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Conformational Analysis

Exploring the Conformational Space of Bridge-Substituted Dithienylcyclopentenes

Maic Fredersdorf,[a, b] Robert Göstl,[c, d] Andreas Kolmer,[a] Volker Schmidts,[a] Peter Monecke,[b] Stefan Hecht,*[c] and Christina M. Thiele*[a]

Abstract: Stimuli responsive compounds and materials are of high interest in synthetic chemistry and materials science, with light being the most intriguing stimulus due to the possibility to remote control the physicochemical properties of a molecule or a material. There is a constant quest to design photoswitches with improved switching efficiency and especially diarylethene-type switches promise photo cyclization quantum yields up to unity. However, only limited attention has been paid towards the influence of the solution conformation on the switching efficiency. Here, we describe a detailed NMR spectroscopic investigation on the conformational distribution of bridge-substituted dithienylcyclopentenes in solution. We could discriminate between several photoactive and photoinactive as well as two diastereomorphous conformations and show that the trends observed in the switching efficiency match the conformer populations obtained from state of the art NMR parameters in solution.

Introduction

The continuous attraction to photochromic molecules underlines their great potential to control diverse functions and processes on the molecular scale by using light and hence resolved in time as well as in space.[1–3] As highly fatigue resistant P-type photochromes, diarylethene (DAE) have been proven interesting candidates for a number of photocontrollable applications ranging from molecular motion over catalysis to memories.[4–9] However, the already superior switching efficiency still needs to be improved for non-academic applications demanding basically infinite switching cycles, that is, high fatigue resistance and large photo cyclization quantum yields ($\Phi_{oc}$).[10–15] We recently established a synthetic protocol for the bridge-substitution of dithienylcyclopentenes and recorded a significant increase in the $\Phi_{oc}$ value for the substituted derivatives 1–4 (Scheme 1).[16]

As it is generally believed that the distribution between the anti-parallel (a-p) and parallel (p) conformations correlates to the $\Phi_{oc}$ value due to the Woodward–Hoffmann rules,[4] it is reasonable to rationalize the underlying driving force by determination of the fraction of a-p conformers in the ring-opened form. Inexpeditiously and as opposed to benzothiophene-substituted DAEs, direct measurement of this fraction is analytically very demanding for dithienylcyclopentenes if simple freezing of the conformational isomers through variable-temperature 1H NMR spectroscopy[10,11,16] does not lead to unambiguous results or if there is more than one a-p conformation involved.

In fact, it can be seen in Scheme 2 that the dithienylcyclopentenes 1–3 do not only interconvert between the a-p and p conformations but that also the a-p conformation itself is in a dynamic equilibrium between two helically pre-oriented species, that is, a-p ($P^p$, $S^p$, $S^p$) and a-p ($M^a$, $S^a$, $S^a$). The latter interconversion leads to a discrimination between the ring-opened...
a-p conformers and thus yields a distinct diastereomeric excess (de) after the photocyclization to the ring-closed isomers. Certain derivatives, previously described in the literature, could reach de values as large as 99%.[17] Without doubt, measuring the de of a photocyclization process can be performed easily through conventional liquid chromatography. However and most importantly, assignment of an unambiguous structure to the major ring-closed diastereomer is by far more demanding. To the best of our knowledge, until now only in one case the thermodynamically more stable ring-opened helically pre-oriented conformation could be determined in the crystalline phase by X-ray structural analysis,[20] which is a strong hint for the behavior of the molecule in solution but certainly requires a more thorough investigation with regard to the liquid phase. In solution, apart from the photochemically active conformations, other conformations might also be populated and required in the formal description of the cyclization mechanism. It is thus not only highly desirable to develop a method for the determination of the ratio between the a-p and p conformers to gain insight into the mechanism dictating the \( \Phi_{\text{oc}} \) value but at the same time to use this method for identification of the major helically pre-oriented a-p conformer giving rise to a distinct de during the photocyclization process in solution.

Most configurational and conformational investigations on small organic molecules involve analysis of NMR observables such as the determination of scalar coupling constants \( J(H,H) \),[21] distance measurements based on the nuclear Overhauser enhancement (NOE),[20-21] as well as more recently residual dipolar couplings (RDCs). These become observable by orienting the molecule of interest in a suitable weak alignment medium.[22-26]

In this work, we combine the analysis of the switching behavior in solution with NOE and DAD measurements to illuminate the overall underlying conformational equilibrium of the dithienylcyclopentenes 1-4o. Thus, by obtaining a deeper insight into cyclization and cycloreversion quantum yields we disclose the peculiarity of this diastereoselective photochemical event.

