

Fragmentation studies of poly(propelene imine) dendrimers in the gas-phase by using electrospray ionization mass spectrometry (ESI-MS)

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Fragmentation studies of poly(propylene imine) dendrimers in the gas-phase by using electrospray ionization mass spectrometry (ESI-MS)

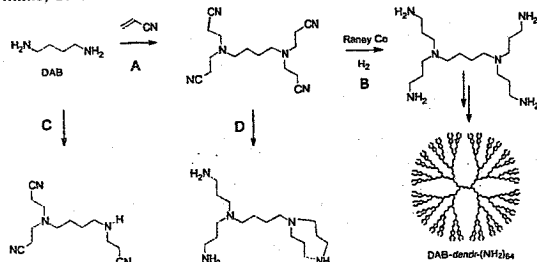
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The synthesis and characterization of well-defined macromolecules like dendrimers constitute a relatively new field of great current interest. Dendrimers can be prepared in either a convergent or a divergent manner. In the convergent strategy the dendritic wedges are prepared separately and connected to a central core in the final step leading to dendrimers of well-defined architecture next to defect dendrimers missing one, or more, dendritic wedges. The resulting large structural differences between the perfect structure and byproducts make purification relatively easy.¹ Dendrimers prepared by the divergent approach, however, often suffer from a number of statistical defects and purification becomes exceedingly difficult with higher generations, because the perfect dendrimers differ from the defective ones by only one, or a few, monomer units.²

Accordingly, a powerful analytical tool is required to discriminate between the defect-free structure and the possible error structures. The analytical techniques that have been applied to characterise these macromolecules so far include: nuclear magnetic resonance (NMR), size exclusion chromatography (SEC), high-performance liquid chromatography (HPLC)^{2e,3}, fast-atom bombardment mass spectrometry (FAB-MS)⁴, liquid secondary ion⁵, matrix assisted laser desorption ionization time of flight (MALDI-TOF)⁶ and more recently electrospray ionization mass spectrometry (ESI-MS)⁷. Although the development of ESI-MS is still ongoing, this technique is an increasingly important and efficient tool to investigate macromolecules. The advantages offered by ESI-MS include its high sensitivity, "soft" ionization and the generation of multiple charged ions allowing not only for structural information to be obtained but also for broad molecular weight ranges to be measured.⁸

In this paper we report on the preliminary results obtained from the investigation of fragmentation reactions of the commercially available poly(propylene imine) dendrimers in ESI-MS by performing MS/MS and MS/MS/MS mass spectrometry on singly charged molecular ions. Recently, we presented a paper concerning a detailed ESI-MS analysis on poly(propylene imine) dendrimers accompanied by simulations obtained by using a simple (iterative) statistical calculation program.⁹ The synthesis of poly(propylene imine) dendrimers is outlined in Scheme 1 along with the occurring side reactions.¹⁰



Scheme 1. Synthesis of poly(propylene imine) dendrimers and possible side reactions.

The alternating sequence of Michael addition (A) and hydrogenation (B) leads in ten steps from diaminobutane (DAB) to DAB-dendr-(NH₂)₆₄. Incomplete Michael addition (C) and ringformation during hydrogenation (D) result in the formation of imperfect structures. Accordingly, the perfect DAB-dendr-(NH₂)₆₄ obtained only after 248 successful reactions is accompanied by dendrimers containing statistical errors (even when the reactions involved are optimized to the extreme¹¹), with characteristic mass losses of 57.1 and 17.0, respectively. By calculating the probability factors of both side reactions for the successive generations from the measured ESI-MS spectra the key to the simulation of the consecutive spectra was obtained. The deconvoluted (top) and simulated (bottom) ESI-MS spectrum of DAB-dendr-(NH₂)₆₄ are depicted in Fig. 1.

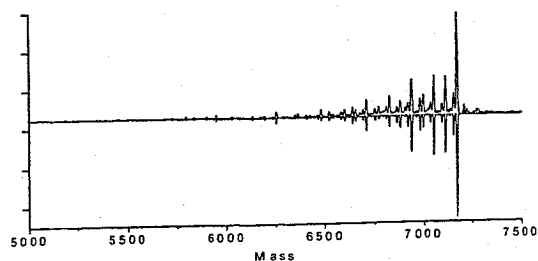


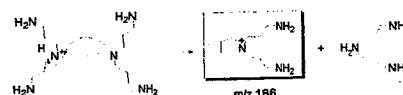
Figure 1. Deconvoluted (top) and simulated (bottom) ESI-MS spectrum for DAB-dendr-(NH₂)₆₄.

