by separation of the organic and aqueous layers. The organic layer (containing the polymer complex) was then filtered over celite and subsequently dried over MgSO$_4$. After filtration, the solvent was removed in vacuo and the polymer silver(I)-NHC was typically obtained in 50–90% yield. The isolated yield depended much on how extensive the celite was washed with dichloromethane after filtration. $^1$H NMR was used to verify the extent of complexation. Upon complexation with silver(I), the downfield signal at 9.2 ppm, which corresponds to the proton bound to the C2 carbon disappeared. In addition, a downfield shift of the signals of the proton bound to C4 and C5, as well as those of the protons attached to the carbons adjacent to N1 and N3 was indicative of silver(I)–NHC complex formation.

3.3 Determination of radical formation rates for different saturation gases

Radical formation rates under ultrasound were investigated for four different gases, having an increasing heat capacity and varying solubility in toluene: argon, nitrogen, methane and isobutane, respectively. The relevant physical parameters of these gases are listed in Table 1. During sonication experiments, the radical formation for each of these gases was quantified by monitoring the consumption of DPPH with UV/Vis spectroscopy (Figures 3a–b).$^{2,29}$ DPPH (Figure 3c; $\lambda_{\text{max}} = 330$ and 520 nm) is a sterically stabilized free radical which reacts with the sonochemically produced radicals to form DPPH$_2$ which has a $\lambda_{\text{max}} = 380$ nm. Figures 3a–b show the strong reduction in radical formation when a high heat capacity gas such as isobutane is used as saturation gas. Under argon, the characteristic absorption profile of DPPH has completely disappeared after 30 min of sonication, whereas hardly any change in the UV/Vis spectrum is observed under isobutane. Similar experiments were performed with nitrogen and methane as saturation gases and the results are summarized in Figure 3d. The radical formation rate (expressed as the amount of DPPH consumed per Joule of energy input) decreases from $2.3 \times 10^{-9}$ mol L$^{-1}$ J$^{-1}$ under argon to $1.1 \times 10^{-9}$ mol L$^{-1}$ J$^{-1}$ under nitrogen and $0.11–0.14 \times 10^{-9}$ mol L$^{-1}$ J$^{-1}$ under methane and isobutane.
Hence, a more than tenfold reduction in radical formation is achieved when changing from argon to methane or isobutane as saturation gas. Simulations of the bubble dynamics revealed that the final temperatures within the hotspots created by the collapsing cavitation bubbles is indeed much lower for methane/isobutane (520 ± 30 K and 460 ± 10 K, respectively) than for nitrogen (540 ± 40 K) and argon (580 ± 50 K). So, the lower radical formation rates are in qualitative agreement with the lower hotspot temperatures which follow the increasing heat capacities of the gases (Table 1). However, the results of the simulation should be treated as qualitative, rather than quantitative since the hotspot temperatures are considerably lower than those of several 1000 K as reported in literature.\textsuperscript{20} The reason for the discrepancy may be the relatively high vapor pressure of toluene compared to other solvents used in literature. Szwarc has reported pyrolysis of toluene starting from temperatures of ca. 740 K and up,\textsuperscript{30} which may be considered a very realistic value for the hotspot in sonication experiments.

![Figure 3](image-url)
3.4 Mechanochemical scission experiments of silver(I)–NHC polymers

The kinetics of mechanochemical scission of supramolecular silver(I)–NHC polymer complex Ag(NHC)₂PF₆ was investigated using standard sonication experiments. A dilute solution of supramolecular polymer complex in toluene (saturated with demineralized water) was prepared. As discussed previously, the water molecules act as a scavenger for any free NHCs that are formed during the sonication experiment. By protonation of the free NHC, the recoordination to the free silver(I) center is prevented and the scission process can be monitored in time by ¹H NMR spectroscopy.

The characteristic peaks corresponding to the silver(I)–NHC supramolecular polymer complex have been assigned with “#” in the top and center ¹H NMR spectra of Figure 4. Upon dissociation of the complex, additional peaks appeared in the ¹H NMR spectrum; these peaks are assigned with “*” and can, indeed, be associated with the peaks corresponding to the polymer imidazolium salt (bottom spectrum). Especially the appearance of the small downfield peak at 9.2 ppm confirms the formation of the imidazolium salt as the mechanochemical scission product. The percentage of mechanochemical scission after 5 min of irradiation with ultrasound was determined from the ratio of the peak integrals at 4.2 ppm (complex) and 4.4 ppm (imidazolium salt). The integral ratio of the more downfield peaks at 7.4 and 7.8 ppm was used as control. In all cases both integral ratios were found to be similar.

In Figure 5 the percentage scission that was found for each saturation gas is overlaid with the measured radical formation rates (as shown in Figure 3d). No (spontaneous) scission of the silver(I)–NHC polymer complex was observed when the solution was set aside at ambient temperature for a few hours without ultrasound irradiation. The percentage values are average values for duplicate or triplicate scission experiments. The large spread of observed scission percentages is ascribed to the inherently low

Table 1 Heat capacities and solubility in toluene for argon, nitrogen, methane and isobutane.

<table>
<thead>
<tr>
<th></th>
<th>Argon</th>
<th>Nitrogen</th>
<th>Methane</th>
<th>Isobutane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat capacity (J mol⁻¹ K⁻¹)</td>
<td>20.9</td>
<td>28.5</td>
<td>35.2</td>
<td>102</td>
</tr>
<tr>
<td>Solubility (10⁻³ mol mol⁻¹)</td>
<td>1.1</td>
<td>0.54</td>
<td>24</td>
<td>~200</td>
</tr>
</tbody>
</table>

¹ Heat capacity data from the National Institute of Standards and Technology (NIST) database (http://webbook.nist.gov).
² Solubility data taken from Ref. 25.
³ Estimated value, based on physical data in process engineering software by Aspen Technology, Inc. (Burlington (MA, USA)).
sensitivity of $^1$H NMR at the low (molar) concentrations in these experiments. However, for monitoring scission of the silver(I)–NHC complexes, $^1$H NMR is the only technique so far that was found to be suitable.

Despite the large spread in data, it is immediately clear that the efficiency of ultrasound-induced scission of the silver(I)–NHC complexes under different saturation gases does not follow the same trend as their radical production rates. Even though a tenfold decrease in radical formation was observed when comparing argon with methane, the observed percentages of complex scission was the identical (within experimental error) for both gases. The slightly lower scission efficiency under isobutane could be explained by the cushioning effect that occurs during sonication under isobutane. Bubble dynamics simulations (see Figure A1) revealed that the hydrodynamic conditions during cavitation bubble collapse under isobutane were much milder than under argon and the other gases (only the results for argon and isobutane are shown in the Appendix, simulation results indicate that the bubble dynamics for nitrogen and methane were very similar to argon). The cushioning effect under isobutane could be directly related to its much higher solubility in toluene compared to the other three gases (see Table 1).25 By comparing both data sets in Figure 5, it is evident that the presence of radicals has negligible—if any—influence the mechanochemical scission efficiency of the silver(I)–NHC supramolecular polymer complexes. Under

Figure 4 $^1$H NMR spectra for the supramolecular polymer complex, Ag(NHC$_{7k}$)$_2$PF$_6$ (top), the polymer complex that was partially dissociated (middle) and the corresponding non-complexed polymer imidazolium salt with PF$_6^-$ as counterion (bottom).
The mechanism of ultrasound-induced scission

similar hydrodynamic conditions during cavitation bubble collapse (i.e., under argon, nitrogen and methane as saturation gases), the percentage scission within a certain sonication time interval is identical within experimental error, even though radical production was lowered by a factor of ten by changing from argon to methane. When the cavitation hydrodynamics become milder, owing to the high solubility of isobutane in toluene, the scission efficiency decreases somewhat. These observations further demonstrate the true mechanochemical nature of polymer chain scission in the silver(I)–NHC supramolecular polymer complexes and exclude the presence of thermal sonochemical effects as being the principal cause for (polymer) ligand dissociation in ultrasound experiments.

3.5 Conclusions

The scission of a supramolecular silver(I)–NHC polymer complex in solution by ultrasound irradiation was investigated experimentally and theoretically in order to gain more insights into the most likely scission mechanism. The mechanisms that are of potential relevance, and that were considered in this work, are thermal scission, scission by radicals and mechanical scission due to strains imposed on the polymer chain during collapse of a cavitation bubble. An (exclusively) thermal mechanism for scission was already excluded before,19 hence in this work we tried to discriminate between scission by radical-induced and true mechanical scission.

Sonication experiments were carried out using DPPH as a radical scavenger and argon, nitrogen, methane or isobutane as saturation gas. By varying the heat capacities of these gases, a reduction in hotspot temperatures could be achieved, leading to
Chapter 3

suppression of radical formation. It was demonstrated that radical production went down by a factor of ten by changing from argon (low heat capacity) to methane and isobutane (high heat capacity). These findings were qualitatively supported by bubble dynamics simulations.

In spite of a tenfold decrease in radical production rate, scission of the silver(I)–NHC polymer was not affected (at least within experimental error). Similar scission percentages were observed under argon, nitrogen and methane (11–14% scission after 5 min of sonication); a slightly lower percentage was seen for isobutane (6%). Bubble dynamics simulation revealed that the lower scission efficiency could be explained by a significant decrease in maximum strain rates which were obtained under isobutane as compared to the other three gases. The milder cavitation collapse under isobutane is a direct result of its much higher solubility in toluene, causing a cushioning effect during cavitation bubble collapse.

In summary, for argon, nitrogen and methane (having similar hydrodynamics of cavitation bubble collapse), mechanochemical scission of the silver(I)–NHC polymer complex was not affected under radical-suppressing conditions. Therefore, it can be concluded that radicals are not responsible for scission of the silver(I)–NHC bond under sonication. This, in turn, leads to the conclusion that the scission has a true mechanical nature, arising from the forces that act on the polymer chains during collapse of cavitation bubbles. This conclusion is in line with the previously observed molecular weight dependence of scission rates, which is also a strong indication for true mechanochemical scission by ultrasound.\(^\text{19}\)

**Experimental section**

**General.** All reagents and solvents were used as received unless stated otherwise. Methyl trifluoromethane sulfonate (methyl triflate; purity 96%), 2,6-di-tert-butylpyridine (DTBP; 97%) ammonium hexafluorophosphate (NH\(_4\)PF\(_6\); 99.99%) and silver(I) oxide (Ag\(_2\)O; 99%) were purchased from Sigma-Aldrich (Germany). N-ethylimidazole (>98%) was obtained from TCI (Belgium). Dowex\(^\text{®}\) ion exchange resin (1x8 50–100 mesh) and 2,2-diphenyl-1-picrylhydrazyl (DPPH, 95%) were purchased from Acros (Belgium). Solvents used in the synthesis and viscosity measurements were obtained from BioSolve (The Netherlands) and of at least AR grade quality. Deuterated solvents for recording NMR spectra were obtained from Cambridge Isotope Laboratories, Inc. (United States). All gases, argon (99.996% v/v), nitrogen (99.999% v/v), methane (99.995% v/v) an isobutane (99.5% v/v) were supplied by Linde (The Netherlands).
The polymerization was carried out under inert argon atmosphere using Schlenk line techniques. After synthesis and work-up, the polymer and its corresponding silver(I) complex were characterized by \( ^1H \) NMR on a Varian 400MR or Varian Mercury 400 spectrometer to confirm end-group functionalization and determine the number-average molecular weight, \( M_n \). In addition, gel permeation chromatography (GPC) was carried out on a PL-GPC 50 Plus system (Polymer Laboratories) using a refractometer for detection. DMF/LiBr (10 mM) was used as eluens. The number- and weight-average molecular weight, \( M_n \) and \( M_w \), were calculated \textit{versus} poly(ethylene oxide) (PEO) calibration standards. All sonication experiments were performed using a Sonics VC750 sonication set-up, using a Sonics 20 kHz titanium alloy ultrasound probe (diameter 0.5 in) with half wave extension (parts 630-0220 and 630-0410). The temperature in the reactor was maintained with a Lauda E300 cooling bath and measured using a 0.5 mm diameter thermocouple which was placed in the sonication solution.

\textit{Synthesis of \( \alpha-\left(N\text{-ethylimidazolium}\right)-\omega\text{-methoxy poly(tetrahydrofuran)}.} Polymer ligand NHC\(_\kappa\) was synthesized \textit{via} cationic ring-opening polymerization of tetrahydrofuran (THF). For the polymerization, THF (100 mL) and DTBP (200 µL, 0.92 mmol) were placed inside a Schlenk round-bottom flask, placed under inert argon atmosphere and cooled to 0 °C in an ice bath. Prior to use, THF was dried and purified over an alumina-packed column. Subsequently, methyl triflate (100 µL, 0.91 mmol) was added to initiate the polymerization. After stirring for 3 h, the polymerization was terminated by adding \( N\text{-ethylimidazole} \) (200 µL, ca. 2.1 mmol). Precipitation of the crude polymer in water (overnight at ambient temperature) resulted in a white polymer film. The film was redissolved in diethyl ether, dried over MgSO\(_4\) and precipitated overnight at −30 °C which yielded the polymer ligand as a white powder in good yields. Ion exchange of the anion to chloride was carried out by stirring the polymer with Dowex\textsuperscript{®} exchange resin in methanol for 2–3 hours. After this period, the exchange resin was removed by filtration and the methanol was evaporated \textit{in vacuo}.

\( ^1H \) NMR (400 MHz, acetone-\( d_6 \)): δ 10.4 (s, 1H, NCHN), 7.8 (d, 2H, CH=CH), 4.5 (m, 4H, NCH\(_2\)CH\(_3\)), 3.2 (s, 3H, OCH\(_3\)), 3.2–3.6 (br, \( n \times 4\)H, CH\(_2\)OCH\(_2\)), 1.3–1.8 (br, \( n \times 4\)H, CH\(_2\)CH\(_2\)), 1.6 (t, 3H, NCH\(_2\)C\(_3\)H\(_3\)).

Subsequent ion exchange of the chloride to hexafluorophosphate (PF\(_6\)^-) anion was carried out by stirring the polymers in the presence of an excess (1.1–1.5 equiv.) of ammonium hexafluorophosphate in methanol for 2–3 hours. After evaporation of the solvent, dichloromethane was added to precipitate the salts, which were then removed by filtration. Evaporation of the solvent gave the final ion exchanged polymer quantitatively.

\( ^1H \) NMR (400 MHz, acetone-\( d_6 \)): δ 9.2 (s, 1H, NCHN), 7.8 (d, 2H, CH=CH), 4.5 (m, 4H, NCH\(_2\)CH\(_3\)), 3.2 (s, 3H, OCH\(_3\)), 3.2–3.6 (br, \( n \times 4\)H, CH\(_2\)OCH\(_2\)), 1.3–1.8 (br, \( n \times 4\)H, CH\(_2\)CH\(_2\)), 1.6 (t, 3H, NCH\(_2\)CH\(_3\)). Calcd. \( M_n = 7.82 \text{ kg mol}^{-1} \). GPC (in DMF/LiBr \textit{versus} PEO): NHC\(_\kappa\): \( M_n = 7.18 \text{ kg mol}^{-1}, M_w = 7.97 \text{ kg mol}^{-1}, \text{PDI} = 1.11. \)
Synthesis of silver(I)–NHC polymer complexes Ag(NHC$_{7k}$)$_2$PF$_6$. The complexation of polymer ligand NHC$_{7k}$ with silver(I) was performed by stirring the polymer (ca. 500 mg) with an excess (2–5 equiv.) of silver(I) oxide in dichloromethane (ca. 5 mL) for at least 48 hours at ambient temperature. To this solution, 1 M sodium hydroxide (1 mL) in water was added to facilitate precipitation of silver(I) hydroxide from the reaction mixture during complexation. Work-up of the complex was done by separating the dichloromethane/water layers, followed by filtration of the dichloromethane layer over celite to adsorb small ionic species. The filtrate was dried over MgSO$_4$ and filtered. Subsequently, the dichloromethane was evaporated *in vacuo* giving the silver(I)–NHC polymer complexes Ag(NHC$_{7k}$)$_2$PF$_6$ in 50–90% yield.

$^1$H NMR (400 MHz, acetone-$d_6$): δ 7.4 (d, 2H, CH=CH), 4.2 (m, 4H, NCH$_2$CH$_3$), 3.2 (s, 3H, OCH$_3$), 3.2–3.6 (br, n × 4H, CH$_2$OCH$_2$), 1.4–1.6 (br, n × 4H, CH$_2$CH$_2$), 1.0 (t, 3H, NCH$_2$CH$_3$).

Determination of radical formation rates. For measuring the radical formation rates under ultrasound, a solution of radical scavenger DPPH in toluene (30 µM) was prepared. Of this solution, 10 mL was transferred into a homemade, double-jacketed glass sonication vessel, cooled using water from a thermostat bath and saturated with argon, nitrogen, methane or isobutane, respectively. After saturation, the solution was sonicated for 5–30 min at 20–30% of the maximum amplitude. The initial temperature was varied so that the bulk temperature within the sonication vessel was 25 ± 3 °C after 1 min of sonication. The formation of DPPH$_2$ was monitored by UV/Vis spectroscopy on a Shimadzu 2501-PC spectrometer. Gaussian peak fitting of the region between λ = 440–580 nm, with a baseline correction for DPPH$_2$ yielded the concentrations of DPPH at any time during the sonication process.

Mechanochemical scission experiments. Mechanochemical scission experiments were carried out on solutions of Ag(NHC$_{7k}$)$_2$PF$_6$ in toluene (at a concentration of 3 mg mL$^{-1}$). The toluene was saturated with demineralized water prior to use. The solution was transferred into the sonication vessel, cooled to 10 ± 0.2 °C and saturated with argon, nitrogen, methane or isobutene for at least 30 min. Subsequently, the solution was sonicated for 5 min at 25% of the maximum amplitude (corresponding to a total power input of 12–17 W, varying per experiment). The bulk temperature of the solution inside the vessel increased to 28 ± 4 °C during the sonication. After 5 min, the sample was withdrawn from the sonication vessel and the solvent was evaporated *in vacuo*. The residual solid was dissolved in acetone-$d_6$ (ca. 0.6 mL) and analyzed by $^1$H NMR to determine the amount of scission.

The $^1$H NMR spectra were processed using standard VNMRJ software (Version 2.2 Revision D, by Inova). The integral regions of the individual peaks were calculated by deconvolution of the peaks in the region between 4.2 and 4.5 ppm when necessary. It should be noted that it was not always possible to resolve all individual peaks in multiplets in the deconvolution software. However, it was assured that the result of the deconvolution procedure was the best possible representation of the original spectrum in all cases.
**Bubble dynamics simulations.** The bubble oscillation model based on that presented in the work of Van Iersel *et al.* was used throughout this work to model the bubble dynamics of gas-filled cavitation bubbles in toluene. All bubble dynamics simulations were performed by J. Rooze (Laboratory of Chemical Reactor Engineering, Eindhoven University of Technology) and are not a part of this thesis. For a more detailed description on these simulation experiments, one is referred to Ref. 32.

**Appendix**

The bubble dynamics simulations have provided more insights into the hydrodynamics and thermal effects associated with cavitation bubble collapse in toluene under different saturation gases. In Figure A1 the evolution of bubble radii (Figure A1a–b) and the strain rates at the bubble/liquid interface (Figure A1c–d) are shown for argon and isobutane. The results for nitrogen and methane are not shown here, because they were qualitatively and quantitatively very similar to argon. In Figures A1c–d, an indication mark has been placed at a strain rate ~10^7 s^{-1}. It was found that this is the order of magnitude of strain rates that are required for coil-to-stretch transition of the supramolecular polymers used in this study (*i.e.*, polymers having a typical molecular weight of ~10^1 kg mol^{-1}).

![Figure A1](image)

*Figure A1* Results of bubble dynamics simulations in toluene using argon or isobutane as saturation gas. (a–b) Bubble radius (initial bubble radius was 10 µm in both cases). (c–d) Strain rate at bubble/liquid interface. These graphs were taken from Ref. 32.
Notes and references

The mechanism of ultrasound-induced scission

Chapter 4

Unfolding and mechanochemical scission of supramolecular polymers containing a silver(I)–NHC coordination bond

Abstract

Mechanochemical scission of supramolecular polymer complexes by ultrasound was investigated using viscosity measurements and molecular dynamics (MD) simulations combined with constrained geometry optimization (COGEF) calculations. The supramolecular polymers used in this study consist of a poly(tetrahydrofuran) (PTHF) backbone that contains a silver(I)–NHC (NHC = N-heterocyclic carbene) coordination complex in the chain center. The longest characteristic relaxation times of the supramolecular polymers were obtained from viscosity measurements which confirmed that the criterion for coil-to-stretch is fulfilled in the sonication experiments. A model DFT study was performed to estimate the value of external force that is required to break a silver(I)–NHC coordination bond. A combination of \textit{ab initio} MD simulations and COGEF calculations provided an atomistic insight in the response of the supramolecular center of the polymer chain to external force. The calculations indicated that the force required to break the chain is between 400 and 500 pN. This is significantly lower than the force of several nN that is typically required to break covalent bonds in polymer backbones. The results confirm that the reduction in limiting molecular weight for chain scission is due to the lower bond strength of the metal–ligand coordination bonds as compared to covalent bonds.

Parts of this chapter have been published:
4.1 Introduction

Polymer mechanochemistry has a long history that started in 1934 when the German scientist Hermann Staudinger first reported about mechanical degradation of polymers. He observed that the molecular weight of polymers decreased under mastication.\textsuperscript{1,2} In the decades that followed, mechanical degradation of polymers using various experimental set-ups was studied extensively.\textsuperscript{3,4} Perhaps the most elaborate and detailed set of studies was carried out in the 1980s and 1990s by the groups of Odell and Keller\textsuperscript{5,6} and Nguyen and Kausch.\textsuperscript{7} Both groups studied the kinetics and mechanisms of mechanochemical scission of polymers in solution using different types of hydrodynamic flows created by various, tailor-made hydrodynamic flow devices. More recently, polymer mechanochemistry has gained a lot of interest for its ability to mechanically activate specific reactive groups (commonly referred to as “mechanophores”) within polymer chains. It has turned out that mechanochemical scission of polymer chains always occurs around the center of the polymer chains due to accumulation of force along the polymer backbone,\textsuperscript{3,5–7} provided that the molecular weight of the polymer chain is higher than a certain limiting molecular weight ($M_{\text{lim}}$) for mechanochemical chain scission.\textsuperscript{4,6,8} However, the characteristic midpoint scission can be altered by the incorporation of weak bond at an off-center position within the polymer chain as shown by the work of Encina \textit{et al.}\textsuperscript{9} and Berkowski \textit{et al.}\textsuperscript{10} Thus the preferential site for mechanochemical chain scission can be tailored by design of the structure of the polymer backbone. Site-specific activation of mechanophores opens the way for a whole new class of mechanoresponsive materials that allow for carrying out chemical transformations using mechanical forces instead of more conventional methods, including thermal and (photo)chemical activation. Examples of such mechanoresponsive behavior include color changes of polymer samples upon deformation,\textsuperscript{11} stress-relief through mechanically triggered intramolecular rearrangements,\textsuperscript{12} and even mechanically activated catalysis (“mechano catalysis”).\textsuperscript{13–15} The latter two of these systems are of potential interest for applications in autonomous self-healing materials. The work of various research groups throughout the world has clearly demonstrated that mechanically activated chemical reactions often proceed via different reaction pathways and may result in completely different reaction products compared to their thermally activated analogues.\textsuperscript{16–19}

A convenient method for imposing hydrodynamic force onto polymers in solution is by subjecting the polymer solution to ultrasound.\textsuperscript{7} When using ultrasound for breaking polymer chains, the hydrodynamic forces arise from a strong extensional flow field in solution upon collapse of a cavitation bubble.\textsuperscript{20} The extensional forces
are highest close to the interface of the collapsing cavitation bubble and become lower at a distance further away in solution. As a result of the extensional forces, polymer chains which are present in the generated force field will undergo a coil-to-stretch transition. When the polymer chains are fully uncoiled, further stretching will result in elongation of individual chemical bonds and eventually, when the forces are high enough, mechanochemical bond scission will occur.

Compared to their fully covalent analogues, supramolecular polymers have a much lower limiting molecular weight for mechanochemical chain scission. Earlier work from our group on ultrasound-induced mechanochemical scission of supramolecular polymers has demonstrated that these polymers undergo efficient mechanochemical scission at molecular weights well below $M_{\text{lim}}$ of covalent poly(tetrahydrofuran) (PTHF) when a palladium(II)–phosphine was incorporated near the chain center. Similar observations were made in later work on silver(I)–NHC (NHC = N-heterocyclic carbene) supramolecular polymer complexes. For these complexes, molecular weights below 10 kg mol$^{-1}$ were already sufficient to allow mechanochemical scission to occur. Mechanochemical scission of covalent polymers is sometimes facilitated by the presence of radicals. However, in recent work, we demonstrated that for the supramolecular polymers studied here, the chain scission efficiency was not affected by the presence of radicals. Here, we try to answer two important issues that remained unanswered: (i) is the low observed $M_{\text{lim}}$ compatible with a mechanism that requires uncoiling of the polymers prior to chain scission (in other words, is the relaxation time of these short polymer chains long enough for them to be uncoiled with the strain rates that are present in ultrasonicated solutions), and (ii) is the mechanical force induced by ultrasound sufficient to break the ligand–metal bond without stabilization of the transition state by coordination with a solvent or water molecule, a process we would like to call chemically facilitated scission?