Results and Discussion

Analyzing the switching performance

The photochemistry of the dithienylcyclopentenes 1–3 has been studied extensively by us in earlier work.[16] Despite increasing the steric demand of the respective alkyl substituents in the bridge moiety (from Me over Et to IPr), the cyclization quantum yields \( \Phi_{\text{oc}} \) remain at values of 0.6 and the cycloreversion quantum yields \( \Phi_{\text{co}} \) are unchanged with a value of 0.01.

The diastereoselective photocyclization was followed by analytical liquid chromatography and clearly shows that a major ring-closed diastereomer c1 and a minor ring-closed diastereomer c2 is formed during the course of the irradiation of compounds 1–3 (Figure 1). The diode array detector (DAD) trace was integrated at the isosbestic point and the de was calculated over the course of the irradiation (Figure 2) for compounds 2 and 3. For DAE 1 the separation of the bands of 1c1 and 1c2 was only successful at the photostationary state (PSS) and hence only one data point could be collected. Two main aspects can be extracted from Figure 2a: 1) the values obtained for the diastereomeric excess during the ring-closing process of compounds 1–3 are practically identical within the margin of error with values from 82–84%, and 2) the de values are constant throughout the course of the irradiation. The latter finding is in agreement with the reasonable assumption that the equilibration between the two helically pre-oriented species a-p \( (P^*,S^*,S^*) \) and a-p \( (M^*,S^*,S^*) \) is rapid at room temperature.

However and interestingly, for the cycloreversion of 3c to 3o the de decreased during the course of the irradiation, suggesting that the abundant amount of 3c1 is depleted more rapidly than the amount of 3c2 (Figure 2b). Regarding the photokinetic rate law, this can only mean that the product of the molar absorptivity and the cycloreversion quantum yield of the major closed form 3c1, \( \epsilon_{31}\times\Phi_{31} \), is different from that of minor closed form 3c2, that is, \( \epsilon_{32}\times\Phi_{32} \). Although the preparative separation of the two diastereomers was not successful, an insight into the underlying reasons for the faster cycloreversion reaction of 3c1 could be gained by comparing the UV/Vis absorption spectra of the closed forms recorded by the diode array detector after analytical liquid chromatographic separation of the irradiated solution at the PSS (Figure 3a). It
becomes clear that the minor diastereomer 3c2 exhibits a hypsochromic shift of its absorption maximum in the visible part of the spectrum of about 30 nm as compared to the maximum of 3c1. Hence, it is only coherent to assume that the absorptivities $\varepsilon_{3c1}$ and $\varepsilon_{3c2}$ are different at the wavelength employed for the cycloreversion reaction ($\lambda_{\text{irr}} = 546$ nm) and that the diastereomer absorbing less light at this wavelength ring-opens more slowly. Furthermore, a superposition of the individual absorption spectra of 3c1 and 3c2 weighted by their relative
occurrence at the PSS (83% of 3c1 and 17% 3c2) yields a superimposed absorption spectrum strongly resembling the originally determined spectrum at the PSS.

This assumption is supported by the comparison of the computed ring-closed geometries of 1c1 and 1c2,[27] in particular the torsion angles within the conjugated double-bond system. Compound 1c2 exhibits a much higher ring strain than 1c1, which could be the reason for the hypsochromic shift of the absorption maximum of compound 1c2 (see Figure 3a).

As a consequence, compound 1c1 would absorb much more light than compound 1c2, under the postulation that the value of $\Phi_{\text{ems}}$ is equal for both species as the molar absorbivity would be different, and therefore the cycloreversion reaction from 1c1 to 1o would be faster, resulting in a depletion of 1c1 and an enrichment of 1c2.

Exactly this behavior of ring-closing with a constant $de$ and a ring-opening with a depleting $de$ can then be exploited altogether to change the overall $de$ in solution over multiple switching cycles (Figure 3b). Over as many as ten switching cycles from structure 3o to structure 3c and vice versa, it was possible to deplete the $de$ of 3c1 from 82 to 55% only by consecutively irradiating the sample with light of alternating wavelengths.