EXPERIMENTAL

MS/MS was achieved by performing collision activated dissociation (CAD) whereas the combination of CAD and collision induced dissociation (CID) enabled us to perform MS/MS/MS. The DAB-dendr-(NH₂)_n are very polar and poly-basic compounds that are partially protonated when dissolved in methanol-water mixtures. This property allows for the direct analysis of these solutions by positive ion ESI-MS. The sample with a concentration of ca. 25 x 10⁻³ mmol.L⁻¹ in MeOH/H₂O (75/25) is directly injected into the Perkin-Elmer Sciex API 300 triple quadrupole mass spectrometer using a syringe pump at a flow rate of 5 μl/min. A voltage of 5.4 kV was applied to the capillary.

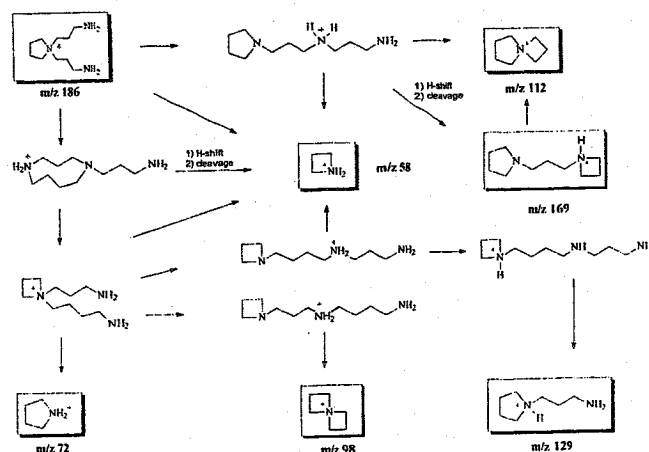
RESULTS AND DISCUSSION

The fragmentation of DAB-dendr-(NH₂)_n (m/z 317) was taken as a starting point and the knowledge obtained from its degradation pattern was subsequently extrapolated to the higher generation dendrimers. Fragmentation led exclusively to the formation of m/z 186. This observation can only be accounted for by assuming that one of the diaminobutane (DAB) nitrogen atoms is protonated while the other one acts as a nucleophile leading to an intramolecular nucleophilic displacement reaction with subsequent loss of bis(propylamine) amine as illustrated in Scheme 2.



Scheme 2. Formation of m/z 186 from [M + H]⁺ of DAB-dendr-(NH₂)₄.

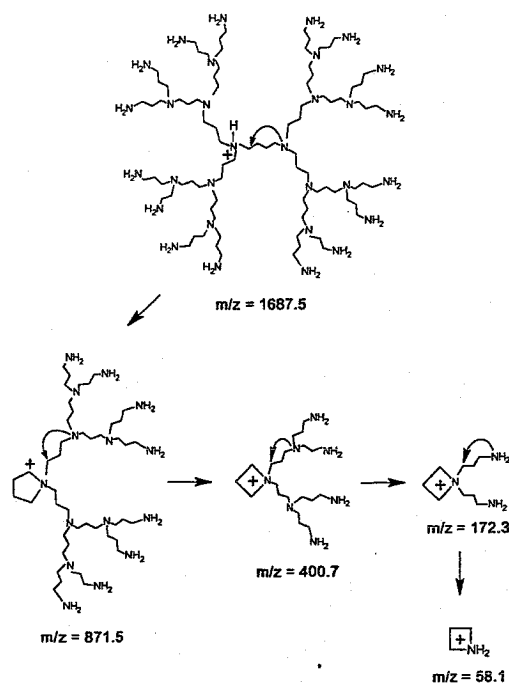
MS/MS/MS performed on m/z 186 led to the formation of m/z 169, 129, 112, 98, 72 and 58. This characteristic fragmentation pattern can be explained when next to nucleophilic displacement reactions, rearrangements and proton shifts are taken into account as depicted in Scheme 3.



Scheme 3. Formation of the main fragment-ions resulting from MS of m/e 186.