The uncoiling of the supramolecular polymers was studied by viscosity measurements in order to determine the longest characteristic relaxation times of the polymer chains. These results were then compared to the typical conditions obtained in ultrasound experiments and the uncoiling behavior of the corresponding covalent polymers in solution. The bond strengths obtained from molecular dynamics simulations in combination with constrained geometry optimization (COGEF) calculations will indicate whether the silver(I)–NHC bond can be broken purely mechanochemical under the prevailing conditions in ultrasound experiments or if facilitation of mechanochemical bond scission by any chemically facilitated process is required.
4.2 Theoretical background

4.2.1 The coil-to-stretch transition of polymer chains under force

Before individual chemical bonds in a polymer chain can be elongated and broken, the polymer chain should first be (partially) uncoiled. The so-called coil-to-stretch transition (abbreviated with C→S) is a crucial step that precedes mechanochemical scission of polymer chains. In hydrodynamic flows, coil-to-stretch transition from a (random) coil to a fully stretched or partially uncoiled state occurs as a result of extensional force and/or shear forces in the fluid. The process of coil-to-stretch transition is governed by the dimensionless Deborah number, $De^{23-25}$

$$De = \dot{\varepsilon} \times \lambda_0$$  \hspace{1cm} (1)

The Deborah number $De$ (sometimes also referred to as Weisenberg number, $Wi$) gives the ratio between the two characteristic timescales involved in the uncoiling of a polymer chain, being the extensional rate in the solution $\dot{\varepsilon}$ (which is equal to the velocity gradient in the solution) and the longest characteristic relaxation mode or relaxation time $\lambda_0$ of the polymer chain. The longest characteristic relaxation mode of the polymer chain represents the relaxation of the full end-to-end vector of the polymer chain (i.e., relaxation of the polymer chain as a whole). If the polymer chain is considered as an elastic spring on which an extensional force is acting through viscous coupling with a solvent, the coil-to-stretch transition occurs when the value of $De$ fulfills the following criterion:

$$De_{crit} = \frac{1}{2}$$ \hspace{1cm} (2)

From this criterion it follows that, since $\lambda_0$ has a fixed value for a given polymer chain in a particular solvent, coil-to-stretch transition occurs when the critical extensional rate is exceeded:

$$\dot{\varepsilon}_{crit} = \frac{1}{2\lambda_0}$$ \hspace{1cm} (3)

At extensional rates below the critical value, the relaxation of the polymer chain is faster than the speed of extension. This means that at lower rates of extension, the polymer chain cannot be fully extended before it relaxes back to its (random) coil conformation. A hysteresis is present between coil-to-stretch (C→S) and stretch-to-
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coil (S→C) transition of a polymer chain in solution under the influence of extensional forces. This is caused by a difference in the longest relaxation time for a polymer chain in its unperturbed coiled state (which is the characteristic relaxation time for C→S transition) and that of a fully extended polymer chain (characteristic for S→C transition). When in its coiled or only weakly perturbed state, hydrodynamic interactions between chain segments play an important role (this state is called the Zimm limit), whereas they can be neglected in the fully extended state (freely draining or Rouse limit). Since $\lambda_{\text{Rouse}} > \lambda_{\text{Zimm}}$, the critical extensional rate is higher for C→S than for S→C transition cf. Equation (3) and hysteresis exists between both processes. A (geometric) prefactor should be included for the calculation of Zimm and Rouse relaxation times from $\lambda_0$, but, since the geometric prefactors are approximately equal to unity, we will not consider them further in this text. Most of the experimental measurements are carried out on polymer solutions in the absence of, or at low shear or extensional forces, so that chain perturbation can be neglected. Therefore, most of these measurements result in determination of the Zimm relaxation times; what follows from the hysteresis is that the polymer chain stretching is governed by the Rouse relaxation times. However, since the Rouse relaxation time is always larger than the Zimm relaxation time we can be sure that once it is confirmed that the coil-to-stretch criterion is fulfilled by $\lambda_{\text{Zimm}}$, it will, for sure, be fulfilled by $\lambda_{\text{Rouse}}$.

4.2.2 The relaxation times of polymer chains in dilute solutions

The longest characteristic relaxation time $\lambda_0$ of a polymer chain in (dilute) solution can be determined by using viscometry since it is directly proportional to the limiting viscosity number $[\eta]_0$, which is a measure for the hydrodynamic volume of a polymer chain in solution.25

$$\lambda_0 = [\eta]_0 \frac{\eta_s M}{RT}$$  \hspace{1cm} (4)

In this equation, $\eta_s$ is the viscosity of the solvent, $M$ is the molecular weight of the polymer, $R$ is the gas constant (8.3145 J mol$^{-1}$ K$^{-1}$) and $T$ the absolute temperature. Often, the Mark–Houwink relation is used to relate the limiting viscosity number to the molecular weight $M$ of a polymer chain:

$$[\eta]_0 = K \times M^a$$  \hspace{1cm} (5)

The constants $K$ and $a$ are uniquely defined for each set of polymer and solvent.
For numerous polymer/solvent pairs, values of $K$ and $a$ are tabulated in literature and polymer handbooks. In addition, the value of the Mark–Houwink exponent $a$ provides information about the solvent quality of a particular solvent for the polymer: for flexible polymers, $a$ ranges from $1/2$ in a $\theta$ solvent (a solvent in which the polymer has no excluded volume effects and where it adopts a perfect random coil conformation, obeying Gaussian chain statistics) to $4/5$ in a good solvent (where excluded volume effects play a role).$^{25}$

Alternatively, the limiting viscosity number can be determined experimentally by determining the specific viscosity $\eta_{sp}$ of dilute polymer solutions having a known polymer concentration $c$. The limiting viscosity number is found by extrapolation of these data to the fictive situation of zero polymer concentration.$^{25}$

$$[\eta]_0 = \lim_{c \to 0} \frac{\eta_{sp}}{c} \quad (6)$$

### 4.2.3 Mechanochemical bond scission; thermally activated barrier to scission (TABS) theory

For covalent bonds, mechanochemical bond scission is often treated according to the thermally activated barrier to scission (TABS) theory.$^{2,6,26}$ TABS theory treats mechanochemical bond scission as being a thermally activated process. It states that the potential energy landscape of a chemical bond, as given by the Morse potential $U(r)$, is lowered under the influence of an external force $F_{ext}$. This reduction is a result of the mechanical work that is put into the system by elongation of the chemical bond and it results in a reduction of the bond dissociation energy $D$ (see Figure 1).

![Figure 1](image.png)

**Figure 1** Morse energy potentials representing a chemical bond in unperturbed state (dash-dotted line) and of a bond under stress (solid line) showing the mechanochemical activation of bond according to the TABS theory. The energy input due to mechanical work is shown as a dashed line.
The force that is accumulated along a (fully extended) polymer chain consisting of \( N \) statistical chain segments (each having a length \( b \)) can be calculated using the bead–rod model:\(^5,^7,^{20}\)

\[
F_{\text{max}} = \frac{3\pi}{4} \eta_s a b \varepsilon S N^2
\]  

(7)

Here \( \eta_s \) is the viscosity of the solvent, \( a \) the radius of a bead, \( \varepsilon = \frac{dV}{dx} \) is the strain rate (equal to the velocity gradient) in solution as a result of distortions in the flow pattern and \( S \) is the so-called “shielding factor” that accounts for hydrodynamic interactions between beads. When a polymer chain is fully extended, these interactions can be neglected and \( S = 1 \). Since the number of statistical chain segments scales proportional to the molecular weight of the polymer chain, it can be deduced that the maximum accumulated force in the center of the polymer chain scales as \( F_{\text{max}} \propto M^2 \).

In thermal activation, the energy barrier for scission is overcome by heating the system in order to increase its internal energy. For mechanochemical activation, TABS theory dictates that mechanochemical scission will occur when the external force is high enough to reduce the dissociation energy to a value \( D' \) which is in the order of the thermal energy of the atoms, i.e. several times \( k_B T \) (with the Boltzmann constant \( k_B = 1.38 \times 10^{-23} \text{ J K}^{-1} \)). In that case, thermal fluctuations which are typically in the order of several \( k_B T \) (\( k_B T \approx 2.4 \text{ kJ mol}^{-1} \) at 25 °C) around the equilibrium position are sufficient to overcome the energy barrier \( D' \).

### 4.3 Kinetics of ultrasound-induced silver(I)–NHC polymer chain scission

To study the physical aspects of mechanochemical chain scission of supramolecular polymers in solution, supramolecular polymer complexes \( \text{Ag(NHC}_x\text{)}_2\text{PF}_6 \) (where \( x = 7k, 10k \) and \( 15k \), being the approximate \( M_n \) of a single polymer ligand) were synthesized using the same procedure as described in Chapter 3. In Figure 2, the structure and the characterization details of all complexes used in this study are shown. Ultrasound-induced chain scission kinetics of \( \text{Ag(NHC}_x\text{)}_2\text{PF}_6 \) polymers could not be monitored by GPC. When analyzed with a chloroform mobile phase, broad and ill-defined peaks were observed for the imidazolium ligands, possibly owing to ionic aggregation and interactions of the polar end groups with the column. When DMF, a more polar mobile phase was used to suppress aggregation, hydrolysis of the silver(I)–NHC complexes took place and all polymeric material eluted from the column as non-complexed imidazolium salts.
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4.4 Relaxation times of silver(I)–NHC polymer complexes in dilute solutions

Ubbelohde capillary viscometry was used to determine the relative viscosities of solutions of the supramolecular polymer complexes Ag(NHC$_x$)$_2$PF$_6$ in toluene at 28.00 ± 0.02 °C. By plotting the specific viscosity of the solutions of these polymer complexes in toluene versus polymer complex concentration (as shown in Figure 3a) it was confirmed that all solutions could be considered as dilute since the slopes of the obtained lines are almost equal to unity. Equation (3.6) was used to determine the limiting viscosity number [$\eta$]$_0$ from these data. The values of $\eta_s$/c were plotted versus polymer concentration c on a double logarithmic scale (the graphs for all complexes Ag(NHC$_x$)$_2$PF$_6$ are shown in Figure 3b). As expected, all data points fall approximately onto a straight line that was extrapolated to c→0 by linear regression to determine [$\eta$]$_0$.

Mark–Houwink parameters for the silver(I)–NHC polymer complexes were determined from the slope and abscissa of a double logarithmic plot of the obtained

Figure 2 Structure of the polymer silver(I)–NHC complexes and characterization details ($M_n$ and PDI) of the polymer imidazolium ligands used in this study.

Figure 3 (a) Specific viscosity $\eta_s$ and (b) intrinsic viscosity of the solutions of polymer complexes Ag(NHC$_x$)$_2$PF$_6$ as a function of polymer concentration c in toluene at 28.00 ± 0.02 °C. The solid line represents the best linear fit of the data.
values for \([\eta]_0\) versus the number-averaged molecular weight \(M_n\) as determined from GPC measurements (see Figure 4a). Linear regression shows that \(a = 0.65\) and \(\log(K) = -2.18\) \(\text{(i.e.,} K = 6.6 \times 10^{-3} \text{ L g}^{-1}\)). Even though these values should be treated as rough estimates which are based on only a small data set, they are consistent with literature, where values of \(a\) ranging between 0.59 and 0.78 are reported for covalent PTHF in toluene.\(^{27,28}\) The precise value of \(a\) depends on the range of molecular weights and the polydispersity of the polymer samples that were used to determine the Mark–Houwink parameters and the temperature at which the experiments were carried out.\(^{27–29}\) In conclusion, it is clear that toluene is a good solvent for PTHF and the analogous polymer silver(I)–NHC complexes, indicated by the fact that \(a > \frac{1}{2}\) in this study and in all cases reported in literature. The longest characteristic relaxation time \(\lambda_0\) of the polymer complex chains is calculated from these data using Equation (4). The results of all the calculations are summarized in Table 1. It is observed that the longest characteristic relaxation times \(\lambda_0\) for the polymer complexes used in this study and in previous work are in the order of several tenths of microseconds \((\sim 10^{-7} \text{ s})\) and that they scale with molecular weight as \(\lambda_0 \propto M^{1.64}\) (Figure 4b).

Table 1 Limiting viscosity numbers, longest characteristic relaxation times and critical strain rates for coil-to-stretch transition for the Ag(NHC\(_x\)\(_2\)PF\(_6\) complexes in this study.

<table>
<thead>
<tr>
<th>Complex</th>
<th>(M_n) (kg mol(^{-1}))(^{a)})</th>
<th>([\eta]_0) (L g(^{-1}))(^{b)})</th>
<th>(\lambda_0) (s)</th>
<th>(\dot{\varepsilon}_{\text{crit}}) (s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag(NHC(_{10k})(_2)PF(_6))</td>
<td>19.9</td>
<td>0.0453</td>
<td>2.0 \times 10^{-7}</td>
<td>2.6 \times 10^{6}</td>
</tr>
<tr>
<td>Ag(NHC(_{15k})(_2)PF(_6))</td>
<td>28.8</td>
<td>0.0583</td>
<td>3.6 \times 10^{-7}</td>
<td>1.4 \times 10^{6}</td>
</tr>
</tbody>
</table>

\(^{a)}\) Calculated as twice the Mn of each polymer ligand according to GPC (see Figure 2). \(^{b)}\) Experimental value, as obtained from Ubbelohde viscometry.
4.5 Estimation of the critical strain rate for coil-to-stretch transition

For the silver(I)–NHC polymer complexes studied in this work, the longest characteristic relaxation times of the polymer chains as a function of total molecular weight were determined. It was shown that for the typical molecular weights that have been used in this and previous work ($M_n = 10$ to $40$ kg mol$^{-1}$), these relaxation times are in the order of $0.1$ to $0.5$ µs ($1 \times 10^{-7}$ to $5 \times 10^{-7}$ s). With these results, the critical strain rates in solution can be calculated. By applying the criterion of the critical Deborah number, as formulated in Equation (3–4), it is found that $\dot{\varepsilon}_{\text{crit}} \sim 10^6$ to $10^7$ s$^{-1}$. The values of $\dot{\varepsilon}_{\text{crit}}$ have been included with Table 1.

Numerical simulations of the cavitation process in toluene were performed, taking into account the typical conditions of scission experiments. It was shown that strain rates as high as $\sim 10^8$ s$^{-1}$ are reached during the first collapse event of a cavitation bubble; in addition, strain rates remain higher than $\sim 10^6$ s$^{-1}$ for the subsequent four to five collapses (“afterbounces”). Based on the simulations and the findings in this work, it can be concluded that the strain rates typically obtained in ultrasound experiments are sufficient for coil-to-stretch transition of the silver(I)–NHC polymer complexes in solution to occur.

Now since the first step in mechanochemical scission of polymer chains, being the coil-to-stretch transition, is apparently not significantly altered when going from a covalent to an analogous supramolecular polymer, it seems obvious that the introduction of a metal–ligand coordination bond in the center of the polymer chain is solely responsible for lowering the limiting molecular weight for mechanochemical scission. In terms of the TABS theory: the weaker metal–ligand coordination bond in the supramolecular polymer has a lower energy potential at rest (hence a lower dissociation energy $D$); therefore, when compared to covalent bonds in a polymer backbone (typically C–C and or C–O bonds which have bond energies around 350 kJ mol$^{-1}$), less mechanical work is required for the bond to lower its dissociation energy to $D' \sim k_B T$. This means that cf. Equation (7) a polymer chain consisting of less statistical segments $N$ (i.e., a shorter polymer chain) is already sufficient to transduce the required force on the central bond.

4.6 The potential energy diagram for Ag–C bonds under external force

In the previous sections we have demonstrated that the strain rates required to achieve coil-to-stretch transition of the polymer catalyst complexes considered is in the order of $10^6$–$10^7$ s$^{-1}$. After extension of the polymer chain, mechanical forces accumulate
along the (contour) length of the polymer chain. These forces are transmitted from the solvent to the polymer chain through viscous coupling as described by the bead–rod model (see Equation (7)). The crucial question to be answered at this stage is whether or not the accumulated forces are enough to cleave the Ag–C bond.

Two series of simulations have been carried in order to answer this question. The first series are the \textit{ab initio} molecular dynamics (MD) simulations, which allowed us to gain insight into the scission phenomenon. Based on their relative bond strengths, the coordination bond is expected to break easier than the covalent bonds; hence it was assumed that the Ag–C bond is the place where scission occurs. MD simulations combined with the steering force could confirm that assumption. However, because the timescale of the MD simulations and the experiments differ by several orders of magnitude (picoseconds \textit{versus} microseconds), the assessment of the rupture force is not accurate in this case.

Therefore, a second series of simulations was carried out, using constrained geometry optimizations (COGEF), where the constraint was identical to that of the MD simulations. The COGEF optimization provided us with the potential energy surfaces similar to those obtained by the groups of Moore,\textsuperscript{16} Martinez\textsuperscript{17} and Marx\textsuperscript{30,31} when studying \textit{e.g.} the mechanochemical ring-opening of benzocyclobutanes. The optimized model is shown in the top left of Figure 5. The central Ag atom is coordinated by two carbon atoms (marked as C1 and C2) that belong to two imidazolium rings. The ethyl groups attached to the rings are the simplified model of the long chain polymer chains that transfer the external force to the central coordination bond. It has been recently reported by Marx \textit{et al.}\textsuperscript{31} that the length of the side-chains is important for the correct assessment of the mechanochemical properties of covalent polymers. They demonstrated that in the case of a benzocyclobutane core functionalized with polyethylene (PE) chains, the angle between the side-chains and the benzocyclobutane moiety (the angle being determined by the length of the PE chain) is the main factor affecting the accuracy of the predicted values of the rupture force. However, because of the much higher flexibility and coordinative nature of bonding within our model as compared to the covalent polymer considered by Marx \textit{et al.}, this factor is expected to be only minor in the case considered here. Therefore, the use of the simplified 1-ethyl-3-methylimidazolium ligands is justified for the purpose of the present study.

In the \textit{ab initio} MD simulations, an initial reorganization of the geometry with respect to the external force is observed, after which the system stabilizes with deformed geometry. In the equilibrium state (without external force acting) the bond length
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equals 2.06 Å. Under an external force, the average bond length between the Ag and C2 atoms increases from 2.10 Å at $F_{\text{ext}} = 0.4$ nN, to 2.13 Å (0.8 nN), 2.16 Å (1.2 nN), and reaches 2.22 Å at $F_{\text{ext}} = 1.6$ nN (Figure 5). When an external force of 2.0 nN is applied, the cleavage of the Ag–C bond is observed within the 10 ps timescale of the MD run.

COGEF analysis provides more insight into the impact of the external force on the mechanochemical scission of the polymer silver(I)–NHC complexes. Seven series of constrained geometry optimization simulations were performed with a gradually increasing external force varying between 82 and 823 pN. Moreover, as a reference, we have carried out one simulation without external force. The energy change upon the increase of Ag–C bond length was monitored for each of the values of external force. The Ag–C distance was initially set to 2.0 Å and was increased to the value of 4.0 Å with steps of 0.1 Å. At each step total energy have been calculated, and the work done by the external force have been evaluated from the equation $W = F_{\text{ext}}(r' - r_0)$, where $W$ is the work done by the force, $F_{\text{ext}}$ is the external force acting on the atoms and $r' - r_0$ is the displacement of these atoms from their optimal
position along the direction of the external force. This procedure resulted in the reaction energy diagrams for the mechanochemical activation of a silver(I)–NHC complex under the influence of the increasing external force which are shown in Figure 6. When no external force is applied, the energy barrier for the Ag–C bond cleavage is just above 2 eV (~200 kJ mol⁻¹) which is in close agreement with bond energies found in literature and indeed much lower than bond dissociation energies for C–C and C–O bonds (both around 350 kJ mol⁻¹). The activation barrier decreases gradually with increasing force until it finally disappears at the external force of 823 pN. It is also noticed that the maximum energy shifts towards shorter bond lengths upon increasing force.

We may now speculate on the magnitude of the force necessary to break the Ag–C bond in the investigated system. From the MD calculations it turns out, that force of 2.0 nN is sufficient to break the Ag–C bond at the very early stage, even before the system stabilizes. Already the first pull caused by the external force is sufficient to overcome the energy barrier. In the simulation with the force of 1.6 nN applied, we can observe that the system remains intact during the run, hence we can conclude that the force necessary to readily break the Ag–C bond would be between 1.6 and 2.0 nN. This calculated value is close to the experimentally observed force for bond cleavage in similar systems applying a force of less than 1 nN. The COGEF simulations show a better agreement with the experiment. A low energy barrier (around 0.2 eV or 20 kJ mol⁻¹) is observed in the presence of an external force of 412 pN and the barrier has completely disappeared for a force of 823 pN. The rate of (mechanochemical) bond dissociation is quantified by the “off rate” νₐ₉ (in s⁻¹). For bond dissociation to take place during ultrasound, the value of ν₀ff should be similar to the reciprocal value of the characteristic experimental timescale, which is in the order of 10⁻⁶ s for ultrasound (so, ν₀ff ~ 10⁶ s⁻¹). Identical to thermal dissociation, bond dissociation
under force is governed by the Arrhenius equation:

$$v_{off}(F_{ext}) = v_0 \exp\left(-\frac{D(F_{ext})}{k_B T}\right) \approx v_0 \exp\left(-\frac{D'}{k_B T}\right)$$

(8)

The exact value of the Arrhenius prefactor $v_0$ is not known, but it can be estimated to be around $10^{13} - 10^{14}$ s$^{-1}$ which is the frequency of chemical bond vibrations. From this, we can estimate that the barrier for bond dissociation should be lowered to $D' \approx 16 - 18 \times k_B T$ under force in order to have significant mechanochemical bond scission in ultrasound experiments. The small energy barrier which is below $10 \times k_B T$ at a force of 412 pN can be overcome readily by thermal fluctuations on typical timescales for ultrasound experiments. Therefore, based on the potential energy diagram in Figure 6, the value for the force required to break silver(I)–NHC coordination bonds can be estimated to be between 400 and 500 pN.

This discrepancy between the MD and COGEF simulations can be explained by the timescale of the simulation with respect to the experiment. As we mentioned before, we have simulated only 10 ps of the life of the system, whereas 1 µs is the timescale of the ultrasound experiment. Equation (8) shows that for an experimental timescale of 10 ps ($v_{off} \sim 10^{11}$ s$^{-1}$), the energy barrier should decrease to almost zero. Additionally, literature provides some more details on the value of the force versus timescale for different types of bonds. Although there is no Ag–C type of bond mentioned, we may assume that the trend will be continued, and we could expect the force to be lowered by approximately 15–25%. This value is even closer to the experiment, despite the simplifications used in our model such as the shorted aliphatic chains at the N1 position of the NHC ligands and absence of the solvent.

The maximum force $F_{ext}$ on polymer chains as a function of increasing molecular weight is shown in Figure 7 for typical strain rates $\dot{\varepsilon} = 10^7$ s$^{-1}$ and $10^8$ s$^{-1}$. These values are rough estimates calculated based on the bead–rod model as given by Equation (7). From these calculations, we would expect $M_{lim}$ for the polymer silver(I)–NHC complexes to be around 30 kg mol$^{-1}$ for $\dot{\varepsilon} = 10^7$ s$^{-1}$ and between 10–15 kg mol$^{-1}$ for $\dot{\varepsilon} = 10^8$ s$^{-1}$, respectively. Taking in account the fact they are only rough estimates, these values are in good agreement with previous experimental observations. Furthermore, these values indicate that purely mechanochemical bond scission is possible under ultrasound conditions without the aid of any chemical process that would facilitate bond scission (chemically facilitated scission). So, even though the contribution of chemically facilitated mechanochemical bond scission is not excluded based on the present results, it can be concluded that its presence is not
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4.7 Conclusions

In the present study, we studied the unfolding and mechanochemical scission of silver(I)–NHC supramolecular polymer complexes. It was confirmed that both (unperturbed) polymer chain dimension as well as the critical strain rate for coil-to-stretch transition is similar for both the supramolecular polymer and its fully covalent analogue, irrespective of the presence of the coordination complex within the polymer chain. Based on the results from earlier numerical simulations of the cavitation process in ultrasound\(^2\(^1\) it was concluded that coil-to-stretch transition is in fact expected to occur readily for these supramolecular polymers, even though their molecular weight is relatively low (well below \(M_{\text{lim}}\) for fully covalent PTHF, see Chapter 2).

In addition, molecular dynamic (MD) simulations, combined with COGEF analysis, resulted in a potential energy diagram for Ag–C bonds under external force. From this potential energy diagram it became clear that application of an external force of 400–500 pN would be sufficient to achieve scission of the Ag–C bonds at room temperature. During none of the performed MD simulations, scission of a covalent bond within the systems was observed. The obtained force for mechanochemical chain scission is about one order of magnitude lower than the forces typically required to break covalent bonds in polymer chains (in literature, for C–C bonds values ranging between 2 and 13 nN are found).\(^2\(^5\)

Taking all these results into account, it is confirmed that the reduction of \(M_{\text{lim}}\) in

\[\text{Figure 7} \quad \text{Maximum force (in pN) on fully extended polymer chains as a function of molecular weight (kg mol}^{-1}\) at typical strain rates of \(10^7 \text{ s}^{-1}(\bullet)\) and \(10^8 \text{ s}^{-1}(\circ).\)\]
supramolecular polymers is due to the incorporation of the metal–ligand coordination bond within the polymer backbone. Such a metal–ligand coordination bond is significantly weaker ($D \approx 200 \text{ kJ mol}^{-1}$ for Ag–C bonds) than typical covalent bonds, such as C–C and C–O bonds that make up the polymer backbone ($D \approx 350 \text{ kJ mol}^{-1}$).

As a result of the weaker bond, a lower force is required to reduce the energy barrier for bond scission to a value that is readily overcome by thermal fluctuations at ambient temperature (as dictated by TABS theory). Radical-induced chain scission can be excluded as a predominant mechanism based on findings in previous work$^{21}$ and the possible role of chemically facilitated mechanochemical chain scission was evaluated here. A possible facilitating mechanism consists of reduction of the dissociation energy barrier by activation of the Ag–C bond in the transition state of the cleavage process. Even though the occurrence of chemically facilitating mechanisms cannot be excluded, it is confirmed that such a mechanism is definitely not required for chain scission of these supramolecular polymers using ultrasound.

Since the Ag–C bond in the silver(I)–NHC coordination complex is several times weaker than a covalent bond, the prevalent conditions in ultrasound experiments allow for purely mechanochemical bond scission.