A hint to which diastereomer 1c1-3c1 is the most prevalent was gathered by synthesizing the bromo-substituted dithienylcyclopentene 5 (Figure 4a). This species was designed to bear heavy bromine atoms to introduce a better crystallization capability into the molecule and to facilitate the determination of the X-ray crystal structure. Indeed, compound 5o was crystallized successfully and the molecular structure was determined (Figure 4b). It can clearly be seen that the helically pre-oriented ring-opened form of compound 5o in the crystal corresponds to the a-p ($P^*, S', S'$) form. This indicates that the relative configuration of 5c is $S^*, S^*, R^*, R^*$ (see Scheme 2) but is certainly no definite proof because kinetic effects could also favor the crystallization of the thermodynamically less stable form. Additionally, packing effects in the solid state could result in a geometry, which is not representative of the conformational ensemble in solution.

**Resolving the conformational ensemble by NMR spectroscopy**

To explore the conformational (a-p vs. p) space and its relation to the diastereoselective switching in solution, we chose to further investigate the dithienylcyclopentene 1o by using variable-temperature (VT) NMR, NOE and RDC measurements. The choice of compound 1o instead of compound 3o (used in the analysis of the switching performance) and compound 5o (used in the X-ray analysis, see Figure 4) is due to both methyl groups of the cyclopentene ring of compound 1o, which provide an additional dipolar carbon–carbon coupling in the RDC measurements, which strongly aids subsequent RDC analysis.

In analogy to the approach used in the previous study of compound 4,[24] we started by recording variable-temperature $^1$H NMR spectra of compound 1o (Scheme 1). Unfortunately, we were unable to quantify the conformer populations by using this method. Only the thienyl protons and the methyl groups showed a slight linear chemical shift of about 0.1 ppm upon lowering the temperature from 300 to 230 K,[27] whereas the other chemical shifts remained unchanged within the experimental errors (<0.05 ppm). A non-linear shifting of the proton signals, which could be used to estimate the $\Delta G^*$ values of the parallel versus anti-parallel equilibrium,[28,31] could not be observed in the VT measurements of compound 1o.

Similarly, the analysis of the scalar coupling constants did not provide further results, as a connection of the interacting nuclei over a few chemical bonds and parameterization of the dihedral angle through a Karplus-type relation are required. The high content of quaternary centers in compounds 1o–3o interrupting the coupling pathway, as well as the a priori unknown parameterization for such systems, prevent the use of scalar couplings in the analysis of the dithienylcyclopentenes. Therefore, we extended the investigations of the conformational equilibria in the dithienylcyclopentenes to include the distance and orientational information from NOE and RDC measurements, respectively.

**Computational investigation of the conformational space and considerations of molecular symmetry**

As a first step, structural models of compound 1o were generated by a conformational search by using molecular modeling (Maestro, Schrödinger suite 2012, OPLS force-field, solvent CHCl$_3$).[27] A total of twenty unique, low-energy conformations could be identified, of which only eight show major differences in the torsion of the thienyl moiety with respect to the cyclopentene core. Within these conformations, the cyclopentene core is not planar, but is suggested to adopt two “envelope” conformations. Thus, we arrived at four geometries (i.e., geometries A–D in Figure 5), each with a corresponding ring-flipped envelope conformation (A–D’, indicated by an orange arrow in Figure 5). When comparing the calculated structures...
to Scheme 2, conformer A is in accordance to the aforementioned a-p (P*,S*,S*) form and conformer B to the a-p (M*,S*,S*) form. Conformer C is a mixed geometry, and although inactive in terms of a Woodward–Hoffmann-allowed photocyclization, the conformer might be populated in solution and therefore should be compared to the experimental data as well. Lastly, conformer D corresponds to the p conformation shown in Scheme 2. The rotation of the phenyl rings has been ignored in the conformational selection process, because these do not contribute to the NOE- and RDC-based conformational analysis of the central moieties.

To characterize this system further, the eight geometries were subsequently re-optimized by using density functional theory calculations (B3LYP/6-311+G(d,p)), IEFP model for CHCl₃ solvent, Gaussian 09.[27] The nature as a local minimum for each geometry was confirmed by vibrational frequency analysis, also giving access to the relative Gibbs free energies calculated from thermochemistry. Based on these calculations, the a-p (P*,S*,S*) geometry clearly has the lowest computed energy. The other a-p conformers are 6.8 [a-p (M*,S*,S*)] and 5.2 kJ·mol⁻¹ (a-p mixed) higher in energy, whereas the p conformer (averaged over both ring-flipped conformers) is 5.3 kJ·mol⁻¹ higher in energy.[22] The change in the envelope conformation of the cyclopentene core does not change the energy significantly, as the respective differences in energies are usually less than 0.5 kJ·mol⁻¹.[23] Although the computed energies are only rough estimates within the confines of the chosen method, they match well with the trends observed in other, experimental methods (see below).