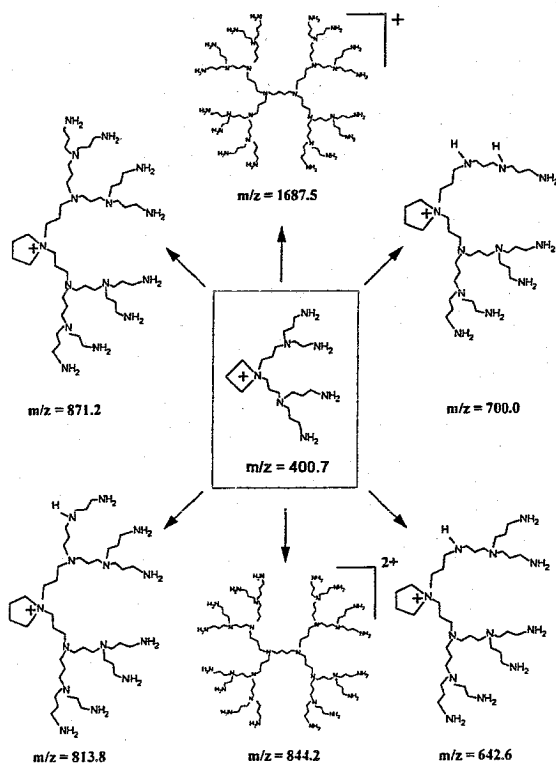
Although the overview of reaction pathways outlined in Scheme 3 does account for all the signals observed, it is still incomplete. There are many other routes feasible leading to the fragments observed which have been omitted here for reasons of clarity. Although it is impossible to determine the extent to which each individual reaction pathway contributes to the formation of particular fragment-ions, one would expect m/z 58 and 112 to be predominant because there are many conceivable reaction pathways leading to these fragments. This was indeed observed experimentally.

The main fragmentation pattern of [M + H]⁺ for DAB-dendr-(NH₂)₈ (m/z 774) and DAB-dendr-(NH₂)₁₆ (m/z 1687) is essentially the same and involves a chain reaction as is shown in Scheme 4 for DAB-dendr-(NH₂)₁₆. The first step consists of a cleavage of the central DAB core, analogous to DAB-dendr-(NH₂)₄, leading to a split dendrimer carrying a charged five-membered heterocyclic ring which acts as a leaving group in the second nucleophilic displacement reaction along the chain. The charged four-membered ring formed during this process acts subsequently as a leaving group in the third nucleophilic displacement reaction. Thus during each nucleophilic displacement reaction the leaving group for the next displacement along the chain is introduced. As anticipated, MS performed on the separate ions in the chain led to the formation of the subsequent fragment-ions along the chain.



Scheme 4. Main fragmentation pattern for DAB-dendr-(NH₂)₁₆

However, all the fragments depicted in Scheme 4 can in principle also be envisaged as directly resulting from [M + H]⁺. The protonation site in that case determines which particular fragment-ion is formed. Protonation of a first generation nitrogen atom, for instance, could give rise to the direct formation of m/z 172 whereas dendritic ions carrying a second generation protonated nitrogen atom could directly yield m/z 58. It is obvious that the basicity of the tertiary nitrogen atoms in the successive dendritic layers determine the extent to which both mechanisms are operative.¹²



Scheme 5. Precursor ion scan of m/z 400 from DAB-dendr-(NH₂)₁₆

The site of protonation in [M + H]⁺ from DAB-dendr-(NH₂)_n (n = 4, 8, 16) was investigated by performing very mild collision associated dissociation on the [M + H]⁺ ions limiting successive fragmentations to a negligible extent. The fragments thus obtained provide direct information regarding the position of the proton in the precursor-ion. In all cases mild fragmentation led predominantly to the formation of 'half' dendrimers indicating that the tertiary DAB nitrogen atoms are the most basic ones in all three generations. Accordingly, the chain mechanism is the main mechanism operative although the direct formation of the chain fragments from [M + H]⁺ does occur to a slight extent. Additional prove for the chain mechanism was obtained by performing precursor ion scans on the separate ions in the chain. A typical example of the information obtained from a precursor ion scan is shown in Scheme 5 for m/z 400 from DAB-dendr-(NH₂)₁₆. Evidently, m/z 400 is not only derived from the half dendrimer at m/z 871, but also from defect half dendrimers and to a smaller extent from [M + H]⁺ and [M + 2H]²⁺. Unfortunately, the degradation of [M + H]⁺ from DAB-dendr-(NH₂)₃₂ and DAB-dendr-(NH₂)₆₄ could not be investigated due to the limited m/z range (m/z range = 3000) of the ESI-MS apparatus.

CONCLUSIONS

In conclusion, we have shown that the degradation of the [M + H]⁺ ions from DAB-dendr-(NH₂)_n (n = 4, 8, 16) all follow the same mechanistic pathway involving a chain mechanism. The reason this mechanism is the main operative can be understood in terms of the basicity of the nitrogen atoms in the successive dendritic layers. Apparently, the diaminobutane (DAB) nitrogen atoms are the most basic ones present (in the gas-phase) and hence protonation almost exclusively leads to dendrimers carrying a protonated DAB-core. Consequently, the first nucleophilic displacement reaction predominantly leads to the formation of half dendrimers constituting the start of each chain. Currently, we are investigating the collision associated dissociation reactions of multiple charged dendritic ions.

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