**Experimental section**

**General.** All reagents and solvents were used as received unless stated otherwise. Solvents were obtained from BioSolve (The Netherlands) and of at least AR grade quality. Deuterated solvents for recording NMR spectra were obtained from Cambridge Isotope Laboratories, Inc. (United States).

All polymerizations were carried out under inert argon atmosphere using Schlenk line techniques. After synthesis and work-up, the polymers and their corresponding silver(I) complexes were characterized by $^1H$ NMR to confirm end-group functionalization and determine their number-average molecular weight, $M_n$. In addition, gel permeation chromatography (GPC) was carried out on a PL-GPC 50 Plus system (Polymer Laboratories) using a refractometer for detection. DMF/LiBr (10 mM) was used as eluens. The number- and weight-average molecular weights, $M_n$ and $M_w$, were calculated versus poly(ethylene oxide) (PEO) calibration standards. $^1H$ NMR spectra were recorded on a Varian 400MR or Varian Mercury 400 spectrometer and chemical shifts are reported in ppm relative to TMS.

**Synthesis of $\alpha$-(N-ethylimidazolium)-$\omega$-methoxy poly(tetrahydrofuran).** The synthetic procedure for polymer ligand NHC$_{7k}$ was described in Chapter 3. The other polymer ligands NHC$_{10k}$ and NHC$_{15k}$ were synthesized using the same procedure. The target molecular weight could be controlled by varying the reaction times; i.e., for NHC$_{10k}$ and NHC$_{15k}$, the polymerization times were 4 and 6 h, respectively.
Unfolding and mechanochemical scission of supramolecular polymers

$^1$H NMR (400 MHz, acetone-$d_6$): $\delta$ 9.3 (s, 1H, NCHN), 7.8 (d, 2H, CH=CH), 4.4 (m, 4H, NCH$_2$CH$_3$), 3.2 (s, 3H, OCH$_3$), 3.2–3.6 (br, $n \times 4$H, CH$_2$OCH$_2$), 1.3–1.8 (br, $n \times 4$H, CH$_2$CH$_2$), 1.6 (t, 3H, NCH$_2$CH$_3$). Calcd. NHC$_7$k: $M_n$ = 7.82 kg mol$^{-1}$; NHC$_{10}$k: $M_n$ = 11.7 kg mol$^{-1}$; NHC$_{15}$k: $M_n$ = 15.0 kg mol$^{-1}$. GPC (in DMF/LiBr versus PEO): NHC$_7$k: $M_n$ = 7.18 kg mol$^{-1}$, $M_w$ = 7.97 kg mol$^{-1}$, PDI = 1.11; NHC$_{10}$k: $M_n$ = 9.97 kg mol$^{-1}$, $M_w$ = 10.7 kg mol$^{-1}$. PDI = 1.10; NHC$_{15}$k: $M_n$ = 14.4 kg mol$^{-1}$, $M_w$ = 16.7 kg mol$^{-1}$, PDI = 1.16.

**Synthesis of silver(I)–NHC polymer complexes Ag(NHC$_x$)$_2$PF$_6$.** The experimental procedure for complexation of polymers NHC$_x$ with silver(I) was described in Chapter 3.

$^1$H NMR (400 MHz, acetone-$d_6$): $\delta$ 7.4 (d, 2H, CH=CH), 4.2 (m, 4H, NCH$_2$CH$_3$), 3.2 (s, 3H, OCH$_3$), 3.2–3.6 (br, $n \times 4$H, CH$_2$OCH$_2$), 1.4–1.6 (br, $n \times 4$H, CH$_2$CH$_2$), 1.0 (t, 3H, NCH$_2$CH$_3$).

**Viscosity measurements.** Ubbelohde viscosity measurements were carried out using a capillary viscometer (manufactured by Schott Instruments, Germany; internal diameter 0.40 mm). For temperature control, the glass capillary was immersed in a thermostat bath (Schott Instruments CT52, by Schott Instruments, Germany) equilibrated at 28.00 ± 0.02 °C. For the viscosity measurements, solutions were prepared containing between 2.5 and 12.5 mg mL$^{-1}$ of polymer complexes Ag(NHC$_x$)$_2$PF$_6$ in toluene. The specific viscosities of these polymer solutions were calculated by comparing their elution times $t$ with that of the pure solvent as reference $t_s$ according to

$$\eta_s = \frac{\eta - \eta_s}{\eta_s} \approx \frac{t - t_s}{t_s}$$

Strictly speaking, this relation is only valid when the density of the polymer solution is approximately the same as the density of the pure solvent, i.e., under dilute solution conditions. For all experiments in this work it was confirmed that this criterion was fulfilled.

**Molecular dynamics simulations.** *Ab initio* molecular dynamics (MD) simulations were performed on the silver(I)–NHC system. All simulations were performed by Dr. B.M. Szyja and Dr. E.A. Pidko (Schuit Institute of Catalysis, Eindhoven University of Technology). The experimental details of these simulations have been described in full detail in Ref. 35.

**Notes and references**

Chapter 4


8. Typically, for covalent polymers the value for $M_{lim}$ is between 40–100 kg mol$^{-1}$, see e.g. Refs. 4(a), 4(d), 5(b), 19, 20 and G.J. Price, P.F. Smith, *Polym. Eng. Sci.* **1993**, 34, 4111–4117


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34. For calculation of $F_{\text{max}}$, the following values have been used for the typical parameters in Equation (7): $\eta_s = 5.6 \times 10^{-4}$ Pa s (viscosity of toluene at 25 °C; F.J.V. Santos et al., *J. Phys. Chem. Rev. Data* **2006**, 35, 1–8); $a = 2.5 \times 10^{-10}$ m (cross-sectional diameter of a methylene group); $b = 1.0 \times 10^{-9}$ m (approximate persistence length of PTHF, calculated based on data in: J. Brandrup et al., In *Polymer Handbook*, 4th ed.; John Wiley & Sons, Inc.: Hoboken (NJ), 1999) and $S = 1$.
Chapter 5
The effect of catalyst concentration on catalytic activity in mechanochemically activated transesterification using NHC latent catalysts

Abstract

We have investigated the effect of the concentration and molecular weight on the activity of polymeric silver(I)–NHC (NHC = N-heterocyclic carbene) catalyst complexes in ultrasound-induced mechanochemical catalyst activation. A strong dependence of the turnover number (TON) on initial catalyst concentration was observed in the transesterification of vinyl acetate with benzyl alcohol. The main findings of this study are that the concentration and molecular weight effects on TON are caused by competition between mechanochemical catalyst activation and deactivation, most likely by reactive species produced during the sonication process. Carrying out the transesterification reaction under radical-suppressing conditions resulted in a significant increase of TON. This result clearly demonstrates the increased catalyst lifetime when reducing the amount of sonochemical impurities and it highlights the importance of controlling and suppressing secondary, sonochemical processes when using ultrasound-induced mechanochemical generation of reactive species such as catalysts.

Parts of this chapter have been published:
5.1 Introduction

Since the first observation of polymer degradation under mechanical deformation by Staudinger in the 1930s, polymer mechanochemistry has developed into an actively researched field of polymer chemistry. The use of mechanical forces to activate and break chemical bonds, as an alternative to conventional activation methods like thermal or (photo)chemical activation, is gaining a lot of interest recently. It has often been observed that mechanochemical reactions have completely distinct pathways from their thermal analogues. The products of mechanochemically activated chemical transformations can be completely different; sometimes, chemical transformations that are impossible to carry out thermally become accessible using a mechanochemical strategy. The main reason for this is that mechanical energy, in contrast to thermal and (photo)chemical energy is anisotropic (i.e., “force has a direction”); hence it can completely change the potential energy landscape of the bonds under stress. In order to transfer macroscopic mechanical forces to the level of individual chemical bonds, the use of polymer chains as “handles” for force transduction has been frequently employed. The build-up of force along a fully or partially extended polymer chain follows a parabolic distribution, reaching a maximum value at the center of the chain. For efficient mechanochemical activation, the reactive unit (mechanophore) should, therefore, be placed near the center of a polymer chain.

Very often, ultrasound has been used to carry out mechanochemical transformations on polymer chains in solution. During irradiation of solutions with ultrasound, cavitation bubbles are generated as a result of the acoustic pressure wave in solution. Cavitation nuclei are formed by gas molecules that are dissolved in the solvent and, subsequently, migration of volatile compounds from the solution causes them to expand. When the bubbles become too large, they become unstable and rapidly collapse. The collapse of cavitation bubbles creates local regions of high fluid strain in solution. Polymer chains present in these regions will uncoil and break, provided that the accumulated strain is high enough.

In our research group, we have modified organometallic catalyst complexes with polymer chains, which allows them to be mechanochemically activated, as demonstrated in earlier work. These complexes are based on the coordination of silver(I) or ruthenium(II) species to N-heterocyclic carbene (NHC) ligands. When complexed with two NHC ligands, the catalysts are inactive, but, upon dissociation they become active catalysts in a series of chemical transformations, such as transesterification reactions, ring-opening polymerizations of lactides or olefin
The effect of catalyst concentration on catalytic activity

metathesis reactions. In this work, we focus on the use of polymer silver(I)–NHC catalyst complexes for the use in transesterification reactions. The mechanocatalytic activation of the polymeric silver(I)–NHC latent catalyst complexes Ag(NHCₓ)₂PF₆ (with x being the approximate Mₙ of a single polymer ligand) was studied in the transesterification reaction of vinyl acetate (VAc) with benzyl alcohol (BnOH) (Figure 1). This reaction is a useful benchmark for the activity of latent catalysts, because the equilibrium of this transesterification reaction is shifted towards the formation of benzyl acetate (BnAc) as a result of rapid tautomerization of one of the reaction products, vinyl alcohol, to acetaldehyde (thus preventing the reverse reaction).

In the mechanocatalysis experiments, an increase in catalyst activity with catalyst concentration was observed. As an example, under one set of specific conditions the turnover number (TON, defined as the moles of product formed per mole of latent catalyst present in total) after 30 min of sonication increased from 130 at a latent catalyst concentration of 0.6 mM to 810 when the latent catalyst concentration was increased to 3 mM. Since a large excess of substrate was used, the reaction rate was expected to be proportional to the active catalyst concentration which would result in a TON that is independent of the initial concentration of latent catalyst. The data therefore suggested an effect of concentration on the activation rate of the latent catalyst. In this work, we have further investigated ultrasonic and thermal activation of complexes Ag(NHCₓ)₂PF₆ with different molecular weights in order to establish the effects of concentration on activation and deactivation rate and catalyst activity.

5.2 Synthesis of polymers and mechanocatalyst complexes

Polymer silver(I)–NHC catalyst complexes Ag(NHCₓ)₂PF₆ (with x = 7k, 10k, 15k and 20k) were used for the thermally and mechanically activated catalytic tests
and all supporting experiments in this work. They were synthesized from their corresponding \( N \)-ethylimidazolium-functionalized poly(tetrahydrofuran) (PTHF) polymers \( \text{NHC}_x \) using the procedure described in Chapters 3 and 4. Fully covalent, non-functionalized PTHF, \( \text{P}^{20k} \) was synthesized using a similar procedure (described in more detail in Chapter 2). Table 1 summarizes the properties of all polymer ligands \( \text{NHC}_x \) and the covalent \( \text{P}^{20k} \) which were used in this study.

### 5.3 Catalytic activity in mechanochemically and thermally activated catalysis

Catalysis experiments were performed in a mixture of toluene and reactants VAc and BnOH (in a volumetric ratio of 5:3:2). For each experiment, conversion of BnOH in time was determined by \( ^1\text{H} \) NMR or gas chromatography (GC-FID). Without sonication, the catalyst complexes showed low background activity in control reactions at the same internal temperature at which the sonication experiments were performed (10 \( \pm \) 2 °C). However, the TONs in these control reactions were low up to a reaction time of 30 min. Therefore, TON after 30 min of reaction is reported as a measure to assess catalyst efficiency in all mechanically activated catalysis experiments since the contribution of thermal background conversion can be neglected up to this point.

Results of sonication and thermal control experiments using catalyst complex \( \text{Ag(\text{NHC}_{10k})_2PF}_6 \) at latent catalyst concentrations between 0.60 and 3.0 mM are shown in Figure 2a as the observed TON after 30 min versus total latent catalyst concentration. In the sonication experiments, the concentration dependence of catalyst activity is strong (a hundredfold increase is observed over the entire range), whereas in the thermal control reaction, TON is independent of catalyst concentration within experimental error.\(^{22}\)

### Table 1

<table>
<thead>
<tr>
<th>Polymer</th>
<th>End group</th>
<th>( M_n ) (kg mol(^{-1}))(^{a)})</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{NHC}_{7k} )</td>
<td>( N )-ethylimidazolium</td>
<td>7.21</td>
<td>1.13</td>
</tr>
<tr>
<td>( \text{NHC}_{10k} )</td>
<td>( N )-ethylimidazolium</td>
<td>9.97</td>
<td>1.10</td>
</tr>
<tr>
<td>( \text{NHC}_{15k} )</td>
<td>( N )-ethylimidazolium</td>
<td>14.4</td>
<td>1.16</td>
</tr>
<tr>
<td>( \text{NHC}_{20k} )</td>
<td>( N )-ethylimidazolium</td>
<td>19.4</td>
<td>1.09</td>
</tr>
<tr>
<td>( \text{P}^{20k} )</td>
<td>Methoxy</td>
<td>21.3</td>
<td>1.15</td>
</tr>
</tbody>
</table>

\(^{a)}\) Determined by GPC in DMF/LiBr using poly(ethylene oxide) as calibration standard.
The effect of catalyst concentration on catalytic activity

Catalysis experiments with complexes of lower and higher molecular weight, \( \text{Ag(NHC}_{10k}\text{)}_2\text{PF}_6 \) (total \( M_n \) is ca. 14 kg mol \(^{-1}\)) and \( \text{Ag(NHC}_{20k}\text{)}_2\text{PF}_6 \) (ca. 40 kg mol \(^{-1}\)), confirmed the concentration dependence of the catalytic activity observed for \( \text{Ag(NHC}_{10k}\text{)}_2\text{PF}_6 \) (Figure 2b). In addition to this, the results in Figure 2b show that the higher molecular weight complex \( \text{Ag(NHC}_{20k}\text{)}_2\text{PF}_6 \) is significantly more efficient than \( \text{Ag(NHC}_{10k}\text{)}_2\text{PF}_6 \) at corresponding molar concentrations, while the lower molecular weight complex \( \text{Ag(NHC}_{7k}\text{)}_2\text{PF}_6 \) is quite ineffective as a mechanocatalyst. The molecular weight dependence of the TON therefore reflects the molecular weight dependence of scission rates, whereas the positive trend in concentration dependence of the TON is in contrast to the negative trend in scission rate which has been typically observed at increasing polymer concentrations. The catalytic activity of silver(I) ions was excluded by stirring BnOH and VAc in the presence of ca. 3 mM AgPF\(_6\); no BnAc formation was observed after overnight stirring at ambient temperature.

In addition, the concentration dependence of thermally activated transesterification catalysis was investigated at 50 ± 2 °C using complex \( \text{Ag(NHC}_{20k}\text{)}_2\text{PF}_6 \) at two different catalyst concentrations (0.25 mM and 0.75 mM). TONs after 30 min were 680 and 1150, respectively. So, there is an increase in catalyst activity with higher total catalyst concentration in thermal experiments as well, but the effect is much lower than for mechanically activated catalysis (a sixfold increase over the same concentration range). The increase in catalytic activity can be attributed to the increase in solution viscosity at higher polymer catalyst concentrations since the deactivation pathways of the active catalyst species (e.g., reformation of the silver(I)–NHC complex and/or reaction with trace amounts of water) can be assumed to be diffusion-limited.

**Figure 2** (a) Catalyst activity for the transesterification reaction of VAc with BnOH using polymer catalyst complex \( \text{Ag(NHC}_{10k}\text{)}_2\text{PF}_6 \) at different concentrations for thermally and mechanically activated catalysis at 10 ± 2 °C. The error bars represent the typical experimental error as a result of analysis by \(^1\)H NMR which gives a conversion with ± 1% accuracy. (b) TON versus catalyst concentration for different polymer catalyst complexes \( \text{Ag(NHC}_{x}\text{)}_2\text{PF}_6 \) used in this work.
processes. This statement was further supported by the considerably lower catalytic activity of the lower molecular weight complex Ag(NHC7)2PF6 at 1.0 mM: after 30 min at 50 ± 2 °C, the TON was only 470. This is considerably lower than in previous experiments with higher molecular weight catalyst, even though the concentration was higher.24

So, to summarize the results so far, a chemical origin of the concentration dependent catalyst activity is very unlikely. Additional catalytic activity of silver(I) ions was excluded and the presence of trace amounts of deactivating impurities after synthesis and work-up of the catalysts complexes is also not very likely to be the principal cause, since very good batch-to-batch reproducibility of the catalysis experiments was observed throughout this work. Since concentration dependence is only observed in ultrasound-induced catalysis experiments, the most plausible explanation for its origin is the existence of a sonochemical process that causes an increase in observed catalyst activity. Such a sonochemical process can either have a purely mechanochemical nature (e.g., changes in cavitation behavior in more concentrated polymer solutions) or it can be a result of thermal effects during sonication, like radical formation.13,15

5.4 Concentration dependence of mechanochemical scission efficiency

The molecular weight dependence of ultrasonic scission rates of covalent polymers is well established, and we have reported a molecular weight dependent scission rate for complexes Ag(NHC)x2PF6.25 On the other hand, there is less agreement on the effects of polymer concentration on mechanochemical scission. Some authors have reported faster scission upon increasing polymer concentration above the overlap concentration c*, which they ascribed to more efficient force transduction of forces within a transient network.26,27 However, most often, a negative or negligible effect of polymer concentration on scission efficiency has been observed.23

In order to investigate the effect of concentration on scission rate in polymers Ag(NHC)x2PF6, the critical overlap concentration c* was determined for all polymer complexes (Table 2, see the Appendix for more details). Scission efficiencies at concentrations below and above c* were determined for complex Ag(NHC15)2PF6 in toluene (saturated with water)28 using a similar experimental protocol as in earlier work on mechanochemical scission of silver(I)–NHC complexes.29 At 6 mg mL−1, below the overlap concentration (c/c* ≈ 0.5), scission was 26 ± 2% after 15 min of sonication, whereas at 36 mg mL−1, well above the overlap concentration (c/c* ≈ 3),
The effect of catalyst concentration on catalytic activity

it was 15 ± 5% (values based on duplicate experiments). It is, therefore, evident that scission rate is decreasing with polymer concentration, which is in full agreement with most literature reports.

Additional proof that transient network formation is not responsible for increased catalyst activity was found when the dependence of TON on polymer concentration was further investigated. This was done by using a mixture of polymer silver complex Ag(NHC$_{x}$)$_{2}$PF$_{6}$ with non-functionalized P$_{20k}$. Sonication experiments were carried at a catalyst concentration of 0.4 mM, just above the critical overlap concentration $c^\ast$ of the polymer complex, in the presence of ca. 2 mM P$_{20k}$, bringing the total polymer concentration to more than three times $c^\ast$. A TON of 1 was found after 30 min of sonication, compared to a TON of ca. 20 for the same experiment in the absence of P$_{20k}$. After 30 min of sonication, the reaction mixture was heated to 50 °C for an additional 30 min, leading to an increase of TON to ca. 5. The small increase in TON after heating shows that most of the latent catalyst had been activated during sonication, but that the catalytic activity remained low throughout the sonication experiment.

5.5 Mechanocatalysis experiments under radical-suppressing conditions

Considering the lower scission (i.e., activation) rate at higher polymer catalyst concentrations, it is even more remarkable that the mechanocatalytic activity was actually higher in these catalysis experiments. The TON, as a measure of catalyst activity, reflects effects of steady state concentration and lifetime, as well as the activity of catalytically active species. A priori, little difference in catalytic activity of the free NHC as active species is expected, since all catalytic experiments were carried out under very high substrate-to-catalyst ratios. Under these conditions the
reaction rate is expected to be first order in catalyst concentration, which is confirmed by the weaker concentration dependence in the thermally activated reactions. This leaves the steady state concentration of the active species as determining factor. The negative trend in scission kinetics at increased concentration implies that at higher initial catalyst concentrations, the steady state fraction of surviving active species is larger, giving rise to a higher TON. Hence, a process that deactivates NHCs and that is occurring only in the sonicated, but not in the thermally activated system may therefore explain the observations.

Before going further into the discussion on the sonochemical effects, the role of changing solvent composition, as the transesterification reaction proceeds, needs to be discussed. Changes in concentration of components with a low vapor pressure (BnOH and BnAc) will not influence cavitation dynamics, because these components will not migrate into the growing cavitation bubble. At the same time, the consumption of volatile VAc (vapor pressure 89.1 mmHg at 20 °C) is replaced by the more volatile acetaldehyde (760 mmHg at 20 °C). The increasing concentration of acetaldehyde during the reaction, will reduce the intensity of the cavitation and will slow down mechanochemical effects of cavitation to some extent. However, it is not easy to quantify this effect. Moreover, we anticipate that the largest change in solution properties arises from the decrease in solvent viscosity as a result of continuous scission of polymer chain, especially higher polymer concentration ranges, where the scaling relation between solution viscosity and molecular weight starts to deviate from linearity.\(^{24}\) In general, it has been observed that the cavitation behavior is promoted at lower and suppressed at higher solution viscosities, respectively.\(^{13,23}\)

Irradiation of solutions with ultrasound leads to the formation “hotspots”: small regions of extremely high temperatures and pressures in solution at the locations of collapsing cavitation bubbles.\(^{15}\) Under these extreme conditions, reactive species, such as radicals, are formed as a result of pyrolysis of volatile compounds in the cavitation bubbles.\(^{15,31}\) These radical species, and/or their secondary reaction products (from now on referred to as sonochemical impurities) can be expected to deactivate the highly reactive free NHCs. Suppression of thermal effects was realized by using a gas with a high heat capacity, such as methane, as saturation gas in sonication experiments instead of argon.\(^{29,30}\) The use of saturation gases with high heat capacities lowers the maximum hotspot temperatures during (adiabatic) collapse of the cavitation bubbles and thereby reduces the formation of sonochemical impurities.\(^{29–32}\) In Table 3, the TON of the transesterification of VAc with BnOH are compared for different concentrations of polymer catalyst complex Ag(NHC\(_{20k}\))\(_2\)PF\(_6\) under argon and methane.
The effect of catalyst concentration on catalytic activity

A concentration dependence of the TON is found under both gases. However, the catalyst activity is (much) higher under methane than under argon for all concentrations investigated. Only at the lowest concentration that was investigated for methane (i.e., 0.25 mM), there still seems to be effective competition between mechanical activation of the polymer catalyst and deactivation of the free NHCs by sonochemical impurities. However, the catalyst activity seems to reach a steady state value already at a concentration of 0.50 mM, whereas, for the argon experiments, TON is still gradually increasing at 1.0 mM. This indicates that, under argon, the deactivation process still plays an important role even at high catalyst concentrations. This further confirms that formation of sonochemical impurities is less when using methane as a saturation gas.

Based on these results, we can explain the catalyst activity profiles as a function of catalyst concentration for different molecular weights as shown in Figure 1b. The formation rate of sonochemical impurities is—to a first approximation—indeed of molecular weight and concentration of the latent catalyst. In solutions containing high latent catalyst concentrations, the absolute amount of active catalyst that is produced per unit time is higher than at low concentrations. Therefore, at higher concentrations the active catalyst production rate is able to compete successfully with the sonochemical production of deactivating species. Similarly, when high molecular weight latent catalysts are used, the increased formation rate of NHCs outweighs the rate at which sonochemical impurities are formed, and a higher steady state concentration of active catalyst is maintained than for low molecular weight latent catalysts.

A good illustration showing the difference in the amount of active catalyst species in argon and methane sonication experiments is found when monitoring the remaining

<table>
<thead>
<tr>
<th>Catalyst concentration (mM)</th>
<th>Argon</th>
<th>Methane</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>0.50</td>
<td>20</td>
<td>380</td>
</tr>
<tr>
<td>0.75</td>
<td>60</td>
<td>480</td>
</tr>
<tr>
<td>1.0</td>
<td>130</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

See also Figure 1b.
catalytic conversion of VAc and BnOH after sonication has been stopped. While hardly any remaining catalytic activity could be observed in experiments under argon (less than 1% additional conversion in 30 min), significant catalyst activity was retained under methane, with BnOH conversion increasing from 10.5% to 13.4% in a period of 30 min after stopping the sonication.

5.6 Identification of the nature of the sonochemical impurities

The next question that remains to be answered is about the exact nature of the sonochemical impurities. It is not yet clear whether the radicals that are formed within the hotspot regions themselves are responsible for catalyst deactivation or whether the deactivation is caused by reaction of the active catalyst species with reaction products of secondary sonochemical processes (e.g. radical recombination reactions). In Figure 3a, the time–conversion plots are shown for the mechanochemically catalyzed transesterification reaction under argon with and without the addition of a radical scavenger (BHT; 2,6-di-tert-butyl-4-methylphenol). When ca. 19 equivalents of BHT are added compared to the total amount of catalyst complex Ag(NHC20k)2PF6, the conversion slightly increases from 0.5% (TON = 20) to 0.7% (TON = 25) after 30 min of sonication. The amount of BHT consumed during this period was around 1% or less, as determined by GC-FID. From this, we conclude that radicals are not the predominant deactivating species in mechanochemically activated catalysis using ultrasound.