Based on the observation of one signal set in the experimental spectra, we believe the ring-flip from conformer A into A’ (similarly for the other conformers) to be fast on the timescale of the NMR experiment, leading to a pseudo-C₂-symmetric ensemble of 50% conformer A and 50% conformer A’ (denoted A–A’, B–B’, and C–C’ accordingly), whereas the respective parallel D–D’ ensemble is part of the C₂ point group. Subsequently, the stereodiscrimination during the switching event should not be influenced by this process.

In an isotropic solution, the rapid interconversion of the envelope conformations leads to a reduced set of observables in the NMR analysis, as chemical shifts and J couplings are only determined for non-equivalent sites. In the case of the NOE, only an average of the distance of interacting nuclei on both sides of the molecules is experimentally accessible.[22] In an anisotropic environment, the molecular symmetry often reduces the number of independent order parameters or imposes the restrictions on the choice of the molecular frame for some specific point groups.[34,35] In the special case of a chiral alignment medium however (as used in this study) for both C₂- and C₂-symmetric molecules, the effective molecular symmetry is reduced to C₁.[35] This allows for the same mathematical treatment of C₂ and C₁, as for C₂ and thus the same software could be used in the analysis of the RDCs in these molecules. As indicated in Figure 5, the ring-flip averaged distances between the single protons of the cyclopentene moiety and thiophene rings vary greatly. A main distinctive feature is the rather small interproton distance of averaged 2.58 Å in the A–A’ [a-p(P*,S*,S*)] ensemble. All other computed ensembles clearly show larger averaged distances up to 4.75 Å (in the case of the a-p mixed ensemble C–C’).

### Determination of the conformer populations from averaged NOE distances

From quantitative measurements of the interproton distances by nuclear Overhauser enhancement (NOE) experiments,[36–39] we should therefore be able to distinguish between the conformations of compound 1. We obtained distances from a mixing time series of 1D PFGSE NOE experiments[40–42] with suppression of zero-quantum artifacts,[43–45] by using the PANIC approach.[46,47]

As reference distance, the distance between the protons from the methyl group located at the cyclopentene ring (H6–H6'...
in rigid compounds.\textsuperscript{52-57} As each conformer is treated as a rigid geometry and related to a distinct tensor, we refer to this method as the single-conformer–single-tensor fit (SCST).

When investigating flexible molecules like the dithienycyclopentenes (see Scheme 2), the situation is different because a second motional process must be considered in the RDC analysis. In addition to the tumbling motion of the entire molecule in the medium, as it is also the case in rigid molecules, the internal conformational mobility also has to be taken into account. A common way to describe this is to use an ensemble of conformers as a model for the structure proposal in the RDC calculation.\textsuperscript{26,58} In the generalized approach, each structure of the conformer ensemble is described with a distinct alignment tensor (multi-conformer–multi-tensor fit, MCMT).\textsuperscript{59,60} Although this allows for a general treatment, the disadvantage of this method is the rather large amount of experimental RDCs required to determine each alignment tensor. This problem can be circumvented by assuming a single common alignment tensor for the whole ensemble of structures (multi-conformer–single-tensor fit, MCST). Similar to the SCST approach, only six linearly independent RDCs are needed in the MCST, however special care has to be taken in the choice of a common molecular frame.\textsuperscript{61,62} Analysis of the MCST fit again relies on the back-calculation of the RDCs and comparison to experimental values to find the best-fitting one. Investigations into the applicability of the approximations introduced in the MCST approach are still ongoing. However, there are a few recent examples, where the MCST fit method was successfully applied to the RDC analysis of conformationally flexible molecules.\textsuperscript{59,60,63}

As the investigated compound shows a reduced set of signals due to its symmetry, it is essential to obtain as many RDCs as possible. Thus we used in addition to the established (CLIP)-ADEQUATE\textsuperscript{64} and HETLOC\textsuperscript{65,66} experiments, the \textit{J}-modulated 1,1-\textit{D}-modulated 1,1-ADEQUATE experiment for the determination of one-bond carbon–carbon couplings. Due to the low natural abundance of \textsuperscript{13}C and the challenging measurements in anisotropic environments, there are very few examples of RDC analyses making use of these couplings in non-isotopically labeled small molecules.\textsuperscript{66,70} To the best of our knowledge this is the first application of the \textit{J}-modulated 1,1-ADEQUATE experiment in anisotropic media. Without the additional couplings, the RDC analysis would not be applicable, as only an insufficient number of experimental couplings would be available for the fitting procedure.