To demonstrate that the deactivating species is persistent, i.e., is formed as (one of the) products of secondary sonochemical reactions, we compared the catalyst activity in freshly prepared and presonicated reaction mixtures (see Figure 3b). For

Figure 3 (a) Time–conversion plots comparing the conversion of VAc and BnOH using catalyst complex Ag(NHC20k)2PF6 (0.51 mM) with and without the addition of radical scavenger BHT. (b) Time–conversion plot showing the effect of presonication of the reaction mixture under argon and methane (presonication time = 30 min, catalyst concentration = 0.25 mM, temperature = 50 ± 2 °C).
the presonicated reaction mixtures, the standard reaction mixture of toluene, VAc and BnOH (in a volumetric ratio of 5:3:2) was prepared and sonicated under argon or methane for 30 min without catalyst. After the presonication step, the mixture was taken out of the sonication vessel and the appropriate amount of catalyst complex was dissolved in the mixture (total catalyst concentration ca. 0.25 mM). Subsequently, catalysis was thermally activated at 50 ± 2 °C. It can be seen in Figure 3b that the solution sonicated under argon shows a dramatic decrease in catalyst activity compared to the freshly prepared solution, while presonication under methane leads to only a small decrease in catalyst activity. These results, in combination with those obtained from the catalytic tests in the presence of BHT, confirm that the species that is deactivating the free NHC active catalyst species is a persistent species, which is stable after stopping the sonication process. The radicals, which are formed as the primary products of thermal effects in sonochemistry do not significantly influence the mechanocatalyst activity. Direct analysis of the sonicated solutions by GC-MS, GC-FID and 1H NMR, however, did not reveal the exact nature of the sonochemical impurities.

It was possible to gain insight in the nature of the thermal impurities in an indirect way, by carrying out acid–base titration experiments. A 0.058 mM solution of thymol phthalein (TP) indicator in isopropanol was prepared. TP was deprotonated by a substoichiometric amount of potassium tert-butoxide (0.8 equivalents), resulting in a deeply blue-colored indicator solution that disappears upon addition of Brønsted acidic species. TP in its deprotonated form is basic enough to react with very weak Brønsted acids (pH transition range 8.8–10.5). Since free NHCs are very strong bases, the possibility of their deactivation by a weak acid should be taken into account. Dropwise addition of a standard reaction mixture (toluene, VAc and BnOH in a 5:3:2 volumetric ratio) to the TP solution showed unambiguously that the reaction mixture that was sonicated under argon contained three times more protic impurities than the freshly prepared or methane-sonicated reaction mixtures (see Table 4). Addition of the argon-sonicated reaction mixture to a solution of dimethyl yellow (DMY) indicator did not result in any observable color change. DMY has a color transition range at low pH values (2.9–4.0) and therefore, the protic impurity must be a weak Brønsted acid, possibly a carboxylic acid.

We speculate that acetic acid is the source of acidity as it is a likely sonochemical degradation product of VAc. Because of its high vapor pressure, VAc will be one of the main components of the cavitation bubble during sonication of the reaction mixture for transesterification. Assuming that all protic species are acetic acid, the increase in acidity shown in Table 4 corresponds to a VAc conversion of only 0.004%
Chapter 5

Table 4 Results of acid–base titration experiments of freshly prepared and sonicated transesterification reaction mixture\textsuperscript{a).} The reaction mixture was added dropwise to 2.0 mL of 0.058 mM thymol phthalein (TP) solution until decoloration occurred.

<table>
<thead>
<tr>
<th></th>
<th>Freshly prepared reaction mixture</th>
<th>Presonicated reaction mixture\textsuperscript{c)}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Argon\textsuperscript{a)}</td>
</tr>
<tr>
<td>Volume added to TP solution (mL)</td>
<td>1.85</td>
<td>0.60</td>
</tr>
<tr>
<td>Acid content\textsuperscript{b)} (mM)</td>
<td>0.063</td>
<td>0.19</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} Reaction mixture has a standard composition: 2.5 mL toluene (dried prior to use), 1.5 mL VAc and 1.0 mL BnOH. \textsuperscript{b)} Defined as the concentration of protons (H\textsuperscript{+}) in the mixture. \textsuperscript{c)} Presonicated for 60 min.

by thermal effects of sonochemistry inside hotspots. The concentration of protic impurities is indeed in the same range as the concentration of (active) catalyst. The low concentration of acid explains why it was not observed directly before. To demonstrate that the suppression of thermal effects in ultrasound is generally applicable, it should be noted that similar effects on catalyst activity was observed in ring-closing metathesis (RCM) reactions using a ruthenium(II)–NHC mechanocatalyst. For the mechanochemical RCM reaction, catalyst deactivation is also caused by persistent sonochemical impurities.\textsuperscript{17,33} In contrast to transesterification however, sonication of the metathesis reaction mixture (toluene and less volatile diethyl diallylmalonate) under argon did not result in appreciable formation of protic impurities. Brønsted acids are thus less of a concern for deactivation of the mechanochemically activated metathesis catalysts. Instead, the formation of unsaturated hydrocarbons as well-established toluene pyrolysis products may be detrimental for this type of catalyst.\textsuperscript{31,34}

5.7 Conclusions

A molecular weight and concentration dependent catalyst activity under mechanocatalytic reaction conditions was observed in the transesterification reaction of VAc with BnOH using polymeric silver(I)–NHC catalyst complexes Ag(NHC\textsubscript{x})\textsubscript{2}PF\textsubscript{6}. While the (positive) molecular weight dependence was expected for—and, in fact, confirms—mechanochemically activated catalyst activation, the concentration dependence was unexpected and could not be explained in a straightforward manner.

Here, we have investigated the concentration dependence of the catalytic activity in more detail. It was confirmed that the concentration dependent catalyst activity has a sonochemical, rather than a chemical, origin, since it was only observed in mechanocatalytic experiments. First, the possibility of enhanced mechanochemical
activation due to transient polymer network formation in semi-dilute solutions (at polymer concentrations above the critical overlap concentration $c^*$) was investigated. However, it was found that this could not be the reason since the activation rate of the polymer silver(I)–NHC catalyst complexes was found to decrease with increasing catalyst concentration. Furthermore, addition of non-functionalized PTHF to a total polymer concentration well above $c^*$ did not enhance the catalytic activity (in fact, catalytic activity decreased significantly in this case).

Second, the presence of sonochemically produced impurities (such as radicals or their secondary reaction products) during sonication was considered. Even though the presence of radicals/sonochemical impurities does not influence the primary process of mechanochemical chain scission when using ultrasound, their presence does in fact significantly promote deactivation of the free NHC active catalyst species, leading to a reduced efficiency of the catalytic conversion. The impurity which is responsible for catalyst deactivation was shown to be a persistent species which is formed as a product of secondary sonochemical reactions. More specifically, the deactivating species was found to be weak Brønsted acid in case of free NHCs as mechanochemically activated transesterification catalysts. We postulated that acetic acid is formed as sonochemical impurity during sonication under argon, taking in account the composition of the reaction mixture; however, we did not directly identify this. Suppression of thermal effects by using methane as saturation gas significantly increased catalyst lifetime and, with that, catalyst performance in mechanochemically activated transesterification catalysis. Herewith, we have demonstrated that the suppression of thermal effects is of great importance in sonochemistry when the product of mechanochemical scission is used in subsequent chemical processes, such as catalysis. Not only does this finding further confirm the true mechanochemical nature of catalyst activation, it also serves as an important guideline for future work involving sonochemically produced species.

**Experimental section**

**General.** All reagents and solvents were used as received unless stated otherwise. Solvents used in the synthesis and viscosity measurements were obtained from BioSolve (The Netherlands) and of at least AR grade quality, unless stated otherwise. Deuterated solvents for recording NMR spectra were obtained from Cambridge Isotope Laboratories, Inc. (United States). $^1$H NMR spectra were recorded on a Varian 400MR or Varian Mercury 400 spectrometer and chemical shifts are reported in ppm relative to TMS.

For the catalytic tests and/or calibration of GC-FID, benzyl alcohol (BnOH; anhydrous, 99.8% in a Sure/Seal™ bottle), benzyl acetate (BnAc; ≥99%), vinyl acetate (VAc; ≥99%), 2,6-di-
tert-butyl-4-methylphenol (BHT; ≥99%) and dimethyl yellow (DMY) were all obtained from Sigma-Aldrich (Germany). Thymol phthalein (TP) was purchased from Merck (Germany). Argon (99.999% v/v, max. 3 ppm water) and methane (99.995% v/v, max. 5 ppm water) were supplied by Linde (The Netherlands).

Synthesis of $\alpha$-(N-ethylimidazolium)-$\omega$-methoxy poly(tetrahydrofuran) ligands and their corresponding polymer complexes with silver(I). Polymer ligands NHC$_x$ ($x = 7k$, 10k and 15k) were synthesized for previous studies and a detailed experimental procedure can be found in Chapters 3 and 4. Polymer ligand NHC$_{20k}$ was synthesized using the same procedure and a polymerization time of 8 h. The procedure for the synthesis of the corresponding polymer complexes Ag(NHC$_x$)$_2$PF$_6$ can be found in Chapters 3 and 4 as well. The characterization results of polymer ligands NHC$_x$ are summarized in Table 1.

Synthesis of $\alpha$-$\omega$-dimethoxy poly(tetrahydrofuran). Fully covalent, non-functionalized PTHF, P$_{20k}$ was synthesized for previous studies. The full experimental details can be found in Chapter 2. The result of characterization of polymer P$_{20k}$ is summarized in Table 1.

Mechanochemical scission experiments. The appropriate amount of catalyst complex Ag(NHC$_{15k}$)$_2$PF$_6$ was dissolved in toluene (2.5 mL) that was saturated with demineralized water prior to use. Sonication was continued for 15 minutes and after stopping, the full sample was withdrawn from the vessel followed by solvent evaporation in vacuo. The residual solid was redissolved in acetone-$d_6$ for analysis by $^1$H NMR. The percentage of scission of the polymer complex in mechanical activation experiments was determined by $^1$H NMR cf. the procedure reported in Chapter 3.

Mechanocatalytic tests. For a typical mechanocatalytic test, a reaction mixture was prepared consisting of toluene (1.25 mL, dried over 4Å molecular sieves prior to use), VAc (0.75 mL, 8.1 mmol) and BnOH (0.50 mL, 4.8 mmol) in which the appropriate amount of polymer catalyst complex Ag(NHC$_x$)$_2$PF$_6$ was dissolved. After complete dissolution of the catalyst, the reaction mixture was transferred into a 10 mL double-jacketed glass sonication vessel placed under inert argon or methane atmosphere and precooled to 2.0 ± 0.2 ºC using water from a recirculation thermostat bath. The reaction mixture was kept at this temperature for 20–30 minutes during which it was saturated with argon or methane by bubbling through. After this period, sonication was started. Small samples were withdrawn from the reaction mixture prior to starting the sonication and at various time intervals. The samples (20 µL) were diluted with acetone-$d_6$ (ca. 0.6 mL) for analysis by $^1$H NMR (for catalyst complex Ag(NHC$_{10k}$)$_2$PF$_6$ only) or with chloroform for analysis by GC-FID (for complexes Ag(NHC$_{7k}$)$_2$PF$_6$ and Ag(NHC$_{20k}$)$_2$PF$_6$).

Sonication was carried out using a Sonics VC750 sonication set-up operating at 20 kHz and 30% of the maximum amplitude. A pulsed sonication protocol was used for all the mechanocatalytic tests in this work (using a pulse rate of 0.5 s on/1.0 s off). Temperature
measurements indicated that for these conditions, the maximum attained bulk temperature inside the vessel during sonication was 10 ± 2 °C. For the temperature measurements, a 0.5 mm thermocouple was placed directly in the sonication solution.

**Mechanocatalytic tests in the presence of radical scavenger.** The experimental procedure was identical to that of the other mechanocatalytic tests (see above). The catalyst complex \( \text{Ag}(\text{NHC}_{20k})_2\text{PF}_6 \) was used for this experiment at a total concentration of 0.51 mM. Additionally, BHT (5.3 mg; 10 mM, 19 equiv.) was added to the mixture prior to starting the sonication.

**Thermal catalytic tests.** The typical protocol for catalytic tests to investigate thermal background reaction was as follows: a 50 mL 2-necked round-bottom flask was charged with the required amount of polymer catalyst complex \( \text{Ag}(\text{NHC}_{10k})_2\text{PF}_6 \) and toluene (1.25 mL, dried over 4Å molecular sieves prior to use. Then the flask was equipped with an argon bubbler and purged with argon for 5–10 minutes. Subsequently, VAc (0.75 mL, 8.1 mmol) was added after which the mixture was cooled to the desired temperature (10 ± 2 °C) in an ice/water bath. BnOH (0.50 mL, 4.8 mmol) was added swiftly and time measurement was started. At various time intervals, samples (20 µL) were withdrawn from the reaction mixture and diluted with acetone-\( d_6 \) or CDCl\(_3\) (ca. 0.6 mL) for analysis by \(^1\)H NMR.

The experimental protocol for thermal catalytic tests at 50 ± 2 °C (using \( \text{Ag}(\text{NHC}_{7k})_2\text{PF}_6 \) or \( \text{Ag}(\text{NHC}_{20k})_2\text{PF}_6 \)) was similar. However, these experiments were carried out in a capped Schlenk tube under slight argon overpressure to prevent evaporation. A thermostat-controlled oil bath was used for heating the reaction mixture.

**Thermal catalytic tests with presonicated reaction mixture.** The experimental procedure for thermal catalytic tests with presonicated reaction mixture was similar to the thermal catalytic tests at 50 ± 2 °C as reported above. However, for these experiments, the reaction mixture was first sonicated for 30 min using a continuous sonication protocol at 30% amplitude using either argon or methane as a saturation gas. Subsequently, the presonicated reaction mixture was added to the catalyst complex \( \text{Ag}(\text{NHC}_{20k})_2\text{PF}_6 \) in a Schlenk tube under argon. When the catalyst complex had dissolved, the tube was placed in the preheated oil bath.

**Acid–base titration experiments.** Potassium tert-butoxide (3.16 mg, 0.0282 mmol) was dissolved in isopropanol. Prior to its use, the isopropanol was dried over 4Å molecular sieves overnight. TP indicator (15.4 mg, 0.0358 mmol, 1.27 equiv.) was added to the solution which turned to deep blue immediately. This solution was diluted ten times to afford the TP stock solution at 0.058 mM.

A standard reaction mixture for transesterification (in the absence of catalyst) was prepared and added dropwise to the TP solution (2.0 mL) while stirring gently until the indicator
solution turned colorless. Subsequently, standard reaction mixture was sonicated for 60 min (continuous sonication at 30% amplitude) under argon and methane and titrated as well.

**Appendix**

An estimate of the critical overlap concentration of the polymer silver(I)–NHC complexes in solution was made based on the Mark–Houwink relationship for polymer silver(I)–NHC complexes in toluene that was established in our previous work:

\[
[\eta]_0 = 6.6 \times 10^{-3} M_n^{0.65} \tag{A.1}
\]

Where \([\eta]_0\) is the limiting viscosity number of the polymer solution (in L g\(^{-1}\)) and \(M_n\) the number-average molecular weight of the total polymer complex (in kg mol\(^{-1}\)). The critical overlap concentration of polymer in solution (denoted with \(c^*\), in g L\(^{-1}\)) scales inversely with the limiting viscosity number, \(^{36}\) i.e.,

\[
c^* = \frac{0.77}{[\eta]_0} \propto M_n^{-0.65} \tag{A.2}
\]

Additionally, the critical overlap concentration of polymer complexes Ag(NHC\(_x\))\(_2\)PF\(_6\) in toluene was determined from the change in the slope of a (double logarithmic) plot of the specific viscosity \(\eta_s\) versus concentration of the polymer complex (see Figure A1). Ubbelohde viscosity measurements\(^{35}\) were carried out on complexes Ag(NHC\(_7k\))\(_2\)PF\(_6\) and Ag(NHC\(_10k\))\(_2\)PF\(_6\) in toluene over a wide concentration range. When the data points in Figure A1 are divided into two sets, one at lower concentrations (corresponding to the dilute regime) and one at higher concentration (semi-dilute regime) a change in slope between both sets of data points from \(~1.1\) to \(~1.5\) is found for both complexes. This is close agreement with the theory, which predict that, for the intermediate semi-dilute regime, where overlap between the polymer chains starts, the slope of 1 should gradually increase as a function of the reduced concentration \(c/c^*\) until it asymptotically reaches these predicted values (around \(c/c^* \approx 5–10\)).\(^{37}\) For concentrated solutions, where entanglements between polymer chains are present, scaling laws predict that the slope of these plots should increase to a final value between 4.0–5.6.\(^{38–40}\) The critical overlap concentration is equal to the intersection point of the lines defining the dilute and semi-dilute regimes: \(c^* = 20.4\) g L\(^{-1}\) and 15.2 g L\(^{-1}\) for complexes Ag(NHC\(_7k\))\(_2\)PF\(_6\) and Ag(NHC\(_10k\))\(_2\)PF\(_6\), respectively, which is in good agreement with the values reported in Table 2 (cf. Equation (A.2), \(c^* = 20.6\) g L\(^{-1}\) and 16.7 g L\(^{-1}\)).
The effect of catalyst concentration on catalytic activity

Figure A1 Specific viscosity versus polymer complex concentration for polymer complexes Ag(NHC$_{7k/2}$)$_2$PF$_6$ (triangles) and Ag(NHC$_{10k/2}$)$_2$PF$_6$ (circles) in toluene at 28.00 ± 0.02 °C.

Notes and references

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22. $^1$H NMR was used in these experiments to determine the conversion of BnOH. Owing to the limited sensitivity of $^1$H NMR, conversions below approximately 1% could not be accurately determined because the signal-to-noise ratio was too high to allow reliable peak integration.
24. The solution viscosity scales as $\eta = M^n$ in the dilute, and as $\eta = c^\alpha M^\beta$ ($\alpha = 4.0–5.6$ and $\beta = 3.4$) in the semi-dilute unentangled regime, respectively (see Refs. 36, 38).
28. Solubility of water in toluene is between ca. 0.03 g and 0.05 g water per 100 g of solvent at 0 °C and 20 °C, respectively (data taken from NIST database: http://srdata.nist.gov/solubility). The density of toluene 0.87 g mL$^{-1}$, which gives a water concentration of 14–24 mM; this is at least a tenfold excess compared to the concentrations of Ag(NHC$_{18k}$)$_2$PF$_6$ (being 0.20 or 1.2 mM).
34. R.D. Smith, *Combust. Flame* 1979, 35, 179–190 (including references therein)
39. See Note 24, and for semi-dilute unentangled polymer solutions the following scaling relation for viscosity with reduced concentration ($c/c^*$) is found (Ref. 40): $\eta = \eta(c/c^*)^{1/(3\nu−1)}$, where the Flory exponent $\nu = 0.55$ for Ag(NHC$_{18k}$)$_2$PF$_6$ in toluene (calculated from data in Ref. 35).
Chapter 6

Synthesis and mechanochemical scission of a polymer based on the adduct of an NHC and isothiocyanate

Abstract

The adduct of an N-heterocyclic carbene (NHC) and aromatic isothiocyanate was synthesized and incorporated at a central position within a polymer chain. In this scheme, the NHC–isothiocyanate is a potential mechanocatalyst and provides a (metal-free) alternative to previously explored silver(I)–NHC mechanocatalyst complexes. The catalytic activity of the NHC–isothiocyanate adduct was evaluated and it was found that this is indeed a latent catalyst having a very high activation temperature (ca. 100 °C) in thermally activated transesterification catalysis. Near-midpoint scission of the polymer adduct by ultrasound irradiation was demonstrated. However, mechanochemically activated catalysis (“mechanocatalysis”) was not observed. When identifying the product of mechanochemical scission, it was verified that scission does not occur at the putative NHC–isothiocyanate mechanophore and that, in contrast to thermal scission, no free NHCs are formed in this process. It was concluded that, in the current scheme, the NHC–isothiocyanate adduct is not a suitable mechanophore for mechanocatalysis.
6.1 Introduction

In the past few years, our group has developed latent organometallic catalyst complexes that can be activated by mechanical forces (“mechanocatalysis”), in contrast to conventional methods for catalyst activation which include thermal and (photo)chemical activation. These mechanocatalysts that have been developed up to now are based on coordination complexes of N-heterocyclic carbene (NHC) ligands and transition metal centers, such as silver(I),\textsuperscript{1-3} ruthenium(II)\textsuperscript{1,4} or palladium(II) and platinum(II).\textsuperscript{5} These latent catalyst complexes can be activated by mechanical forces after incorporation at the central position of a polymer chain. The polymer chain acts as a “handle” for transduction of macroscopic mechanical forces onto individual chemical bonds.\textsuperscript{6,7} For this purpose, we have chosen to functionalized the NHC ligands with a poly(tetrahydrofuran) (PTHF) chain.\textsuperscript{2} In examples by Bielawski and co-workers, poly(methylacrylate)-functionalized palladium(II)– or boronium–pyridine complexes were used as mecanochemically activated catalysts.\textsuperscript{8} In all examples of mechanocatalysis so far, irradiation of the polymer catalyst by ultrasound in the presence of reactants has been used.\textsuperscript{9} During the collapse of cavitation bubbles, high strain rates will be imposed on the polymer chains in solution.\textsuperscript{9,10} As a result of these strain rates, the polymer chains will uncoil, stretch and eventually break.\textsuperscript{10,11}

The silver(I)–NHC complexes used in our group for mecanochemically activated transesterification catalysis are suitable mechanocatalysts, but possess some limitations. Most prominently, significant background catalysis is always observed unless the reaction mixture is cooled below ca. 10 °C.\textsuperscript{3} The exact reason for this is not completely clear to us, but it may have to do with the highly dynamic nature of the silver(I)–NHC coordination bond. At room temperature, ligand exchange in solution occurs on a timescale of approximately one second.\textsuperscript{12} Alternatively, the silver(I)–NHC complex may become more susceptible towards dissociation or disproportionation reactions in the presence of substrate molecules in solution (in this case alcohols and esters which are relatively polar compounds).

Owing to their remarkable electronic properties, NHCs coordinate with all metals (transition metal and main group elements), as well as with a variety of non-metallic species, such as alcohols, amines, chloroform, halogens and boranes.\textsuperscript{13-17} A special group of NHC derivatives consists of the betaines, which are zwitterionic adducts formed by reaction of NHCs with (hetero)allenes such as CS\textsubscript{2} or CO\textsubscript{2} and iso(thio) cyanates.\textsuperscript{13} Winberg and Coffman were the first to report the formation of such a zwitterionic adduct in 1965 when studying the cleavage of a bis(imidazolium) dimer with phenyl isothiocyanate.\textsuperscript{18} Five years later, Schönher and Wanzlick were
the first to report NHC–isothiocyanate adduct formation after deprotonation of the corresponding imidazolium salt with a strong base.\textsuperscript{19} In later studies, the generality of this approach was demonstrated by successful syntheses of betaine derivatives of benzimidazolium, thiazolium, triazolium, and (saturated) imidazolidinium salt as well.\textsuperscript{13}

The use of NHC–isothiocyanate adducts as organocatalysts was recently reported by Norris \textit{et al.}\textsuperscript{20} They synthesized a variety of adducts based on 1,3-dimesitylimidazolylidene and aromatic isothiocyanates and investigated the role of different substituent groups on the aromatic ring (electron-donating or electron-withdrawing and steric effects) on the activation temperature of the adduct in the [2+2+2] cyclotrimerization reaction of phenyl isocyanate. In addition, they successfully demonstrated the ring-opening polymerization of $\text{dl}$-lactide. Temperatures higher than 70–80 °C were required to activate the catalyst, even for the most sterically crowded ($\text{ortho}$-diisopropyl-substituted) isothiocyanates. The high latency was directly attributed to the extremely high equilibrium constant of adduct formation $K_{eq}$, being in the order of $10^{14}$ M$^{-1}$. In principle, the excellent latency makes the NHC–isothiocyanate adduct an ideal (and metal-free) alternative to silver(I)–NHC mechanocatalyst complexes.

In this chapter, the design and synthesis of a latent transesterification catalyst is reported, based on the adduct between an NHC and isothiocyanate and inspired by the work of Norris \textit{et al.}\textsuperscript{20} In a second step, the model catalyst is converted into a mechanocatalytic system by incorporation of the adduct as putative mechanophore in a polymer (PTHF) chain and its mechanocatalytic activity is evaluated. The so developed mechanocatalyst could be an interesting and more stable alternative to the silver(I)–NHC mechanocatalyst complexes that are studied in our group.

### 6.2 Synthesis of non-polymeric NHC–isothiocyanate model catalyst

The synthesis of the non-polymeric NHC–isothiocyanate model catalyst was carried out using a similar procedure as reported by Norris \textit{et al.}\textsuperscript{20} However, free NHC was generated \textit{in situ} by deprotonation of 1-ethyl-3-methyl imidazolium hexafluorophosphate salt in dry THF by addition of 1.2 eq. of a 1 M LiHMDS solution in THF (see Figure 1). Subsequent coupling with 4-methoxyphenyl isothiocyanate afforded the model catalyst NCS–NHC.

Norris \textit{et al.} have reported the use of NHC-isothiocyanate adducts which were comparable to NCS–NHC as catalysts in phenyl isocyanate [2+2+2]
cyclotrimerization and ring-opening polymerization (ROP) reaction of lactides. For the current study, the adduct was tested as a catalyst in the transesterification reaction of vinyl acetate (VAc) with benzyl alcohol (BnOH). This transesterification reaction has been used in our group to assess mechanocatalytic activity of silver(I)–NHC latent catalyst complexes. When a mixture of vinyl acetate and benzyl alcohol was stirred in the presence of ca. 0.1% of at room temperature, formation of benzyl acetate was too small to be quantified. Upon heating the reaction mixture to 70 °C, ca. 0.5% conversion was observed after one hour. These results indicate that the NHC–isothiocyanate adduct is an excellent latent catalyst showing no activity at room temperature. The relatively high activation temperature (i.e. heating to at least 70 °C is required in order to obtain catalytic activity) is in full agreement with the observations made by Norris et al. Therefore, an NHC–isothiocyanate adduct was used as mechanophore by incorporation in the center of a PTHF chain, as an alternative to previously explored silver(I)–NHC catalysts.

6.3 Synthesis of the NHC–isothiocyanate polymer adducts

In a first design, the idea was to synthesize the polymer NHC–NCS adduct by coupling a NHC-functionalized PTHF building block (henceforth denoted by NHC$_x$, with $x$ being the approximate number-average molecular weight) to a NCS-functionalized polymer building block NCS$_x$. Polymer building blocks NHC$_{7k}$ and NHC$_{20k}$, having an imidazolium end group, were already synthesized previously, as described in Chapters 3–5. The synthesis of a polymer with an isothiocyanate end group was attempted using a similar strategy by terminating the cationic ring-opening polymerization (CROP) of THF with 4-nitrophenol, followed by the conversion of the nitro group to the corresponding isothiocyanate in two steps (Figure 2). However, termination of the polymerization with neither 4-nitrophenol nor its sodium salt was successful owing to the poor nucleophilicity of the oxygen atom and the limited solubility of sodium nitrophenolate in THF. The primary alcohol...
Synthesis and mechanochemical scission of a polymer NHC–NCS adduct

derivative 2-(4-nitrophenoxy)-ethanol was found to be a slightly better nucleophile, but complete end functionalization was not achieved with this compound either.

In a modified synthetic scheme (see Figure 3), 2-(4-nitrophenoxy)-ethanol was reacted with 1-chloro-4-nitrobenzene to give the bifunctional nitro building block. Catalytic reduction with hydrogen over a Pd/C catalyst afforded amine in quantitative yield. The target bifunctional isothiocyanate building block (henceforth referred to as B) was obtained in two steps by reaction with CS$_2$ and base, followed by treatment with $p$-toluenesulfonyl chloride (TsCl). Conversion of the amino groups was monitored by FT-IR spectroscopy. In the first step, CS$_2$ was added to the reaction mixture until the two bands around 3400–3300 cm$^{-1}$ (–NH$_2$) in the IR spectrum of the reaction mixture had disappeared. The appearance of a new band around 2100 cm$^{-1}$ confirmed the formation of the dithiocarbamic acid salt. When conversion was complete, TsCl was added to convert the dithiocarbamate into an isothiocyanate group. The resulting bifunctional isothiocyanate building block B was used as a linker unit between two polymeric NHC$_x$ building blocks to form the desired NHC–isothiocyanate adduct.

Coupling of B with the NHC$_x$ polymer ligands to form the NHC$_x$–B–NHC$_x$ adduct was carried out by in situ deprotonation of the polymer building block NHC$_x$ with 1 M LiHMDS solution in THF, followed by (slow) addition of 0.5 eq. of B. A color change of the reaction mixture to bright yellow was observed, which is indicative for the formation of the adduct. $^1$H NMR analysis after work-up showed that the peak corresponding to the C2 proton of the imidazolium group fully disappeared; in addition, the change in characteristic chemical shifts for the C4/5 protons of the imidazolium, the methylene protons adjacent to the N1/3 and the aromatic protons
next to the NCS group of the B indicated that coupling was successful. Further analysis by GPC showed a bimodal molecular weight distribution, where the two (top) molecular weights correspond to the mono- and bifunctional polymer adduct (see Table 1). The absence of peaks corresponding to the free polymer ligand NHC\textsubscript{x} in the \textsuperscript{1}H NMR reveals that a fraction of the polymer is present as the monofunctional polymer adduct B–NHC\textsubscript{x}. For the purpose of the present studies, however, this is not a major concern. Deconvolution of the GPC traces was performed to quantify the amounts of mono- and bifunctional polymer in each case.

6.4 Mechanochemical scission kinetics of polymer NHC–isothiocyanate adducts

The kinetics of mechanochemical scission of the NHC\textsubscript{20k}–B–NHC\textsubscript{20k} polymer adduct were investigated. Approximately 60 mg of NHC\textsubscript{20k}–B–NHC\textsubscript{20k} (batch no. 1 in Table 1; weight fraction bifunctional = 0.66) was dissolved in 5 mL of toluene. The toluene was spiked with 1% (v/v) of acetic acid to act as a proton source for scavenging free NHC\textsubscript{20k} polymer ligands formed during the mechanochemical scission. Samples of the sonication mixture were taken at regular intervals and analyzed by GPC to follow the scission kinetics. Typical GPC traces as obtained are shown in Figure 4a. During sonication, the low molecular weight shoulder (henceforth denoted as peak 2) increases relative to the high molecular weight peak (peak 1). The weight fractions of both high and low molecular weight species was calculated from the relative areas of peak 1 and peak 2, obtained by deconvolution of the GPC trace using a double Gaussian fitting function (Equation (1)).

\[
I(x) = \frac{A_1}{w_1 \sqrt{\pi/2}} \exp\left( -\frac{x - x_{c,1}}{w_1} \right)^2 + \frac{A_2}{w_2 \sqrt{\pi/2}} \exp\left( -2 \left( \frac{x - x_{c,2}}{w_2} \right)^2 \right)
\] (1)
In this equation, \( A_i \), \( w_i \) and \( x_{c,i} \) represent the area, width and retention time at the peak center of species \( i \) \((i = 1 \text{ and } 2)\). In the fitting protocol, the peak width for the bifunctional polymer adduct and scission product was fixed to be equal, \( w_1 = w_2 = w \), since we expected selective midpoint scission.\(^{26}\) At any time \( t \) during the sonication experiment, the weight fraction of bifunctional polymer adduct \( C_1(t) \) is then calculated from the relative area of the peak 1:

\[
C_1(t) = \frac{A_1(t)}{A_1(t) + A_2(t)}
\]

The insets of Figure 4 show plots of the kinetics for mechanochemical scission of the polymer catalysts. A first order kinetic plot is shown here with \( \ln(C_1(t)/C_1(0)) \) plotted versus sonication time \( t \). The data show a slight deviation from first-order scission kinetics. Initially, the scission is somewhat slower, but catches up and eventually accelerates. However, the effect may be a result of limited accuracy of the deconvolution procedure. Although the fit is not perfect, linear regression was performed and gave a rate constant for mechanochemical scission \( k_{sc} = 4.4 \pm 0.29 \times 10^{-3} \text{ min}^{-1} \). A similar value was obtained when the scission kinetics were analyzed using the Malhotra method \( (k_{sc} = 4.0 \pm 0.35 \times 10^{-3} \text{ min}^{-1}) \).\(^{27}\) This means that the activation rate is ca 0.4% of the remaining bifunctional polymer adduct per minute. A control sample that was kept at room temperature did not show any thermally induced scission. To confirm the mechanochemical nature of scission, the analogue polymer adduct \( \text{NHC}_7\text{k–B–NHC}_7\text{k} \) was synthesized and subjected to ultrasound under identical experimental conditions. After one hour of sonication, there was no detectable scission for this shorter polymer chain (Figure 4b), which demonstrates the need for a chain length in excess of 14 kg mol\(^{-1} \) to transfer enough force onto the mechanophore. This confirms the mechanochemical nature of chain scission.

### Table 1
Characterization details for the NHC\(_x\) polymer building blocks and their corresponding NHC–isothiocyanate polymer adducts.

<table>
<thead>
<tr>
<th>( M_{top} ) (kg mol(^{-1}))(^{a)} )</th>
<th>( M_{top} ) (kg mol(^{-1}))(^{a)} )</th>
<th>Weight fraction bifunctional</th>
</tr>
</thead>
<tbody>
<tr>
<td>B–NHC(_7k)</td>
<td>7.61</td>
<td>NHC(_7k)–B–NHC(_7k)</td>
</tr>
<tr>
<td>B–NHC(_{20k})</td>
<td>22.8</td>
<td>NHC(<em>{20k})–B–NHC(</em>{20k})</td>
</tr>
<tr>
<td></td>
<td>21.4</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a)}\) Top molecular weights as measured by GPC in THF using PS calibration standards; a correction factor was applied which was determined by the use of an external PTHF standard.
Using the relationship between the molecular weight and the observed $k_{sc}$ for covalent PTHF, we realize that the bifunctional polymer adduct $\text{NHC}_{20k} - \text{B} - \text{NHC}_{20k}$ does not break significantly faster than covalent PTHF having a similar molecular weight. In addition, several experiments raised doubts that mechanochemical scission does, in fact, not take place at the NHC–NCS bond, which would lead to the generation of a free NHC and isothiocyanate. The outcome of these experiments are discussed in more detail below, but may be summarized as follows: (i) the formation of NHCs as scission products could not be observed by $^1$H NMR; (ii) there was no reaction of free NHCs with fluorescein isothiocyanate as scavenger after mechanochemical scission of $\text{NHC}_{20k} - \text{B} - \text{NHC}_{20k}$; (iii) no mechanocatalytic activity in transesterification reactions was observed upon ultrasound-induced scission of the adduct.

In Figure 5a the $^1$H NMR spectrum of the product after a typical sonication experiment of $\text{NHC}_{20k} - \text{B} - \text{NHC}_{20k}$ is compared with the $^1$H NMR spectrum of the polymer ligand $\text{NHC}_{20k}$. After comparing both $^1$H NMR spectra in Figure 5a, it is immediately clear that $\text{NHC}_{20k}$ is not one of the scission products: the characteristic far downfield peak of the C2 proton is completely absent (see inset). It is known that the exact chemical shift of this proton varies for different counterions, but generally never appears below 9 ppm. In addition, the signal of the protons on the carbons adjacent to the N1 and N3 positions (around 4.2 ppm and generally much less sensitive to the type of counterion) did not recover to the original position for $\text{NHC}_{20k}$ (which is around 4.4 ppm).

In Figure 5b a zoom of the region between 4–8 ppm is given of the $^1$H NMR spectrum of the adduct $\text{NHC}_{20k} - \text{B} - \text{NHC}_{20k}$ after sonication. Comparison of the integrals values of the relevant peaks before and after sonication shows that the ratio has remained
the same. The relevant peaks that have been compared are the peaks belonging to the C4/5 protons of the imidazolium ring (labeled “a” in the ¹H NMR spectrum), the aromatic protons (“b”) and the glycolic and methylene protons adjacent to N1 and N3 (“c”). It should be noted that the initially obtained ratio of these integrals (a/b/c = 0.28/0.64/1.0) is fully consistent with the amount of monofunctional polymer adduct as obtained from GPC measurements. This observation confirms that mechanochemical scission did not take place at the NHC–isothiocyanate bond and that, in fact, the entire adduct has remained intact during the scission process.

In addition, scission experiments were performed in the presence of excess fluorescein isothiocyanate (F). Selective mechanical scission of the bond between the NHC and isothiocyanate linker would result in the formation of a free carbene NHC₂₀k which is subsequently scavenged by fluorescein isothiocyanate to form the polymer adduct F–NHC₂₀k as shown in Figure 6a. This adduct is UV active and can be identified using GC in combination with UV/Vis detection. However, the characteristic bands of the fluorescein absorption spectrum (λ_{max} = 495 nm) were not observed in the GPC trace around the retention time x_{c,2} that was expected for the low molecular weight adducts B–NHC₂₀k/F–NHC₂₀k.

Figure 5 (a) Normalized ¹H NMR spectra (in CD₂Cl₂) after sonication of NHC₂₀k–B–NHC₂₀k (blue) and the free polymer ligand NHC₂₀k (red). Inset: the C2 proton of NHC₂₀k is absent after scission. (b) Zoom of the region between 4–8 ppm of the ¹H NMR spectrum after sonication. The integrals of peaks corresponding to NHC₂₀k–B–NHC₂₀k still match their initial values (a/b/c = 0.28/0.64/1.0).
Chapter 6

Furthermore, the scission rate of $\text{NHC}_{20k}-\text{B}-\text{NHC}_{20k}$ was found to be independent of the presence of fluorescein isothiocyanate or any other scavenger for free NHCs (see Figure 6b). The NHC–isothiocyanate bond is reversible and has an extremely high equilibrium constant; therefore, recombination of the NHC and NCS end groups is expected and an increased net scission rate should be observed when recombination is suppressed in the presence of any trapping agent.

Finally, there was a complete lack of (mechano)catalytic activity in the transesterification reaction of vinyl acetate with benzyl alcohol under sonication conditions. Heating of the reaction mixture to 100 °C in the presence of $\text{NHC}_{20k}-\text{B}-\text{NHC}_{20k}$ did lead to the formation of benzyl acetate (less than 0.5%). Studying the thermal scission process by GPC showed that at 100 °C the amount of chain scission was 5–10% within one hour; in addition, the formation of (correspondingly small amounts of) imidazolium salt was confirmed by $^1$H NMR.

6.5 Conclusions

The adduct of two polymer $N$-heterocyclic carbene (NHC) ligands with a bifunctional isothiocyanate linker molecule B was successfully synthesized. Mechanochemical scission of polymer adduct $\text{NHC}_{20k}-\text{B}-\text{NHC}_{20k}$ by ultrasound was indeed possible and scission occurred close to the chain midpoint. However, the product of mechanocatalytic scission was not the desired free NHC and, therefore, carrying out mechanocatalytic transesterification was not possible using the anticipated $\text{NHC}_{20k}-\text{B}-\text{NHC}_{20k}$ mechanocatalyst.

Figure 6 (a) Reaction scheme for the proposed formation of the fluorescein-labeled polymer adduct F–$\text{NHC}_{20k}$ after ultrasound-induced scission of $\text{NHC}_{20k}-\text{B}-\text{NHC}_{20k}$. (b) Comparison of scission kinetics (assuming selective midpoint scission) in the presence of acetic acid or fluorescein isothiocyanate as trapping agent for free NHC ligands and in the absence of any trapping agent.
The exact reason why mechanochemical scission of $\text{NHC}_{20k}-\text{B}-\text{NHC}_{20k}$ does not result in the formation of free NHC and isothiocyanate is unclear. Evidently, the NHC–NCS bond is not the weakest bond along the polymer chain, that is, it is equally strong, or even stronger than the C–C and C–O bonds making up the polymer backbone under the high loading rates and forces imposed by ultrasound. The high loading rate and consequently short experimental timescale may result in a loss of selectivity of mechanochemical bond scission. Therefore, it would be interesting to see how the mechanophore behaves under lower loading rates which can be achieved in, e.g., AFM experiments. Even though it remains speculative, the selectivity of scission may be regained under these experimental conditions. The only definitive conclusion that can be drawn based on the work in this chapter, is that the polymer NHC–NCS adduct is not a good candidate for replacing the silver(I)–NHC complexes as mechanocatalysts since the NHC–NCS adduct is, at least in the current mechanochemical scheme, not a suitable mechanophore.

**Experimental section**

**General.** All reagents and solvents were used as received unless otherwise stated. For syntheses, Ammonium hexafluorophosphate (99.99%), 4-methoxyphenyl isothiocyanate (98%), lithium bis(trimethylsilyl)amide (LiHMDS, 1.0 M in THF), 2-(4-nitrophenoxy)ethanol (≥97.0%), triethylamine (≥99%) and carbon disulfide (CS$_2$; ≥99.9%) were purchased from Sigma-Aldrich (Germany). 1-ethyl-3-methylimidazolium chloride (97%), sodium hydroxide (NaOH; pellets, extra pure), palladium on charcoal (10% Pd/C), $p$-toluenesulfonyl chloride (TsCl; ≥99%) were obtained from Acros (Belgium) and 1-chloro-4-nitrobenzene (>98%) from Fluka (Switzerland). Solvents were obtained from BioSolve (The Netherlands) and of at least AR grade quality. Deuterated solvents for recording NMR spectra were obtained from Cambridge Isotope Laboratories, Inc. (United States). For the scission experiments and catalytic tests, benzyl alcohol (BnOH; anhydrous, 99.8% in a Sure/Seal™ bottle), and vinyl acetate (VAc; ≥99%) were purchased from Sigma-Aldrich (Germany). Acetic acid (HAc; AR grade) was obtained from BioSolve (The Netherlands) and fluorescein isothiocyanate (≥90%) from Fluka (Switzerland). Argon (99.999% v/v, max. 3 ppm water) was supplied by Linde (The Netherlands).

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian 400MR or Varian Mercury 400 spectrometer and chemical shifts are reported in ppm relative to TMS. Mass spectra (MALDI-TOF) were recorded on a Voyager DE Pro mass spectrometer (PerSeptive Biosystems). FT-IR spectra were taken using a PerkinElmer mass spectrometer with Universal ATR (UATR) and GC-MS analysis was performed on a Shimadzu GC-17A gas chromatograph, coupled to a Shimadzu GCMS-QP5000 mass spectrometer for detection. GPC analysis was carried out on a Shimadzu LC-10AD chromatograph equipped with refractive index and UV/
Vis detectors (Shimadzu RID-10A and Shimadzu SPD-M10A photodiode array detector), using either THF or chloroform as eluens and polystyrene (PS) as calibration standards. Molecular weights of PTHF were corrected by using a PTHF sample of known \( M_n \) \( (21.4 \text{ kg mol}^{-1}) \) and low PDI \(<1.2\) as external standard. All sonication experiments were carried out using a Sonics VC750 sonication set-up operating at 20 kHz and 30% of maximum amplitude using continuous sonication protocol.

**Synthesis of \( \alpha \)-(N-ethylimidazolium)-\( \omega \)-methoxypoly(tetrahydrofuran).** Synthesis of polymer ligands NHC\(_{7k}\) and NHC\(_{20k}\) was described in Chapters 3 and 5, respectively. The polymer ligands were freeze-dried from distilled 1,4-dioxane prior to use.

**Synthesis of model catalyst NCS–NHC.** Ion exchange from 1-ethyl-3-methylimidazolium chloride to 1-ethyl-3-methylimidazolium hexafluorophosphate was carried out using the same procedure for ion exchange as was used for the polymer imidazolium salts (Chapters 3–5). 1-ethyl-3-methylimidazolium hexafluorophosphate (256 mg, 1.0 mmol) was placed in a Schlenk round-bottom flask, suspended in dry THF (ca. 5 mL, dried and purified by passage over an alumina column) and cooled in an ice bath. 1 M LiHMDS in THF (1.2 mL, 1.2 mmol, 1.2 equiv.) was added. After addition, the ice bath was removed and the reaction mixture was allowed to warm up to ambient temperature while stirring. After ca. 30 min, a solution of 4-methoxyphenyl isothiocyanate (140 µL, 1.0 mmol, 1.0 equiv.) in dry THF (2 mL) was added. Slowly, the reaction mixture became a bit turbid and changed color from yellow to orange. After stirring for 2 h, the reaction mixture was transferred into a round-bottom flask and solvent evaporation **in vacuo**. The resulting solid residue was dissolved in dichloromethane, dried over MgSO\(_4\) and filtered to give a clear bright yellow solution. This solution was immediately filtered over an alumina plug and the plug was washed with dichloromethane (ca. 50 mL) and acetone (ca. 50 mL). After evaporation of the solvent in the combined product fractions, the product was obtained as yellow-orange oil in 85% isolated yield (235 mg, 0.85 mmol). In the course of several days to a week, the oil slowly crystallized out to form yellow crystals. These crystals were collected from the flask and used in further experiments.

\(^1\)H NMR (400 MHz, acetone-\(d_6\)): \( \delta \) 7.67 (d, 2H, Ar–H), 7.41 (d, 2H, CH=CH), 6.85 (d, 2H, Ar–H), 4.33 (q, 2H, NCH\(_2\)CH\(_3\)), 3.88 (s, 3H, NCH\(_3\)), 3.77 (s, 3H, Ar–OCH\(_3\)), 1.50 (t, 3H, NCH\(_2\)CH\(_3\)). \(^{13}\)C NMR (100 MHz, acetone-\(d_6\)): \( \delta \) 165.0, 155.7, 144.8, 124.3, 120.1, 118.0, 112.8, 54.7, 43.3, 34.3, 14.8. MALDI-TOF: Calcd for C\(_{14}\)H\(_{18}\)N\(_3\)OS 276.12 [M+H]\(^+\); Found 276.19.

**Synthesis of 1,2-bis(4-nitrophenoxy)-ethane.** The bifunctional nitro building block bNO\(_2\) was synthesized using a synthetic procedure based on Ref. 23. 2-(4-nitrophenoxy)-ethanol (915 mg, 5.0 mmol) and 1-chloro-4-nitrobenzene (953 mg, 6.0 mmol, 1.2 equiv.) were weighed and dissolved in DMSO (ca. 5 mL). Powdered NaOH (590 mg, 15 mmol, 3.0 equiv.) was added in small portions, while cooling the reaction mixture in and ice bath. After addition, the ice bath was removed and the reaction mixture was stirred overnight at ambient
temperature. The yellow precipitate that had formed was filtered off using a Büchner funnel and washed three times with water and once with ethyl acetate. The product was obtained as a light yellow powder in 54% yield (819 mg, 2.7 mmol).

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.24 (d, 4H, Ar–H), 7.02 (d, 4H, Ar–H), 4.47 (s, 4H, OCH$_2$CH$_2$O). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.3, 126.0, 114.6, 66.8. GC-MS: Calcd for C$_{14}$H$_{12}$N$_2$O$_6$ 304.07 [M$^+$]; Found 304 (47%), 166 (100%).

**Synthesis of 1,2-bis(4-aminophenoxy)-ethane.** The bifunctional nitro building block (500 mg, 1.6 mmol) was dissolved in a mixture of ethanol (15 mL) and THF (30 mL). 10% Pd/C (50 mg) was added and the vessel was placed under 40 psi hydrogen (H$_2$) atmosphere. After 45 min, the H$_2$ pressure was reduced to 32 psi and remained stable. The suspension was then filtered to remove the solid Pd/C particles and the solvent was evaporated in vacuo to give the bifunctional amine building block in as a slightly off-white powder in quantitative yield (376 mg, 1.6 mmol)

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.79 (d, 4H, Ar–H), 6.64 (d, 4H, Ar–H), 4.21 (s, 4H, OCH$_2$CH$_2$O), 3.43 (br, 4H, Ar–NH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 151.9, 140.3, 116.3, 116.1, 67.5. FT-IR: ν (cm$^{-1}$) 3403 (m), 3328 (m) (both N–H stretch). GC-MS: not observed.

**Synthesis of 1,2-bis(4-isothiocyanatophenoxy)-ethane.** The bifunctional amine building block (350 mg, 1.4 mmol) was transferred to a 3-necked round-bottom flask, placed under argon atmosphere and dissolved in THF (20 mL, dried and purified by passing over and alumina column prior to use). Triethylamine (2 mL, 14 mmol, 10 equiv.) was added through a septum. Subsequently, CS$_2$ (0.30 mL, 5.0 mmol, 3.5 equiv.) was slowly added to the reaction mixture while cooling in an ice bath. Reaction progress was monitored by FT-IR: after 2.5 h the double band around 3300 cm$^{-1}$ (N–H stretch) disappeared. The reaction mixture was cooled in an ice bath and TsCl (686 mg, 3.6 mmol, 2.5 equiv.) was added. After 1 h, aqueous 1 M HCl (35 mL) was added and the reaction mixture was extracted twice with diethyl ether (2 × 35 mL). The combined organic layers were dried over MgSO$_4$, filtered and evaporated in vacuo.

The crude product was purified by column chromatography using $n$-hexane/toluene (1:9 v/v) as eluens. The column fractions containing the product were combined and solvent was evaporated in vacuo. To the solid residue was then added $n$-hexane (ca. 5 mL) and the mixture was heated to boiling in an oil bath at 70 °C. Toluene (ca. 3 mL) and THF (ca. 5 mL) were added until the residue had dissolved. Slow cooling to room temperature afforded the bifunctional isothiocyanate building block B as white, needle-shaped crystals in 38% isolated yield after filtration (181 mg, 0.55 mmol).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.18 (d, 4H, Ar–H), 6.90 (d, 4H, Ar–H), 4.31 (s, 4H, OCH$_2$CH$_2$O). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 157.4, 127.0, 124.2, 115.5, 66.7. FT-IR: ν (cm$^{-1}$) 2121 (brs) (C=N stretch). GC-MS: Calcd for C$_{16}$H$_{12}$N$_2$O$_2$S$_2$ 328.03 [M$^+$]; Found 328 (100%), 178 (45%), 151 (58%), 134 (57%).
Synthesis of polymer adducts NHC<sub>x</sub>–B–NHC<sub>x</sub> (x = 7k or 20k). For a typical synthesis of the polymer adducts, NHC<sub>7k</sub> (140 mg, ca. 0.020 mmol) or NHC<sub>20k</sub> (400 mg, ca. 0.020 mmol) was transferred into a Schlenk round-bottom flask and dissolved in dry THF (ca. 5 mL). 1 M LiHMDS solution in THF (0.10 mL, 0.10 mmol, ca. 5 equiv.) was added and the reaction mixture was stirred for 30 min at ambient temperature under inert argon atmosphere. Then, a solution of B (3.4 mg, 0.010 mmol, 0.5 equiv.) in dry THF (0.5 mL) was added. The reaction flask was placed in a warm water bath and stirred for 5 h. The color of the reaction mixture gradually changed to yellow. After this period, the reaction mixture was filtered over alumina and flushed with dry THF to give a bright yellow filtrate. The solvent was evaporated in vacuo and the polymer was air-dried overnight. After subsequent freeze-drying from distilled 1,4-dioxane, the product was obtained in good yield (50–90%) and analyzed by ¹H NMR and GPC in THF as eluens.

¹H NMR (400 MHz, CDCl<sub>3</sub>; integrals are not given here, see Note 31): NHC<sub>7k</sub> and NHC<sub>20k</sub>: δ 7.58 (d, CH=CH), 6.99 (d, Ar–H, coupled to NHC<sub>x</sub>), 6.93 (s, Ar–H, not coupled to NHC<sub>x</sub>), 4.34 (br, NC<sub>2</sub>H<sub>3</sub> and OC<sub>H</sub><sub>2</sub>C<sub>H</sub><sub>2</sub>O), 3.2–3.6 (br, CH<sub>2</sub>CH<sub>2</sub>O), 1.4–1.6 (br, CH<sub>2</sub>CH<sub>2</sub>). GPC (in THF, versus PS and corrected for PTHF): NHC<sub>7k</sub>: M<sub>top,1</sub> = 13.4 kg mol<sup>–1</sup> and M<sub>top,2</sub> = 7.61 kg mol<sup>–1</sup>; NHC<sub>20k</sub>: M<sub>top,1</sub> = 42.1 kg mol<sup>–1</sup> and M<sub>top,2</sub> = 22.1 kg mol<sup>–1</sup> (average of two batches).

Thermal catalytic tests with model catalyst NCS–NHC. A 2.5 M stock solution of NCS–NHC (2.09 mg, 7.6 × 10<sup>–3</sup> mmol) in dry toluene (3.0 mL) was prepared. A fixed amount of this stock solution (0.5 mL) was added to a mixture of dry toluene (0.75 mL), BnOH (0.50 mL) and VAc (0.75 mL) in a sealed Schlenk tube. The reaction mixture was kept either at ambient temperature or heated to 70 ± 2 °C in an oil bath. Samples (20 µL) were taken at regular time intervals and diluted with chloroform (ca. 0.6 mL) for analysis by GC-FID.

Mechanochemical scission experiments. Polymer adducts NHC<sub>20k</sub>–B–NHC<sub>20k</sub> (ca. 60 mg, 1.5 × 10<sup>–3</sup> mmol) or NHC<sub>7k</sub>–B–NHC<sub>7k</sub> (ca. 22 mg, 1.5 × 10<sup>–3</sup> mmol) were dissolved in toluene (ca. 5 mL, dried over 4Å molecular sieves prior to use). To the mixture, Acetic acid was added (50 µL, ca. 0.90 mmol, 580 equiv.) A small fraction (ca. 1 mL) of this solution was set aside at ambient temperature or heated to 70 ± 2 °C in an oil bath. After saturation with argon, the solution was sonicated for 60 min. Samples (ca. 0.2 mL) were taken at regular time intervals. Solvent was evaporated in vacuo and the residue was dissolved in THF (ca. 0.8 mL) for analysis by GPC. GPC traces were deconvoluted using the Origin® 8.5 software package (OriginLab Co.).

Mechanochemical scission experiments in the presence of fluorescein isothiocyanate. Polymer adduct NHC<sub>20k</sub>–B–NHC<sub>20k</sub> (ca. 52 mg, 1.3 × 10<sup>–3</sup> mmol) was dissolved in toluene (ca. 3.5 mL, dried over 4Å molecular sieves prior to use). A solution of fluorescein isothiocyanate (5 mg, 1.3 × 10<sup>–2</sup> mmol, 10 equiv.) in THF (0.5 mL) was added. The resulting suspension was sonicated and analyzed in the same way as for the scission experiments with acetic acid.
**Mechanocatalytic tests.** The polymer adduct NHC$_{20k}$–B–NHC$_{20k}$ (ca. 60 mg, $1.5 \times 10^{-3}$ mmol) was dissolved in a standard reaction mixture, consisting of toluene (1.75 mL, dried over 4Å molecular sieves prior to use), VAc (0.75 mL, 8.1 mmol) and BnOH (0.50 mL, 4.8 mmol). After complete dissolution of the catalyst, the reaction mixture was transferred into a 10 mL double-jacketed glass sonication vessel placed under inert argon atmosphere and cooled to 10.0 ± 0.2 ºC using water from a recirculation thermostat bath. The reaction mixture was kept at this temperature for 20–30 minutes during which it was saturated with argon. After this period, sonication was started. Small samples were withdrawn from the reaction mixture prior to starting the sonication and at various time intervals. The samples (20 µL) were diluted with chloroform (ca. 0.6 mL) for analysis by GC-FID.

**Notes and references**

5. A. Balan, R.P. Sijbesma, unpublished results
12. S. Karthikeyan, G.M. Pawar, R.P. Sijbesma, unpublished results
26. In Chapter 2, the double Gaussian fitting equation from Ref. 4 was adapted to account for different polydispersities of the starting polymer and the scission product. In the starting polymer, however, both polymer populations have, by definition, the same polydispersity.
28. Using the data in Chapter 2, it is calculated that for non-functionalized PTHF with $M_{\text{top}} \approx 42$ kg mol$^{-1}$, the scission rate constant varies between $k_{\text{sc}} = 3.7–5.4 \times 10^{-3}$ s$^{-1}$.
30. Roughly, the ratio of mono- and bifunctional NHC–isothiocyanate adducts is 30/70% (by weight), as determined by GPC (see Table 1). The ratio between the molecular weights of the species is 1/2, hence the molar ratio between mono- and bifunctional species is roughly 45/55%. In the monofunctionalized species, $a = 2H$, $b = 8H$ and $c = 8H$; in the bifunctional species, $a = 4H$, $b = 8H$ and $c = 12H$. This results in an approximate ratio $a/b/c = 3.1/8.0/10.2 \approx 0.3/0.8/1$.
Chapter 7

Mechanocatalyst activation on single molecule level using atomic force microscopy

Abstract

The use of atomic force microscopy (AFM) for mechanochemical bond scission on the level of a single molecule is reported. Preliminary results on mechanochemical scission of a NHC–isothiocyanate adduct (NHC = N-heterocyclic carbene) using AFM show a bimodal distribution of rupture forces, with the first set of rupture events corresponding to desorption of non-specifically absorbed polymer chains on the glass surface ($F_{\text{abs}} = 0.23 \pm 0.09$ nN). The second rupture event ($F_{\text{rup}} = 0.69 \pm 0.56$ nN) indicates scission of a bond that is considerably weaker than typical covalent bonds (were several nN are expected). Although a conclusive experiment has not yet been performed, the results suggest that the NHC–NCS adduct is dissociated because the relatively low rupture force is compatible with the relatively low dissociation energy of the adduct. Furthermore, control experiments show no rupture events in the sub-nN force regime when the adduct is absent. The observed difference in outcome of mechanochemical scission of the AFM experiments compared to ultrasound-induced polymer scission are explained by the significantly longer timescale and lower force loading rates in AFM experiments.
Chapter 7

7.1 Introduction

In Chapter 1, two main aims were defined for the work described in this thesis. The first aim was to gain more insight and better understanding of the processes and mechanisms underlying mechanochemical activation of catalysts (“mechanocatalysis”). The second aim was to use this knowledge for rational design and implementation of alternative methods for mechanocatalyst activation. We were especially interested in activation of mechanocatalysts by well-defined (laminar) flows inside microfluidic channels\textsuperscript{1–3} and activation in solid state. The possibility of catalyst activation in solid state would be of particular interest for the development of truly autonomous self-healing materials.\textsuperscript{4} Alternatively, activation of mechanocatalyst molecules on the level of single molecules, \textit{e.g.} by atomic force microscopy (AFM) is of interest from a more fundamental point of view.\textsuperscript{5}

In the previous chapters, we have discussed our efforts to gain a better understanding of the physical aspects of ultrasound-induced chain scission and behavior of the supramolecular polymer chains in solution subjected to ultrasound irradiation. In this chapter, we show the preliminary results of mechanocatalyst activation on the level of a single molecule in AFM experiments. The study of receptor–ligand interactions measured on a single molecule level were reported by Florin \textit{et al.} in 1994, who studied the interaction of immobilized biotin and avidin with AFM.\textsuperscript{6} Unbinding events occurred at forces that were quantized as integer multiplicities of the single biotin–avidin rupture force (160 ± 20 pN). The first supramolecular coordination complex that was investigated with AFM is the NTA/histidine-tag coordinated to a variety of metal ions (Ni\textsuperscript{2+}, Co\textsuperscript{2+}, Cu\textsuperscript{2+} or Zn\textsuperscript{2+}) in independent research by Conti \textit{et al.}, Schmitt \textit{et al.} and Kienberger \textit{et al.} around the year 2000.\textsuperscript{7} Around the same time, Kudera \textit{et al.} reported the use of AFM for the first studies on force-induced scission of a fully synthetic supramolecular metal–ligand complex.\textsuperscript{8} Their strategy consisted of immobilization of \textit{α}-carboxy-\textit{ω}-terpyridine poly(ethylene glycol) (PEG) polymers on amine-functionalized AFM cantilever and glass using EDC coupling of the NHS-activated ester. Subsequently, the contact between cantilever and substrate was established by \textit{in situ} reduction of Ru\textsuperscript{3+} to Ru\textsuperscript{2+}, which led to the spontaneous conversion of the corresponding terpyridine monocoordinated complexes to biscoordinated complexes. Upon retraction of the AFM cantilever, rupture of the ruthenium(II)–bis(terpyridine) complexes was observed with a peak rupture force at 95 pN and, additional rupture events at 171 pN and 253 pN (corresponding to two and three simultaneous rupture events, respectively).

In the years that followed, AFM was used by several groups to determine bond
strengths and equilibrium constants of reversible interactions. For example, Craig and co-workers were able to determine dissociation kinetics of palladium(II) pincer complexes with pyridine ligands in DMSO by AFM single molecule experiments. After correction for the presence of external force, the dissociation rate constants were in excellent agreement with values obtained from dynamic NMR experiments and oscillatory rheology measurements on corresponding poly(4-vinylpyridine) (PVP) organogels. In several works by Vancso and co-workers, AFM was used to study thermodynamics and kinetics of β-cyclodextrin (β-CD) supramolecular host–guest complexes and hydrogen-bonded systems. For the hydrogen-bonded systems, the researchers developed a method that allowed the determination of all relevant parameters (rupture force, bond lifetime at zero force, etc.) for multiple uncooperative bond rupture events from a single experiment using only one loading rate. For the β-CD host–guest complexes they found that the rupture force for all guest molecules was independent of the loading rate in AFM experiments. They claim that this is because binding/unbinding events are very fast on the AFM timescale so that the system is always under thermodynamic equilibrium. When comparing the force-induced dissociation of different guest molecules, they found that the trend in rupture forces correlates well with the free energy of binding for each host–guest systems as determined by calorimetry.

Here, we present the design, synthesis and surface immobilization of an amine-functionalized imidazolium salt and explorative experiments on the scission of its corresponding adduct with an aromatic isothiocyanate (which was investigated in more detail in Chapter 6) by using AFM. In particular, we are interested to see how the outcome of mechanochemical scission is related to the experimental timescale and corresponding force loading rates. When comparing the force loading rates in AFM with the equivalent strain rates obtained in ultrasound experiments, we realized that they are six orders of magnitude lower for AFM than for ultrasound, while experimental timescale is at least a factor 10^5 longer. The Bell–Evans theory predicts that dissociation rates of chemical bonds under force strongly depend on the timescale of the experiment. Hence, bond strength under mechanical force may strongly depend on experimental timescale and loading rate; for example, when comparing mechanochemical scission of C–N and C–C bonds, it was found that the former was stronger at experimental timescales below ca. 1 s, whereas it became weaker than a C–C bond at longer experimental timescales. Based on the timescale dependence, we may expect a different outcome of mechanochemical scission of the NHC–NCS adduct in AFM experiments compared to the results obtained in the ultrasound experiments in Chapter 6, where it was shown that the NHC–NCS bond was not the weakest bond within the system.
7.2 Synthesis of an amine-functionalized imidazolium salt

The synthesis of 1-ethyl-3-(11-ammonioundecyl)-imidazolium hexafluorophosphate (NH$_2$–NHC.PF$_6$), starting from 11-bromoundecanol, is shown in Figure 1. Steps (i)–(iii) are straightforward and partially based on literature procedures; coupling reactions of N-ethylimidazole, step (iv), have been carried out frequently in our group and proceeded smoothly as well. However, it was difficult to remove the excess N-ethylimidazole from the product, even though washing with $n$-hexane usually works quite well. Since only a slight excess was used and since the remaining N-ethylimidazole is not expected to interfere with subsequent reaction steps of surface functionalization, we decided to carry out ion exchange (step (v)) and deprotection of the amine group (step (vi)) without further purification.

Work-up after deprotection of the amine group was not straightforward with this amine: literature procedures suggest precipitation of the amine as its hydrochloric salt from acidic water after removal of the organic solvents. However, since NH$_2$–NHC.PF$_6$ is essentially an ionic liquid, it did not precipitate out of solution and could not be dried efficiently owing to its hygroscopic character. Extraction of the aqueous layer with CH$_2$Cl$_2$ was not successful: even though the product was obtained from the organic layer, it was only in low yields. Drying the remaining water layer in vacuo yielded the remaining amount of product, but partially degraded as a result of the elevated temperatures (ca. 60 °C) to which it was exposed during water evaporation. An optimized work-up procedure was devised where only a slight excess of hydrazine hydrate was used for deprotection. The remaining hydrazine was
then removed by precipitation of its hydrochloric salt after addition of aqueous HCl. After filtration, evaporation of the organic solvent in vacuo was possible at moderate temperature (below 40 °C) and the remaining yellow liquid was diluted in distilled 1,4-dioxane and freeze-dried to give the final product as a yellow waxy solid.

### 7.3 Surface functionalization of AFM glass substrates

In the AFM experiments, standard microscope cover slips were used as AFM substrates. After a pretreatment step with UV/ozone, they were functionalized with epoxy groups by incubation in a solution of (3-glycidyloxypropyl)trimethoxysilane in ethanol/water, followed by thermal curing at 95 °C (see Experimental Section for more details). A schematic overview of the subsequent steps in surface functionalization is shown in Figure 2. In the first step, the epoxy-functionalized glass slide was incubated for several days in a solution of an amine-functionalized imidazolium salt (NH₂–NHC.PF₆) in DMSO, containing a few drops of HCl. After washing the glass slide with ethanol to remove any unbound NH₂–NHC.PF₆, the glass slide was immersed in n-butylamine to passivate the unreacted epoxy groups. Subsequently, the glass slide was divided in two pieces. One of these pieces was functionalized with p-phenylene diisothiocyanate (following steps (ii)–(iii) in Figure 1; this substrate is henceforth denoted as substrate S1), while the other piece was kept for control experiments (substrate S2).

To prove surface functionalization of S1 with NCS groups, substrates S1 and S2 were brought in contact with an amine-functionalized dye (Atto 633, λ_{ex} = 629 nm, λ_{em} = 657 nm). After incubation, the substrates were washed and analyzed with fluorescence microscopy. Images of all substrates are shown in Figure 3. In Figure 3a, substrate S2 does not show fluorescence, indicating that the surface was completely

![Figure 2](image-url) Schematic overview of surface functionalization: (i) NH₂–NHC.PF₆, DMSO, HCl, 4–7 d, r.t.; (ii) KOTBu, THF, Ar, 30–60 min, r.t.; (iii) p-phenylene diisothiocyanate, THF, Ar, 30–60 min, r.t.
passivated after the reaction with \(n\)-butylamine. As a consequence, the fluorescence from substrate S1 confirms the presence of free NCS groups on this part of the glass surface which are available to bind the amine-functionalized dye. As an additional control experiment, parts of the same substrates were reacted with Atto 633 where the amine group was deactivated by reaction with excess of NHS-activated ester. Non-specific physisorption of the dye molecules on substrates S1 and S2 could be excluded based on these control experiments because fluorescence is absent for both substrates when brought in contact with the deactivated dye (Figure 3b).

7.4 Single molecule mechanochemical scission experiments using AFM

The single molecule mechanochemical scission experiment of the NHC–NCS adduct was carried out using a surface construct as shown schematically in Figure 1. However, to allow comparison of the AFM results with the results obtained in ultrasound experiments, 1,2-bis(4-isothiocyanatophenoxy)-ethane (\(b\)NCS) was used as linker (see Chapter 6). The AFM cantilever was functionalized with amine groups by incubation with, subsequently, \((3\)-glycidyloxypropyl)trimethoxysilane and polyallylamine (PA, average \(M_w \approx 65\) kg mol\(^{-1}\)). PA was chosen to maximize the number of available amine groups on the cantilever; since the coupling reaction between amine and isothiocyanate was found to be slow, this was a requirement for having a high enough success rate in AFM experiments. The AFM experiments were carried out in benzyl alcohol (BnOH) and were performed by establishing a thiourea link between the amine-functionalized cantilever and NCS groups on the glass surface during a 3 s waiting period (see Figure 4a). Subsequently, the cantilever was retracted from the surface at a constant retraction speed \(\dot{x} = 0.2\ \mu\text{m s}^{-1}\). At this
retraction speed, it was possible to obtain a significant number of successful binding/rupture events during the AFM experiment. A characteristic force–displacement curve is shown in Figure 4b. Predominantly, single rupture events were observed, because thiourea formation is slow. Therefore, the formation of more than one link between surface and cantilever during the 3 s waiting time is rare. Multiple ruptures were sometimes encountered, but these were filtered out by manual sorting of the force–displacement curves of successful binding/rupture events. For verification of single chain unbinding events, the part of the curve corresponding to the elongation of the polymer chain is fitted with either the standard freely jointed chain (FJC) or worm-like chain (WLC) model. This way, force–displacement curves of 767 successful experiments (out of a total 7836 pulling experiments, giving a success rate of ca. 10%) were identified and analyzed. The distribution of the observed rupture forces ($F_{rup}$) is plotted in the histogram of Figure 4c.

Two control experiments were carried out to account for events of non-specific physisorption of the PA on the surface (experiment C1) and to exclude scission of

![Figure 4](image_url)

**Figure 4** (a) Schematic representation of AFM surface constructs during approach, binding and retraction of the AFM cantilever. (b) Typical force–displacement curve obtained in the AFM experiments. (c) Histogram showing the rupture force distribution obtained in the AFM experiments (based on 767 successful rupture events) showing $F_{rup} = 0.69 \pm 0.56$ nN (mean ± standard deviation).
any covalent bonds along the PA backbone or scission of the thiourea bonds (C2). For control experiment C1, the epoxy-functionalized glass slides were incubated with NH$_2$–NHC$_2$PF$_6$ only (step (i) in Figure 1); steps (ii)–(iii) were not carried out, so that there were no free NCS groups on the glass surface during the AFM experiment. For control experiment C2, commercial amine-coated glass slides were functionalized with NCS groups by incubation with p-phenylene diisothiocyanate in BnOH for 1.5 days.

The histogram in Figure 4b shows a bimodal distribution of rupture forces during the AFM experiment. Control experiment C1 confirmed that the rupture events at forces below ca. 0.4 nN are due to non-specific absorption on the glass surface (Figure 5a). In these experiments the success rate was around 1% (262 rupture events in 22483 pulling experiments), which is significantly lower than the success rate of 10% which was observed in the AFM experiments with NCS groups present. A double Gaussian distribution function was fitted to the data set in Figure 4b. The first component of this fit was fixed using the fitting parameters of a single Gaussian fit to the data set for non-specific absorption in Figure 5a ($F_{\text{abs}} = 0.23 \pm 0.09$ nN), whereas the second component gives a rupture force $F_{\text{rup}} = 0.69 \pm 0.59$ nN for the actual rupture event of the polymer linker.

It is immediately clear that the observed rupture force is much lower than what would be expected for scission of a covalent bond; rupture forces up to several nN have been reported for these bonds in literature.$^7$ Control experiment C2 clearly supports this statement by the absence of rupture events below 1 nN when the NHC–NCS adduct is not present in the surface construct (except for those corresponding to the non-specific interactions between PA and the surface, see Figure 5b). It was not

![Figure 5](image_url)

**Figure 5** (a) Histogram of control experiment C1 showing the rupture force distribution associated with non-specific absorption on the glass substrate (262 successful events) with $F_{\text{abs}} = 0.23 \pm 0.09$ nN (mean ± standard deviation). (b) Histogram of control experiment C2 showing only rupture events which correspond to non-specific absorption and rupture events at force above 1 nN (total: 273 successful events).
possible to fit the data of control experiment C2 accurately, due to the low number of events and broad distribution of rupture forces. However, we can conclude that the main rupture event that we have observed in AFM experiments is definitely not due to scission of (i) C–C backbone bonds within the PA polymer chain; (ii) dissociation of the thiourea groups or (iii) surface detachment of the silane bonds from the glass slide. This implies that the rupture events must take place at the \( \text{NH}_2-\text{NHC} \) mechanophore unit. This result is in clear contrast to the outcome of ultrasound-induced scission experiments as described in Chapter 6. Apparently, the reduction in strain rates as obtained in AFM experiments, and the increase in experimental timescale, has significantly reduced the bond strength of one of the mechanophore bonds. In ultrasound, these bonds are of equal or higher strength as the C–C backbone bonds of PTHF, but in AFM experiments scission is observed in the sub-nN force regime. An estimate of the equivalent strain rates in the present AFM experiments is obtained as follows: when a polymer chain is elongated from its original contour length \( L_0 \) to a length \( L \), its elongation \( \varepsilon \) is defined as

\[
\varepsilon = \frac{L - L_0}{L_0}
\]  

(1)

Taking the derivative of Equation (1) gives the relationship between rate of elongation and the (equivalent) strain rate \( \dot{\varepsilon} \):

\[
\dot{\varepsilon} = \frac{d\varepsilon}{dt} = \frac{1}{L_0} \frac{dL}{dt}
\]  

(2)

Where the rate of elongation equals the retraction speed of the cantilever, by definition, \( i.e., \frac{dL}{dt} = \dot{x} \). If we use Equation (2) with \( \dot{x} = 0.2 \ \mu m \ s^{-1} (= 200 \ nm \ s^{-1}) \) and \( L_0 \approx 10^2-10^3 \ nm \), the (equivalent) strain rate in these AFM experiments is \( \sim 10^{-1} \ s^{-1} \), which is about six orders of magnitude lower than the strain rates in ultrasound experiments. We propose that the most likely candidate for such a strong dependence of rupture force is indeed the NHC–NCS adduct bond, since this bond has a dynamic character, as emphasized earlier. However, we do realize that more experimental evidence is required in order to confirm this statement. In this context, it may be especially interesting to look at the loading rate dependence of the rupture force. However, here we are limited by the design and specifications of the experimental set-up. With the current set-up, and using the current experimental conditions, we can only increase the loading rate by one order of magnitude (to \( \sim 2 \ \mu m \ s^{-1} \)), which is probably a too small range for obtaining a data set that shows quantitative trends in loading rate dependence of the rupture force.
7.5 Conclusions and outlook

A significant different outcome for mechanochemical scission of a polymer chain, containing a NHC–isothiocyanate adduct bond was obtained in AFM experiments, compared to the results that were obtained earlier by using ultrasound (Chapter 6). In ultrasound experiments, we have confirmed that scission of the polymer chain occurred along the PTHF polymer backbone instead of at the desired NHC–NCS adduct bond. However, in AFM experiments, preliminary results strongly suggest scission of the NHC–NCS mechanophore at rupture forces well below those of covalent bonds. The main difference between both experimental schemes is their timescale and the imposed strain rates on the molecule upon elongation. We speculate that, on the timescale of AFM experiments (0.1–1 s), the difference in bond strength between the coordinative NHC–NCS bond and bonds in the polymer backbone is much more pronounced than in the case of the microsecond timescales attained in ultrasound experiments. This could lead to a dramatic increase—or maybe even a complete reversal—in mechanochemical bond scission selectivity. To the best of our knowledge, this would be the first comparison made of the use of two individual experimental techniques, leading to a fundamentally different outcome of the mechanochemical scission event. However, we do realize that, at this moment, we are not able to define the rupture site in AFM experiments more specifically and that conclusions should be drawn with care. Our current efforts are aimed at confirming proposed dissociation of the NHC–NCS adduct by demonstration of mechanocatalytic activity after AFM-induced rupture. This is aimed for by using a combined AFM-TIRF (TIRF = total internal reflection fluorescence) set-up: if free NHCs are indeed the main product of mechanochemical scission, their formation can be proven by the emergence of fluorescence upon hydrolysis of fluorogenic starting material such as fluorescein diacetate (Figure 6).

If we can indeed demonstrate that the NHC–NCS adduct bond is broken under the influence of mechanical force, it is the first time that an alternative force method is successfully applied for mechanocatalyst activation. The use of single molecule force spectroscopy opens up new and exciting possibilities to study the mechanocatalyst activation process in more detail on a fundamental level, something which is already well-established for other mechanopores and supramolecular host–guest systems. However, surface chemistry will remain a limiting factor in the choice of mechanocatalytic systems for this purpose. Mainly, all functionalization steps should be fully compatible with the mechanocatalyst systems, which may be very sensitive organometallic complexes. The use of the silver(I)–NHC complex in AFM experiments will be non-trivial owing to the high structural dynamics of
this complex; in addition, the preparation of the complex is a heterogeneous, three-phase reaction (organic/water/solid) that is clearly not compatible with surface functionalization strategies.

To conclude, further studies on mechanocatalyst activation using single molecule force spectroscopy and in solid state are recommended for the future. Where the first technique is very useful for studying mechanocatalyst activation on a fundamental level, the latter application is of high interest as the real advantageous application of mechanocatalysis lies in its use in truly autonomous self-healing materials.

**Acknowledgements**

All surface functionalization and AFM experiments reported in this chapter were carried out by M.J. Jacobs from the Institute for Molecules and Materials (IMM, Radboud Universiteit Nijmegen). M.J. Jacobs and Dr. K. Blank are gratefully acknowledged for carrying out and evaluating the experiments, the fruitful discussions and collaboration on this project.

**Experimental section**

**General.** All reagents and solvents were used as received unless otherwise stated. For syntheses, 11-bromoundecanol (98%), potassium phthalimide (98%), triethylamine (≥99%), lithium bromide (LiBr, ≥99%), N-ethylimidazole (99%), ammonium hexafluorophosphate (99.99%), and hydrazine hydrate (98%) were purchased from Sigma-Aldrich (Germany); p-toluenesulfonyl chloride (TsCl; ≥99%) was purchased from Acros (Belgium). Solvents were obtained from BioSolve (The Netherlands) and of at least AR grade quality. Deuterated
solvents for recording NMR spectra were obtained from Cambridge Isotope Laboratories, Inc. (United States). $^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian 400MR or Varian Mercury 400 spectrometer and chemical shifts are reported in ppm relative to TMS. Mass spectra (MALDI-TOF) were recorded on a Bruker Autoflex Speed mass spectrometer. For AFM experiments, (3-glycidyloxypropyl)trimethoxysilane ($\geq 98\%$), potassium tert-butoxide (KO$t$Bu; 95%), $p$-phenylene diisothiocyanate (98%), polyallylamine (PA, $M_w \approx 65$ kg mol$^{-1}$; 20% (w/w) solution in water) and benzyl alcohol (BnOH, anhydrous, 99.8% in a Sure/Seal™ bottle) were obtained from Sigma-Aldrich (Germany). Standard microscope cover slips or commercially available amine-coated glass slides (obtained from Schott Nexterion) were used as substrates.

2-(11-hydroxyundecyl)-isoindoline-1,3-dione. 11-bromoundecanol (10.0 g, 39.8 mmol) and potassium phthalimide (11.0 g, 59.4 mmol) were suspended in dry DMF (80 mL) and stirred overnight at 130 °C. The hot reaction mixture was filtered off and the filtrate was subsequently precipitated in aqueous 0.5 M HCl (150 mL). The precipitate was filtered off and obtained as a wet and light yellow powder. This powder was dissolved in ethyl acetate and washed subsequently with 0.5 M HCl solution, demineralized water and brine (80 mL for each portion). The aqueous layer was washed again with ethyl acetate (100 mL) and the organic layers were combined. After drying over MgSO$_4$, solvent was evaporated in vacuo yielding the product as a white powder in 86% isolated yield (11.0 g).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.84 (m, 2H, Ar–$H$), 7.71 (m, 2H, Ar–$H$), 3.67 (t, 2H, C$_2$H$_2$–Phth), 3.64 (t, 2H, C$_2$H$_2$–OH), 1.67 (m, 2H, CH$_2$), 1.56 (m, 2H, CH$_2$), 1.32 (m, 6H, C$_2$H$_2$), 1.27 (m, 8H, C$_2$H$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.5, 133.8, 132.2, 123.1, 70.7, 38.1, 32.8, 29.5, 29.4, 29.3, 29.1, 28.6, 26.8, 25.7.

2-(11-bromoundecyl)-isoindoline-1,3-dione. The product from the previous step (9.80 g, 30.8 mmol) and NEt$_3$ (7.5 mL, 54 mmol) were dissolved in CH$_2$Cl$_2$ (80 mL) and then cooled to 0 °C in an ice/water bath. TsCl (8.00 g, 42.0 mmol) were added in small portions over a period of 10 min while stirring. The reaction mixture was left at 0 °C for 1 h after which the ice/water bath was removed and the mixture was allowed to warm up to ambient temperature. The reaction mixture was stirred overnight at ambient temperature. Work-up was done by washing twice with aqueous 0.5 M HCl (60 mL each) and once with brine (60 mL). The aqueous layer was washed with CH$_2$Cl$_2$ (60 mL) and the combined organic layers were dried over MgSO$_4$ and evaporated in vacuo to yield the crude product as a orange-brown oil. Recrystallization from methanol (40 mL) afforded the tosylate intermediate as a waxy solid in 81% yield (11.8 g).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (m, 2H, Ar–$H$), 7.78 (d, 2H, Ar–$H$), 7.72 (m, 2H, Ar–$H$), 7.34 (d, 2H, Ar–$H$), 4.01 (t, 2H, CH$_2$–OTs), 3.67 (t, 2H, CH$_2$–Phth), 2.45 (s, 3H, Ar–CH$_3$), 1.68–1.59 (m, 4H, CH$_2$), 1.31–1.20 (m, 14H, CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.5, 144.6, 133.8, 133.3, 132.2, 129.9, 129.8, 129.6, 127.9, 123.1, 70.7, 38.1, 29.4, 29.3, 29.1, 28.9, 28.8, 28.6, 26.8, 25.3, 21.6.
Mechanocatalyst activation on single molecule level using AFM

The tosylate intermediate (8.00 g, 17.0 mmol) was dissolved in acetone (50 mL) and LiBr (3.00 g, 34.5 mmol) was added. The reaction mixture was stirred over the weekend at ambient temperature. The precipitate was filtered off and the solvent evaporated in vacuo. The residue was dissolved in CH₂Cl₂ (40 mL) and washed once with brine (40 mL). The organic layer was dried over MgSO₄ and evaporated to yield the bromide as a brown liquid that slowly crystallizes. The product was obtained in 93% yield (6.0 g).

¹H NMR (400 MHz, CDCl₃): δ 7.83 (m, 2H, Ar–H), 7.70 (m, 2H, Ar–H), 3.67 (t, 2H, CH₂–Phth), 3.40 (t, 2H, CH₂–Br), 1.85 (m, 2H, CH₂), 1.67 (m, 2H, CH₂), 1.43–1.27 (m, 14H, CH₂).

¹³C NMR (100 MHz, CDCl₃): δ 168.5, 133.8, 132.2, 38.1, 34.1, 32.8, 29.4, 29.4, 29.1, 28.7, 28.6, 28.2, 26.8.

1-Ethyl-3-(11-(1,3-dioxoisoindolin-2-yl)undecyl)-imidazolium hexafluorophosphate.

The product from the previous step (5.70 g, 15.1 mmol) and N-ethylimidazole (1.65 mL, 17.1 mmol) were dissolved in toluene (50 mL) and stirred overnight at 100 °C. Overnight, the dark brown oil-like product precipitated out of the reaction mixture. The supernatant toluene layer was decanted while still hot and the last amount of solvent was evaporated in vacuo. The resulting viscous oil was washed twice by stirring with n-hexane (30 mL) at 50 °C. The n-hexane layers were decanted and the oil was dried further in vacuo to give the bromide salt.

Ion exchange to hexafluorophosphate (PF₆⁻) counterion was performed by stirring the all the bromide salt with ammonium hexafluorophosphate (3.05 g, 18.7 mmol) in methanol for 3 h at ambient temperature. The methanol was evaporated and the residue was suspended in CH₂Cl₂. The insoluble salts were filtered off and the solvent was evaporated in vacuo giving the PF₆⁻ salt as a brown viscous oil in 70% isolated yield (5.8 g). From the ¹H and ¹³C NMR spectra it is clear that there is still a small amount of N-ethylimidazolium salt present after work-up. It is particularly difficult to remove; since this does not interfere with any subsequent reaction step and/or surface immobilization, it was decided to use this material without additional purification. Peaks corresponding to this compound have been omitted in the NMR peak list below.

¹H NMR (400 MHz, CDCl₃): δ 8.56 (s, 1H, NCHN), 7.82 (m, 2H, Ar–H), 7.72 (m, 2H, Ar–H), 7.36/7.31 (d, 2H, CH=CH), 4.24 (q, 2H, NCH₂CH₃), 4.15 (t, 2H, NCH₂C), 3.66 (t, 2H, CH₂–Phth), 1.86 (m, 2H, CH₂), 1.65 (m, 2H, CH₂), 1.55 (t, 3H, NCH₂CH₃), 1.37–1.12 (m, 14H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 133.8, 132.9, 123.1, 123.1, 122.1, 122.0, 50.4, 45.3, 38.0, 29.9, 29.3, 29.3, 29.2, 29.1, 28.8, 28.5, 26.8, 26.1, 15.0. MALDI-TOF: Calcd for C₂₄H₃₄N₃O₂ 396.26 [M–PF₆⁺]; Found 396.28.

1-Ethyl-3-(11-ammonioundecyl)-imidazolium hexafluorophosphate (NH₂–NHC.PF₆⁻).

Part of the product of the previous step (1.16 g, max. 2.14 mmol) was transferred into a 100 mL round-bottom flask. THF and ethanol were added (both 20 mL) and the oil was dissolved in the mixture. Hydrazine hydrate (50–60 % w/w in water) was added (0.50 mL, ca. 8 mmol) and the solution was stirred overnight at ambient temperature. The next day, the precipitate was filtered off and 37 % HCl solution in water (ca. 2 mL) was added slowly to the filtrate, leading to precipitation of the hydrazine as it hydrochloric salt. After filtration, the filtrate
was evaporated in vacuo. Care was taken that the temperature did not exceed 30 °C during evaporation. The result was a clear yellow aqueous suspension of the product that was diluted with distilled 1,4-dioxane and freeze-dried to give the final product as a waxy yellow solid in 0.60 g isolated yield. The percentage yield is estimated to be ca. 60%, but could not be determined more precisely because N-ethylimidazolium salt was still present.

$^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 8.95 (s, 1H, NC$\text{H}_2$N), 7.63 (d, 2H, CH$\text{H}=$CH), 4.26 (q, 2H, NC$\text{H}_2$CH$_3$), 4.20 (t, 2H, NCH$_2$CH$_3$), 2.91 (m, 2H, CH$_2$–NH$_2$), 1.89 (m, 2H, CH$_2$), 1.63 (m, 2H, NCH$_2$CH$_3$), 1.54 (t, 3H, NCH$_2$CH$_3$), 1.40–1.29 (m, 14H, CH$_2$).

$^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 134.1, 123.8, 123.4, 50.9, 46.1, 40.8, 31.1, 30.5, 30.4, 30.4, 30.2, 30.1, 28.6, 27.4, 27.3, 15.6. MALDI-TOF: Calcd for C$_{16}$H$_{32}$N$_3$ 266.26 [M–PF$_6$]$^+$; Found 266.35.

**General procedure for surface functionalization.** Glass slides were activated by UV/ozone treatment for at least 30 min. The activated slides were immersed in a 2% (v/v) solution of (3-glycidyloxypropyl)trimethoxysilane in ethanol/MilliQ water (ca. 9:1 (v/v)) for 30 min and washed subsequently with ethanol and MilliQ water. After drying the slides in a N$_2$ flow, they were cured at 95 °C for 1 h. The epoxy-functionalized substrates were incubated for 4–7 days at room temperature in a solution of NH$_2$–NHC.$\text{PF}_6$ in DMSO to which a few drops of aqueous HCl solution were added. After washing with ethanol and drying under N$_2$ flow, the substrate was immersed for 30–60 min in a solution of KO$_2$Bu in dry THF under argon atmosphere. A solution of $\delta$NCS in dry THF was added and allowed to react with the free NHCs on the glass surface for 30–60 min. After an additional cleaning step by washing with THF and ethanol, the NCS-functionalized substrate was ready to use in AFM experiments.

**Control experiments of surface functionalization using Atto 633 dye.** The Atto 633 stock solution (1 mg mL$^{-1}$ in DMSO) was diluted 1000 times in toluene. For deactivating the amine group, 10 equivalents of NHS-activated ester (BCN–NHS) was added to part of this solution and allowed to react for 1 h. The coverslip pieces were then incubated in either of the dye solutions for 1 h at room temperature. Fluorescence of the glass slides was then imaged in a microarray scanner.

**General procedure for cantilever functionalization.** The AFM cantilever was activated by UV/ozone treatment for at least 30 minutes followed by incubation in neat (3-glycidyloxypropyl)trimethoxysilane for 1 min. After cleaning the cantilever with toluene and MilliQ water, followed by removal of the liquid using filter paper, the cantilever was cured at 95 °C for 30 min. Subsequently, the cantilever was immersed in a solution of PA in a high ionic strength buffer for 1–3 days before it was ready to use.

**General procedure for AFM experiments.** The sample substrate and PA-functionalized cantilever were mounted into the AFM (JPK Force Robot) and the sample chamber was filled with BnOH. Subsequently the cantilever was allowed to equilibrate in BnOH for a period of at least 2 h. The spring constant of the cantilever (MLCT-E) was tuned according to the “Viscous ThermalTune Method”. The AFM experiments were carried out using a constant
retraction speed of 0.2 µm s⁻¹ and a waiting time at the surface of 3 s. These conditions assured a significant number of successful events during the experiment.

Notes and references

9. F.R. Kersey, W.C. Yount, S.L. Craig, *J. Am. Chem. Soc.* **2006**, 128, 3886–3887; the relaxation rates of PVP organogel networks that were cross-linked with bifunctional Pd(II) pincer complexes were found to be similar to the observed dissociation rate kinetics of the model complexes, see: W.C. Yount, D.M. Loveless, S.L. Craig, *J. Am. Chem. Soc.* **2005**, 127, 14488–14496
15. For preliminary tests and proving surface functionalization, the commercially available p-phenylene diisothiocyanate was used. In the actual AFM and control experiments C1 and C2 1,2-bis(4-isothiocyanatophenoxy)-ethane was used. The synthesis and characterization of this compound was reported in Chapter 6.
Two principal aims were set for the work described in this thesis: (i) to gain a better understanding of the fundamental processes and mechanisms underlying mechanochemical activation of (polymer) mechanocatalysts and (ii) to use this knowledge for a rational design and development of alternative activation methods for these mechanocatalysts, next to ultrasound-induced polymer scission.

Through studying the behavior of silver(I)–NHC supramolecular polymer chains in solution under the influence of force, better insights were obtained in the physical aspects of the coil-to-stretch transition of these polymers. These studies, combined with a computational study that resulted in the construction of a potential energy diagram of the Ag–C bond under force, unambiguously showed that the conditions in typical ultrasound experiments match the requirements for mechanochemical bond scission in the silver(I)–NHC supramolecular polymers (Chapter 4). It was calculated that the strong reduction in limiting molecular weight for mechanochemical chain scission compared to covalent PTHF was entirely due to the presence of a weak metal–ligand coordination bond.

The formation of radicals and other impurities as a result of thermal sonochemical reactions within the hotspots of collapsing cavitation bubbles in ultrasound does not have a significant effect on the mechanochemical scission and activation of mechanocatalysts, as was confirmed by the work in Chapter 3. However, the concentration dependence of mechanocatalyst activity of the silver(I)–NHC catalyst in transesterification reactions was found to be a direct result of competition between ultrasound-induced mechanocatalyst activation and deactivation of the active catalyst species by acidic impurities formed as a result of such thermal reactions (Chapter 5). Not only have these findings further confirmed the true mechanochemical nature of catalyst activation, they also constitute an important guideline for future work using ultrasound to carry out mechanochemical transformations. These findings show that it is crucial to consider the occurrence of undesired sonochemical side reactions and they provide adequate methods to prevent them when required.

Based on this, we can conclude that the work in this thesis has successfully accomplished the first aim: a better and more detailed understanding was obtained of what exactly happens when mechanocatalyst solutions are exposed to ultrasound and how the mechanocatalyst activity depends on the experimental conditions. One remarkable insight that was gained in the course of this thesis work, is that not every latent catalyst can be turned into an active catalyst by force. This was observed
while studying the mechanochemical scission and potential mechanocatalytic activity of NHC–isothiocyanate adducts in Chapter 6. These studies revealed that mechanochemical activation of bonds is indeed fundamentally different from thermal activation. In some cases, mechanochemistry allows certain chemical transformations that cannot be achieved thermally. However, in the case of the NHC–isothiocyanate adducts, it was found that it is not possible to break the C–C bond between the NHC and isothiocyanate by ultrasound, although the adduct is reversibly dissociated by heating (although the equilibrium constant for dissociation is extremely high, $K_{eq} \sim 10^{14} \text{M}^{-1}$ at 25 °C).

A number of projects were initiated towards accomplishing the second aim of this thesis: design and implementation of alternative activation techniques. Promising results obtained towards AFM single molecule mechanocatalyst activation experiments are reported in Chapter 7 of this thesis, and AFM will be further explored in the near future. The AFM experiments highlight the importance of strain loading rates on the outcome of mechanochemical scission processes. Finally, activation of polymer mechanocatalyst complexes by well-defined shear and/or extensional forces in microfluidic channels was explored in the context of this thesis, but without any success. As a result of the small dimensions and high surface-to-volume ratios of microfluidic devices, all liquid flows inside these devices exists as well-defined (laminar) flows. The mechanochemical scission of high molecular weight polymers using these well-defined flows had already been demonstrated in literature, and it was anticipated that this same principle could provide a good platform for carrying out mechanocatalysis in a more controlled way compared to the use of ultrasound. Both quasi-steady state flows (flows having a stagnation point, e.g., inside cross-slot devices) and transient flows through contraction zones within (micro)fluidic channels were considered for this purpose. However, it was concluded that the critical strain rate for coil-to-stretch transition which is required for the relatively low molecular weight (supramolecular) PTHF chains that are used as mechanocatalysts, cannot be obtained in any of these typical microfluidic devices. The maximum strain rates that can be practically attained in a cross-slot or contraction zone microfluidic device are $\sim 10^4 \text{s}^{-1}$ and $\sim 10^5 \text{s}^{-1}$, respectively. This is still two or three orders of magnitude below the critical strain rate that was calculated for the typical mechanocatalysts used in this work based on their relaxation times ($\lambda_0 = 10^{-6}–10^{-7} \text{s}$). In this respect, it should be noted that the only examples in literature that we are aware of, where mechanochemical polymer scission is achieved in a microfluidic devices use very high molecular weight polymer samples (with molecular weight exceeding 100 kg mol$^{-1}$) or biomacromolecules which have a much higher structural rigidity (resulting in longer relaxation times). Furthermore, even if mechanocatalyst activation could be achieved in microfluidic devices, the corresponding flow rate would be extremely
high. High flow rates, in turn, significantly decrease contact time of the solution inside the microfluidic reactor device, which severely limits the efficiency of the proposed microreactor (in terms of reactant conversion per pass).

In conclusion, the work described in this thesis has contributed to a better understanding of the fundamental processes and mechanisms underlying mechanochemical activation of catalysts and it has demonstrated an alternative approach for mechanocatalyst activation. However, it has also pointed out some limitations and non-trivial results that should be taken into account in mechanocatalyst (experiment) design. All these results are a good basis for future studies in the field of mechanocatalysis and mechanochemistry in general. These future efforts should aim for expanding the mechanochemistry “toolbox” that we have currently available. New mechanocatalysts should be developed, which will open up a new set of mechanocatalytic reactions that can be performed with them. In addition, the physical insights that we have obtained in this work, together with the promising results from preliminary experiments, encourage further studies on alternative activation methods, in particular single molecule force spectroscopy and mechanocatalysis in solid state materials.
Mechanochemical activation of latent N-heterocyclic carbene catalysts

The use of mechanical forces to activate chemical bonds and carry out chemical transformations is called “mechanochemistry”. Mechanochemistry is an alternative method for the activation of chemical reactions, next to activation by heat or by means of (photo)chemical stimuli. Although being discovered centuries ago, mechanochemistry recently experiences a strong revival. It has been shown that mechanochemically activated reactions may proceed via different energetic pathways that result in different reaction products compared to their thermal analogues. In this thesis, the use of mechanical forces to activate latent catalysts is explored. For this purpose, organometallic complexes containing N-heterocyclic carbene (NHC) ligands, coordinated to a silver(I) metal center, have been synthesized. These latent catalyst complexes were functionalized with poly(tetrahydrofuran) (PTHF). These polymer chains act as a handle for transfer of macroscopic forces onto individual chemical bonds. The most convenient way of applying forces on a polymer chain is by exposing them to ultrasound in solution. Ultrasound in solution generates an acoustic pressure wave that passes through the solution. Locally, small gas bubbles (cavities) are formed after nucleation around dissolved gas molecules. The cavitation bubbles grow and when they eventually become too large, they will be unstable and collapse. Collapse occurs within microseconds and gives rise to a variety of sonochemical effects. Next to the thermal effects within the hotspot of the collapsing cavitation bubble, where extreme temperatures and pressures arise, these effects comprise of mechanical effects that occur as a direct result of large a velocity gradient in the solution close to the retracting bubble/liquid interface. When a polymer chain is present in this high strain region, hydrodynamic forces unfold and stretch the polymer chain. When forces are high enough, individual bonds along the polymer backbone are stretched and broken. Mechanochemical scission of polymer chains is a non-random process. Forces accumulate along the stretched polymer chain and reach a maximum value in the center. Therefore, mechanochemical scission takes place around the midpoint of the polymer chain. The selectivity of mechanochemical scission can be increased by incorporation of a weak bond (“mechanophore”) near the polymer chain midpoint. Furthermore, since the chain breaks at its weakest point, the positioning of this mechanophore allows precise tailoring of the location of mechanochemical bond scission.

This thesis can be divided into two parts, each of them covering one of the main aims that were set out for this work. In the first part of this thesis, the aim is to gain more detailed insights in the physical aspects, mechanisms and underlying processes of
mechanochemical activation of latent catalysts (“mechano catalysis”) by ultrasound in solution. In studies prior to the work described in this thesis, conditions had already been established under which catalyst activation by polymer scission through thermal effects could be excluded. In this thesis, the possibility of radical-induced polymer scission is excluded as well. By varying the saturation gas used in sonication experiments, the radical production was lowered by one order of magnitude as the heat capacity of the gas increased from argon to nitrogen to methane and isobutane. However, the percentage of scission during a fixed sonication time remained the same within experimental error for all these gases. This result clearly demonstrates that the formation of radicals during cavitation in ultrasound does not affect the mechanochemical scission (i.e., activation) of silver(I)–NHC polymer catalysts. In addition to this, the importance of creating the right hydrodynamic conditions of cavitation is clearly highlighted in this work. For example, the solubility of isobutane in toluene is so high that the collapse of cavitation bubbles was “cushioned”, which, in turn, led to a reduction in polymer scission efficiency.

Having established the true mechanochemical nature of mechanocatalyst activation, the stretching of polymer chains under the influence of hydrodynamic forces and the subsequent chain scission are further investigated. In previous work, it had already been shown that the silver(I)–NHC supramolecular polymers have a significantly lowered limiting molecular weight for mechanochemical chain scission compared to non-functionalized, fully covalent polymers. The question to be answered is if such a low limiting molecular weight is compatible with a scission mechanism that requires unfolding and stretching of individual polymer chains in solution prior to scission. The longest characteristic relaxation times ($\sim 10^{-7}$ s) of these supramolecular polymers in solution were determined by viscosity measurements in order to verify that the critical conditions for coil-to-stretch transition of these polymers is indeed fulfilled under typical hydrodynamic conditions in ultrasound experiments, where strain rates typically exceed $10^7$ s$^{-1}$. In the next step, molecular dynamics (MD) simulations, combined with COGEF calculations were performed to estimate the forces required for mechanochemical scission of the silver(I)–NHC coordination bond. The typical forces were estimated to be between 400 and 500 pN, which is indeed much lower than the forces that are typically required for scission of covalent bonds (up to several nN). The modeling rationalizes the strong reduction of limiting molecular weight for mechanochemical scission of these supramolecular polymers compared to covalent polymers.

The effect of radicals and their secondary products (referred to as sonochemical impurities) on the mechanocatalytic activity of the active catalyst species is investigated as well. Although it was established that radicals, and/or other sonochemical
impurities, do not influence mechanocatalyst activation, it is anticipated that these reactive species may still be able to deactivate the highly nucleophilic NHC active catalyst species. The transesterification of vinyl acetate with benzyl alcohol to form benzyl acetate was used as a benchmark reaction to determine the catalytic activity. It was shown that the mechanocatalytic activity was significantly increased when sonication experiments are performed under conditions that suppress the formation of sonochemical impurities. Catalytic conversions of the transesterification reaction increased dramatically, from less than 1% to ca. 11% after 30 minutes of sonication when the sonication was performed under radical-suppressing conditions using methane instead of argon as saturation gas. It is shown that the deactivating species in case of the silver(I)–NHC mechanocatalyst is a persistent species, not the radicals themselves. More specifically, the sonochemical impurity was identified as trace amounts of a weak Brønsted acid, possibly acetic acid that is formed during thermal degradation of the reactant vinyl acetate in the hotspot of the collapsing cavitation bubble.

Furthermore, a potential metal-free NHC-based mechanocatalyst complex is designed and synthesized by replacing the silver(I)–NHC coordination complex by the adduct of an NHC and aromatic isothiocyanate. In literature, it had been shown that these NHC–isothiocyanate (NHC–NCS) adducts have a reversible nature, albeit with an extremely high equilibrium constant of ~10^{14} \text{M}^{-1}. At elevated temperatures, between ca. 70 and 100 °C depending on the nature of the isothiocyanate, free NHCs were generated, leading to (thermal) catalytic activity. It is anticipated that incorporation of the NHC–NCS adduct within the center of a PTHF chain results in a latent catalyst that can be activated by mechanical forces. Indeed, near-midpoint scission was observed when the polymer adduct in solution was subjected to ultrasound irradiation. However, mechanochemical scission did not result in the desired mechanocatalytic activity in the benchmark transesterification reaction of vinyl acetate and benzyl alcohol. More careful analysis revealed that the product of mechanochemical scission of the polymer NHC–NCS adduct is not the free NHC. Instead, non-selective, near-midpoint scission of the PTHF chain takes place with a similar scission rate as for non-functionalized PTHF of the same molecular weight. Apparently, the difference in bond strength between the NHC–NCS adduct bond and covalent bonds within the polymer backbone is not large enough to yield a selective mechanochemical scission process on the microsecond timescale of ultrasound experiments.

In the second part of this thesis, the use of alternative techniques for mechanocatalyst activation was studied. Attempts to use well-defined hydrodynamic flows in microfluidic devices have not been successful. Based on the results of relaxation time
measurements of silver(I)–NHC supramolecular polymers as described earlier, it is reasoned that the strain rates obtained in such devices (max. $10^5$ s$^{-1}$) are not sufficient to fulfill the coil-to-stretch criterion, which is a prerequisite for chain scission.

More successes are obtained when using atomic force microscopy (AFM) as an alternative mechanochemical activation technique. Although, in ultrasound experiments, the NHC–NCS adduct does not display mechanocatalytic activity, it is used in these single molecule force experiments owing to its synthetic accessibility. A molecular link between the AFM cantilever and NHC–NCS surface construct was established through thiourea bond formation. Upon retraction of the cantilever, molecular rupture events were observed with a maximum in the rupture force of ca. 690 pN. Clearly, this force is too low to correspond to rupture of a covalent bond (several nN are required for this); in addition, control experiments showed that these rupture events are not present in the absence of the NHC–NCS adduct in the AFM surface construct. So, the rupture events in these AFM experiments must occur at the NHC–NCS adduct, even though the precise location of mechanochemical bond scission has not yet been identified. It is reasonable to assume for now that it is indeed the NHC–NCS adduct bond that is breaking, since the sub-nN rupture forces at the second timescale of AFM experiments are compatible with the dynamic nature of the NHC–NCS bonds. Apparently, on the longer timescale of the AFM experiment compared to ultrasound experiments, the selectivity of mechanochemical bond scission is strongly enhanced.

In summary, the work in this thesis has resulted in new and important insights into mechanochemical activation of polymer mechanocatalysts. These insights have contributed to a better understanding of the process, they have unambiguously demonstrated the true mechanochemical nature of catalyst activation and they were successfully used in the rationalizing design and implementation of alternative activation techniques.
Mechanochemische activering van latente N-heterocyclische carbeenkatalysatoren

Het activeren van chemische bindingen en het uitvoeren van chemische transformaties met behulp van mechanische krachten heet “mechanochemie”. Mechaanochemie is een alternatieve methode voor het activeren van chemische reacties, naast verwarmen of het gebruik van (foto)chemische stimuli. Hoewel mechanochemie al eeuwen geleden is ontdekt, kent de techniek sinds kort een sterke opleving. Mechanochemisch geactiveerde reacties kunnen soms volgens een geheel andere energetische route verlopen dan dezelfde thermisch geactiveerde reacties; de reactieproducten van mechanisch geactiveerde reacties kunnen dan ook anders zijn.

In dit proefschrift worden de resultaten beschreven van het onderzoek naar het gebruik van mechanische krachten voor het activeren van latente katalysatoren. Hiertoe zijn organometaalcomplexen gesynthetiseerd, waarbij twee N-heterocyclische carbeenliganden (NHC’s) zijn gecoördineerd aan een zilver(I) metaalcentrum. Deze latente katalysatorcomplexen zijn gefunctionaliseerd met polytetrahydrofuraan (PTHF). Deze polymeerketens dienen als handvat voor het overbrengen van mechanische krachten op de individuele chemische bindingen. Het blootstellen aan ultrageluidsgolven in oplossing is de meest gebruikte manier om mechanische krachten uit te oefenen op polymeerketens. In een oplossing zorgt de akoestische drukgolf voor de vorming van kleine gasbellen die zich lokaal vormen door nucleatie rond opgeloste gasmoleculen in een prosce dat cavitatie heet. De cavitatiebellen groeien vervolgens tot ze op een zeker moment te groot zijn en instabiel worden. Dit resulteert in een snelle en heftige implosie van de cavitatiebellen (in een tijdsbestek van enkele microseconden), waarbij allerlei sonochemische effecten optreden in deze zogenaamde “hotspot”. Temperatuur en druk in deze hotspots kunnen oplopen tot extreme waarden, maar behalve deze thermische effecten zijn er ook mechanische effecten die worden veroorzaakt door deze implosie. De mechanische effecten zijn een direct gevolg van grote snelheidsverschillen in de vloeistof rondom de imploderende cavitatiebel. Een polymeerketens die zich in de buurt van de terugtrekkende belwand bevindt, zal ontvouwen en worden opgerekt als gevolg van deze snelheidsgradiënt.

Wanneer de krachten op de keten groot genoeg zijn, worden ook de individuele bindingen in de keten opgerekt, waarbij deze kunnen breken. Mechanochemische breuk van polymeren vindt niet plaats volgens een willekeurig proces, maar zal altijd plaatsvinden in de buurt van het midden van de polymeerketen. Dit komt omdat de krachten vanaf de uiteinden van de keten accumuleren tot een maximum waarde in het midden. De selectiviteit van de mechanochemische breuk kan worden verbeterd door het opnemen van een zwakkere binding (“mechanofoor”) rond het midden van de polymeerketen. Omdat een keten bovendien breekt bij de zwakste schakel,
bepaalt de juiste plaatsing van de mechanofoor in de keten, de exacte locatie van mechanochemische breuk.

Dit proefschrift kan worden onderverdeeld in twee delen, waarbij elk deel een van de hoofddoelstellingen van dit proefschrift behandelt. De doelstelling van het eerste deel is om meer inzicht te verwerven in de fysische aspecten, mechanismen en onderliggende processen bij mechanochemische activering van latente katalysatoren (“mechanokatalyse”) in oplossing met behulp van ultrageluid. In onderzoek voorafgaand aan dit proefschrift zijn reeds condities gedefinieerd waarbij de activering (door middel van het breken van polymeerketens) door thermische effecten konden worden uitgesloten. In dit proefschrift is onderzoek gedaan naar de mogelijke rol van radicalen in het activeringsmechanisme van mechanokatalysatoren. De radicaalproductie in ultrageluidexperimenten werd gereduceerd met één ordegrootte bij een toenemende warmtecapaciteit van het gebruikte verzadigingsgas (argon, stikstof, methaan of isobutaan). Echter, het percentage ketenbreuk binnen een bepaalde tijd bleef gelijk binnen de experimentele foutmarge, ongeacht de hoeveelheid radicalen die werd geproduceerd. Hiermee is vastgesteld dat radicalen geen rol spelen in het proces van mechanochemische ketenbreuk van polymere zilver(I)–NHC katalysatoren. Bovendien werd door dit onderzoek het belang aangetoond van het creëren van de juiste hydrodynamische condities tijdens het cavitationproces. De oplosbaarheid van isobutaan in toluëen, bijvoorbeeld, was zo groot dat de implosie van cavitatiebellen werd gedempt, wat vervolgens resulteerde tot een afname van de hoeveelheid mechanochemische ketenbreuk.

Na het definitief vaststellen dat de activering van de mechanokatalysatoren echt mechanochemisch van aard is, werd het oprekken en breken van polymeerketens onder invloed van hydrodynamische krachten verder onderzocht. In eerdere studies was al vastgesteld dat supramoleculaire zilver(I)–NHC polymeren een veel lager limiterend molgewicht hebben voor mechanochemische breuk vergeleken met niet-gefunctionaliseerde, volledig covalente polymeren. De vraag is of een dergelijke laag limiterend molgewicht in overeenstemming is met een mechanisme waarbij de polymeerketens eerst moeten worden opgerekt alvorens ze kunnen breken. De langste karakteristieke relaxatietijd van deze supramoleculaire polymeerketens in oplossing (~10–7 s) werd bepaald door viscositeitmetingen. Hierbij is vastgesteld dat aan de kritische eisen voor het oprekken van polymeerketens wordt voldaan tijdens typische ultrageluidexperimenten, waarbij de reksnellheden in oplossing kunnen oplopen tot 10^7 s⁻¹ en hoger. In een volgende stap werden molecular dynamics (MD) simulaties uitgevoerd, gecombineerd met COGEB-berekeningen om een schatting te maken van de krachten die nodig zijn voor mechanochemische breuk van een zilver(I)–NHC coördinatiebinding. Deze krachten werden geschat op 400 tot 500 pN. Deze
waarden zijn inderdaad veel lager dan de krachten die normaalgesproken nodig zijn voor het breken van covalente bindingen, welke kunnen oplopen tot enkele nN. De resultaten van de modelleringstudies geven hiermee een voldoende verklaring voor de sterke afname van het limiterend molgewicht van supramoleculaire polymeren in vergelijking tot hun covalente tegenhangers.

Verder is de invloed van radicalen en hun secundaire reactieproducten (“sonochemische onzuiverheden”) op de katalytische activiteit van de mechanokatalysator onderzocht. Hoewel deze sonochemische onzuiverheden de activering van de mechanokatalysatoren niet beïnvloeden, is het goed mogelijk dat ze de zeer nucleofiele NHC’s, de actieve katalysator, deactiveren. Als standaardreactie voor het bepalen van de katalytische activiteit is de omestering van vinylacetaat met benzylalcohol tot benzylacetaat gebruikt. De mechanokatalytische activiteit was aanzienlijk hoger wanneer de ultrageluidexperimenten werden uitgevoerd onder condities die de vorming van sonochemische onzuiverheden onderdrukken. Wanneer de omestering werd uitgevoerd onder methaan in plaats van onder argon als verzadigingsgas, steeg de katalytische conversie van minder dan 1% naar ca. 11% na een half uur blootstelling aan ultrageluid. Er werd aangetoond dat de deactiverende onzuiverheid in het geval van de zilver(I)–NHC katalysator een stabiele verbinding is en dat het niet de radicalen zelf zijn die voor deactivering van de vrije NHCl’s zorgen. Er is zelfs specifiek aangetoond dat de sonochemische onzuiverheid een soortje van een zwak Brønstedzuur, waarschijnlijk azijnzuur, is. Het is goed mogelijk dat azijnzuur wordt gevormd door thermische degradatie van vinylacetaat in de hotspot van de imploderende cavitationebel.

In een ander project werd een mogelijke metaalvrije mechanokatalysator ontworpen en gesynthetiseerd. In dit ontwerp is het zilver(I)–NHC coördinatiecomplex vervangen door een adduct van een NHC en een aromatisch isothiocyanaat. In de literatuur is al aangetoond dat dergelijke NHC–isothiocyanaat (NHC–NCS) adducten een reversibel karakter hebben met een extreem hoge evenwichtsconstante (~10^{14} \text{M}^{-1}). Onder verwarmen naar ca. 70 tot 100 °C (afhankelijk van het type isothiocyanaat) worden vrije NHCl’s gevormd die actief zijn als katalysator. De verwachting was dat het inbouwen van dit adduct in het midden van een polymeerketen zou leiden tot een latente katalysator die kan worden geactiveerd met behulp van mechanische krachten. Mechanochemische breuk rondom het middelpunt van de keten werd dan ook waargenomen wanneer een oplossing van dit polymere adduct werd blootgesteld aan ultrageluid. Echter, deze mechanochemische breuk leidde niet tot katalytische activiteit in de standaard omestering van vinylacetaat en benzylalcohol. Een gedetailleerde analyse van het breukproduct van het polymere NHC–NCS adduct toonde dan ook aan dat er geen vrije NHCl’s werden gevormd. In plaats
daarvan trad er niet-selectieve breuk rondom het middelpunt van de PTHF-keten op, waarbij de breuksnellheid gelijk is aan die van niet-gefunctionaliseerd PTHF van een vergelijkbaar molgewicht. Blijkbaar is het zo dat het verschil in bindingssterkte tussen het NHC–NCS adduct en de covalente bindingen in de polymeerketen niet groot genoeg is om voor selectieve breuk te zorgen in ultrageluidsexperimenten.

In het tweede deel van dit proefschrift is onderzoek gedaan naar het toepassen van alternatieve methoden voor activering van mechanokatalysatoren, in plaats van ultrageluid. Het gebruik van goed gedefinieerde hydrodynamische stromingen in microfluïdische kanalen bleek niet geschikt. De resultaten van de eerdere metingen van de relaxatietijden van supramoleculaire zilver(I)–NHC polymeren hebben laten zien dat de minimale reknelheden in oplossing die nodig zijn op het oprukken van de polymeerketens niet kunnen worden gehaald in microfluïdische kanalen. In dit type kanalen zijn snelheidsgradiënten van \(~10^4–10^5\) s\(^{-1}\) de praktisch haalbare limiet. Het gebruik van atomic force microscopy (AFM) voor mechanochemische breuk was succesvoller. Hoewel het NHC–NCS adduct in ultrageluidsexperimenten geen mechanokatalytische activiteit vertoonde, is dit adduct toch gebruikt in de AFM-experimenten, om dat dit adduct makkelijk te synthetiseren is en bovendien stabiel is. Een thioureabinding is gebruikt voor het verkrijgen van moleculaire connectie tussen de AFM-naald en het NCS-gefunctionaliseerde glasoppervlak. Bij het terugtrekken van de naald werd breuk op moleculair niveau waargenomen met een maximum kracht bij breuk van ca. 690 pN. Het is duidelijk dat deze kracht te laag is om overeen te komen met het breken van een covalente binding (waarvoor enkele nN nodig zijn). Bovendien toonden controle-experimenten aan dat er geen breuk optreedt wanneer het NHC–NCS adduct niet aanwezig was op het glasoppervlak. Hiermee lijkt het er op dat de breuk dus plaatsvindt binnen het NHC–NCS adduct, maar het is nog niet gelukt om de precieze locatie van de breuk te bepalen. Vooralsnog lijkt het aannemelijk om er vanuit te gaan dat de breuk inderdaad optreedt bij de binding tussen NHC en isothiocyaanat, aangezien dergelijke lage krachten te verwachten zijn voor het breken van chemische bindingen die een dynamisch karakter hebben. Blijkbaar zorgt de langere experimentele tijdsduur van AFM in vergelijking met ultrageluidsexperimenten voor een sterke verbetering van de selectiviteit van mechanochemische breuk.

Samenvattend kan worden gesteld dat het werk dat is beschreven in dit proefschrift heeft geleid tot nieuwe en belangrijke inzichten in de mechanochemische activering van polymere mechanokatalysatoren. Deze inzichten hebben bijgedragen aan een beter begrip van het proces: ze hebben onomstotelijk bewezen dat de activering werkelijk van mechanochemische aard is en zijn succesvol gebruikt bij het rationeel ontwerpen en uitvoeren van alternatieve activeringsmethoden.
List of publications

Publications related to this thesis

The effect of molecular weight and catalyst concentration on catalytic activity in mechanochemically activated transesterification with silver(I)–N-heterocyclic carbene latent catalysts
R. Groote, L. van Haandel, R.P. Sijbesma

Performance of mechanochemically activated catalysts is enhanced by suppression of the thermal effects of ultrasound
R. Groote, R.T.M. Jakobs, R.P. Sijbesma
*ACS Macro Lett.* **2012**, *1*, 1012–1015

Unfolding and mechanochemical scission of supramolecular polymers containing a metal–ligand coordination bond

DFT study on mechanochemical bond breaking in COGEF and Molecular Dynamics simulations

Mechanism of ultrasound scission of a silver–carbene coordination polymer

Other publications

Porous ceramic mesoreactors: A new approach for gas–liquid contacting in multiphase microreaction technology
Probing single enzyme kinetics in real-time
Q. Chen, R. Groote, H. Schönherr, G.J. Vancso

Werkwijze voor het verstevigen en/of afdichten van een zandgrondlichaam
R. Groote, H. Reezigt, F. de Groot (B&P Bodeminjectie B.V.)
NL Patent 2003443 (2011)
Curriculum Vitae

Ramon Groote was born on June 8th, 1984 in Almelo. After secondary education at the R.K. Scholengemeenschap Pius X College in Almelo, he started studying Chemical Engineering at the University of Twente, Enschede in 2002. He graduated cum laude in 2008 after completing a graduation research project in the Membrane Technology Group under supervision of prof. dr.-ing. M. Wessling and prof. dr. ir. R.G.H. Lammertink. During the graduation project he investigated the integration of membrane technology in microfluidics for carrying out heterogeneously catalyzed multiphase reactions. For this research he was awarded the Unilever Research Prize in December 2009. In January 2009 he started his PhD research project in the Laboratory of Macromolecular and Organic Chemistry under supervision of prof. dr. R.P. Sijbesma. The most important results of this research are described in this thesis.
Dankwoord

Als je begint met promoveren, dan lijkt het schrijven van een proefschrift nog heel ver weg. Maar de tijd vliegt voorbij en voor je het weet, is het onderzoek gedaan, je boekje al geschreven en ben je aangekomen bij die laatste paar pagina’s. Deze pagina’s bevatten geen wetenschap, maar zijn ongetwijfeld (en misschien juist wel daarom) het meest gelezen deel van ieder proefschrift. Ik heb de afgelopen jaren met veel mensen samengewerkt en veel bijzondere mensen leren kennen die allemaal, op welke manier dan ook, hebben bijgedragen aan de totstandkoming van dit proefschrift.

Allereerst wil ik mijn promotor bedanken, prof. dr. Rint Sijbesma. Beste Rint, toen ik vier jaar geleden uit Twente naar Eindhoven kwam, heb jij me de mogelijkheid geboden om in jouw groep aan een uitdagend en nieuw onderzoeksproject te werken. Ik wil je bedanken voor het vertrouwen dat je in mij hebt gesteld en voor de fijne begeleiding de afgelopen jaren. Je hebt me steeds alle vrijheid gegeven om mezelf te ontwikkelen op een voor mij geheel nieuw vakgebied. Jouw deskundigheid, geduld en voortdurende enthousiasme hebben ervoor gezorgd dat ik een geweldige promotietijd heb gehad. Ik hoop dat er nog vele successen uit jouw groep zullen komen en ik wens je het allerbeste voor de toekomst.

Verder wil ik ook de leden van mijn (lees)commissie bedanken, in het bijzonder prof. dr. Bert Meijer en prof. dr. ir. Gerrit Peters. Beste Bert, hoewel we nooit direct samengewerkt hebben, heb ik het als een voorrecht ervaren om de afgelopen vier jaar in jouw “grote groep” te mogen werken. Ik wil je bedanken voor je vertrouwen, je interesse in mijn werk en je nuttige commentaren op mijn proefschrift en natuurlijk voor het plaatsnemen in mijn commissie. Gerrit, we hebben vooral in mijn eerste jaar veel contact gehad, waarbij we samen hebben nagedacht over het gebruik van microfluïdische systemen voor het breken van onze polymere katalysatoren. Bedankt voor al je hulp en advies en dat je plaats hebt willen nemen in mijn commissie. I am very grateful to prof. dr. Stephen Craig for being a member of my defense committee. Dear Steve, thank you very much for reading my manuscript so carefully and for all your useful comments and suggestions. Ik wil ook prof. dr. Joost Reek en prof. dr. Alan Rowan bedanken voor het plaatsnemen in mijn commissie.

Ik heb de afgelopen vier jaar met veel mensen samen mogen werken en ik heb dat altijd als heel prettig ervaren. Mijn eerste samenwerking was met (inmiddels dr.) Joost Rooze. Joost, jouw geweldige idee om de radicaalproductie in ultrageluid te temperen door middel van het variëren van het verzadigingsgas heeft een mooie publicatie opgeleverd en bleek een prima aanknopingspunt voor verder onderzoek. The collaboration with (now dr.) David Fernández Rivas from the Universiteit Twente did, in the end, not give the exciting results we had hoped for. However, David, I enjoyed our collaboration and the visits to Enschede!

I would like to thank dr. Bartek Szyja and dr. Evgeny Pidko for the fruitful cooperation we had doing theoretical calculations on our catalysts under force. Thank you for your enthusiasm to work with us on this project, that was completely new to you as well. Bartek,
I am also very grateful to you for giving me the opportunity to continue our collaboration together with prof. dr. Nikos Doltsinis in Münster. The collaboration with Monique Jacobs and dr. Kerstin Blank from the Radboud Universiteit in Nijmegen seems to be a bigger success than we expected. Monique and Kerstin, thank you for diving into this risky project and spending your time and effort to get the AFM-induced mechanocatalyst scission working. Monique, thank you for the very nice collaboration and good personal interactions. Good luck with the rest of your PhD. Finally, I want to acknowledge Frank Leibfarth from the University of Santa Barbara. Frank, unfortunately we couldn’t get your ketene dimers to break were we wanted them to break… Hopefully, the theoretical calculations that I am carrying out at the moment will reveal the reason why. Good luck finishing your PhD.

I would like to acknowledge dr. Simon Haward of the Massachusetts Institute of Technology and the Universidade do Porto. Simon, our short e-mail conversation of last year has provided us with some very important insights on the feasibility of using microfluidic devices for mechanocatalyst activation. Thank you very much for all your help and advice.

Ik heb het voorrecht gehad om tijdens mijn promotie een aantal zeer enthousiaste en gedreven studenten te mogen begeleiden. Al in mijn eerste jaar kwam Davin Thielen bij ons in de groep voor zijn afstudeerproject. Beste Davin, ik vond het geweldig om met je samen te werken. Je bent een harde werker en prettig in de omgang. Ik wil je graag hartelijk danken voor al je bijdragen aan mijn onderzoek. Hoewel jouw afstudeerwerk dit proefschrift helaas niet heeft gehaald, zijn vooral jouw syntheses van groot belang geweest voor mij en de andere mensen binnen het “mechanokatalyseteam”. Beste Lennart, je hebt me tijdens je majorproject verbaasd doen staan van je enthousiasme en zelfstandigheid. Je werkzaamheden zijn zeker een succes geweest: een mooie gezamenlijke publicatie is iets waar je trots op kunt zijn. Succes met jouw promotie bij SMK! Beste Thijs, onze samenwerking duurde ongewild wat langer dan gepland, maar was uiteindelijk toch zeer succesvol. Het is jammer dat de moleculen die we samen gemaakt hebben niet op de juiste plek wilden breken, maar ze worden nu gebruikt in onze samenwerking met Nijmegen, dus wie weet wat daar nog uitkomt. Succes met de afronding van je studie en met wat daarna gaat komen.

Ik wil langs deze weg het analytisch team van harte bedanken: Lou, Ralf en Joost, dankjulliewel voor alle hulp bij het uitvoeren en optimaliseren van de verschillende analyses en alle ondersteuning aan de analytische apparatuur. Ik wil ook Henk, Hans en alle secretaresses, met name Joke, bedanken voor het zetten van de verse koffie, het regelen van taart/borrels, het bestellen van labbenodigdheden en chemicaliën en alle administratieve taken, maar ook gewoon voor de gezellige praatjes tussen de bedrijven door. Jullie werkzaamheden zijn allemaal van ontzettend groot belang voor het goed draaiende houden van deze grote groep.

Toen ik als nieuweling binnenkwam bij SMO, merkte ik al gauw dat ik op een bijzondere plek was terechtgekomen. Ik wil al mijn (oud-)collega’s dan ook hartelijk danken voor de mooie en gezellige tijd. In het bijzonder wil ik Ashish, Berry, Dana, Katja, Marcel, Wencke en Yulan, Patrick, Sandra en Juliën, Erik en Elise en Alice en Lorenzo bedanken voor alle
gezelligheid op het lab, in de wandelgangen, tijdens de lunch en borrels/avondjes uit en bij alle etentjes en (vriendschappelijk) interlandwedstrijden. Special agents Inga, Martijn, Marie-France and Richard, I enjoyed organizing the very successful retreat to Sauerland. Thanks for the nice time we had, especially while recording the cabaret movie.


voor de gezelligheid op kantoor
en ik wens jou en Hossein het allerbeste. Erik, jij bent er als laatste bijgekomen op kantoor STO 3.46, maar de sfeer in het kantoor is er nog verder door verbeterd. Je mooie verhalen uit Amerika en/of Nijmegen zorgen voor de nodige afwisseling en ontspanning gedurende de werkdag. Ik wens je heel veel succes bij het vinden van een mooie baan in de academische wereld. Beste Martijn, voordat ik naar de derde verdieping verhuisde, waren wij een jaar lang kantoorgenoten. Bedankt voor alle gezelligheid op kantoor STO 4.81! Voor jou is het laatste jaar van je promotie inmiddels ook aangebroken en ik wens je alle succes met de afronding. De etentjes met jou en Tess zijn altijd heel gezellig en ik wens jullie het allerbeste. The time I spent in the office with Daniele, Jitte, Amparo and Amol was only short, but enjoyable. Thank you all for your nice company.

Dear Abidin, you completed the “mechanocatalysis team” more than two years ago and I really enjoyed having you as a colleague and friend. You are one of the most dedicated and hard-working people I have ever worked with. In addition to that, you are also a highly skilled “lab-dancer”… Teşekkürler for being paranymph on my big day in January and for all the good times we had in- and outside the lab. I am very much indebted to Karthik. Karthik, although we only worked together the first year-and-a-bit of my PhD, your help, support and “hands-on” experience with mechanocatalysis and chemistry in general have been crucial to me. I have learned a lot from you and I thank you for that. All the best to you and your wife for the future and hopefully we can meet again sometime.

Een speciaal woord van dank gaat uit naar al mijn familie en vrienden. Jullie zijn met teveel om allemaal bij naam en toenaam te noemen in dit dankwoord (ik zou ruimte tekort komen en dan nog mensen vergeten…). Hoewel jullie geen directe bijdrage hebben geleverd aan de totstandkoming van dit proefschrift, is jullie vriendschap en gezelligheid van onschatbare waarde voor mij in het leven voor, naast en na mijn promotie. Dankjulliewel daarvoor!

Dan wil ik ook mijn schoonfamilie graag bedanken voor hun warmte, liefde en constante
interesse in Veronique en mij. Pa, ma, Yvette en Pascaline, het is altijd weer supergezellig als we bij elkaar zijn. Ik heb het getroffen met jullie als schoonfamilie! Jullie staan altijd voor ons klaar en daarvoor kan ik alleen maar dankbaar zijn.

In de afgelopen 28 jaar heb ik altijd kunnen rekenen op de onvoorwaardelijke liefde, steun en interesse van mijn oale leu. Lieve papa en mama, jullie zijn geweldig geweest! Hoewel het jullie soms “boven de pet ging” wat ik allemaal deed, hebben jullie me altijd gesteund en me alle vrijheid gegeven om de dingen te doen die ik graag wilde en me te ontwikkelen tot wie ik nu ben. Ik hoop (weet) dat jullie trots op me zijn en ik wil jullie bedanken voor alles…eigenlijk gewoon omdat jullie d’r bint. Jeroen en Anne, dankjulliewel voor al jullie gezelligheid en steun. Breurken, sinds dat ik het huis uit ben, zijn we eigenlijk alleen maar dikkere kammerôa geworden en daar ben ik blij om. Ik ben trots op je als ik zie hoe je de vrachtwagen heen en weer manoeuvreert op de smalle grachtjes van Amsterdam en ik beloof je dat ik snel weer een dag met je meega!

Tot slot, de laatste alinea van dit proefschrift schrijf ik voor mijn lieve Veronique. Lieverd, het is de afgelopen vier jaar niet altijd even gemakkelijk geweest. Het “samen promoveren” is de gezelligheid bij ons thuis niet altijd ten goede gekomen, maar we hebben het toch maar mooi gedaan met z’n tweeën (getuige twee schitterende boekjes)! Ik ben ontzettend trots op je en ik ben blij dat je de perfecte baan hebt gevonden. We hebben de afgelopen jaren een leven samen opgebouwd en ontzettend veel leuke dingen gedaan en meegemaakt. Ik kan me een leven zonder jou niet meer voorstellen en ik heb dan ook ontzettend veel zin in de mooie toekomst die we samen nog gaan krijgen. Ik hou van je!

Ramon