We aligned a racemic mixture of dithienycyclopentene \textbf{1} in weak alignment media, being 1) a cross-linked poly-\textgamma-benzyl-L-glutamate (PBLG) gel\textsuperscript{71} and 2) a valine-polyacetylene derivative (PA)\textsuperscript{72} in CDCl\textsubscript{3} to obtain the anisotropic total couplings \textit{T}. The enantiodiscriminating properties of the homochiral phases of 1) and 2) noticeable in line broadening in the anisotropic spectra did not disturb the reliable extraction of the \textit{T}-couplings from the spectra.

A total of five $^{1}D(C,H)$, containing the calculated $^{1}D(C,C)$ from the three methyl groups, one long-range $^{1}D(C,H)$ and two $^{1}D(C,C)$ couplings including their relative signs, could be extracted from the isotropic as well as from the anisotropic spec-
tra. The experimental RDCs from the aligned PBLG gel sample are shown in Table 1 (numbering scheme see Figure 6). The RDCs obtained from the anisotropic polycytele phase are given in the Supporting Information.

For the conformer ensemble analysis we used the RDC module of the software hotFCHT.[58,73] To reflect the molecular symmetry in the calculation of the order tensor, the RDCs of symmetry equivalent couplings were set to the same value. By using any of the calculated structure models in a SCST fit, the quality factor of all models was very poor (best fit Q = 0.490), which is indicative of conformational flexibility.

Combining the conformers from Figure 5 with the opposite cyclopentene ring-flip yielded the four ensembles A–A’, B–B’, C–C’, and D–D’, the MCST approach led to an ensemble with a good representation of the experimental RDC data. Although the Q factors of the ensembles B–B’ [a–p (M*,S*,S*)], C–C’ [a–p mixed], and D–D’ (parallel) are weak (Q > 0.35), the ensemble A–A’ [a–p (P*,S*,S*)] represents the experimental RDCs very well resulting in a Q factor of 0.100 at a conformer population of 50% of conformer A and 50% of conformer A’. In this ensemble, only the experimental carbon–carbon coupling of C11–C10 in the thiophene rings differs in its calculated coupling of (0.08 ± 0.1) Hz from its experimental value of (1.29 ± 0.7) Hz. All other seven couplings are within the experimental error.

The same results are achieved by using PA as alignment medium. Although the degree of order in PA is significantly weaker than in the PBLG gel resulting in smaller dipolar couplings—some are in the range of the measurement error—the ensemble A–A’ [a–p (P*,S*,S*)] gives the best representation of the experimental data. A more detailed view of the PA measurements can be found in the Supporting information.

Although this analysis establishes the description of flexibility in the five-membered ring, the rotation along the C–C bond connecting the thiophene moiety and the central ring has to be studied further. Hence, we pairwise combined the above-described conformers in an ensemble by using the MCST approach to determine the conformational distribution between A–A’/B–B’, A–A’/C–C’, and A–A’/D–D’.

However, no distinct minimum in the conformational distribution can be found, (see Figure 7). As long as the population of the A–A’ sub-ensemble is higher than 50% (25% of conformer A and 25% of conformer A’), the Q factor indicates a good fit (=0.10). But as soon as the other conformers are populated to more than 50% (B–B’ or C–C’ or D–D’—each equally populated), the Q factor worsens quickly. Hence, we cannot exclude populations of the other conformer ensembles as the fit remains more or less equally well for up to 50%. However, when excluding the ensemble A–A’ from the MCST calculations, all fits become worse (Q > 0.20) regardless of the conformer population. The same result is obtained by combining all eight conformers. As soon as the conformers B–B’, C–C’, and D–D’ (each equally populated) are the majority (>50%), the Q factor deteriorates.

Comparison of the conformer populations from the NOE/RDC data to the data from VT NMR spectroscopy

The results of the RDC data show that the major conformation populated in solution is the a-p (P*,S*,S*) form. With a NOE-derived population of 83–91%, this conformation is the thermodynamically more stable helically pre-oriented ring-opened form of DAE 1a. Based on the difference in the Gibbs free energy, statistical weights of 72% a-p (P*,S*,S*), 7% a-p (M*,S*,S*), 10% a-p mixed, and 10% of the p conformer can be estimated according to a Boltzmann distribution,[27] which matches the population obtained from the NOE experiments surprisingly well.

This result is also in good accordance with the results from the X-ray crystallographic data of compound 5a. Hence, it becomes even more reasonable to assume that the relative configuration of the major ring-closed diastereomer (1c1) corresponds to the S*,S*,R*,R* geometry.

Surprisingly, the population of the a-p conformer of compound 10 determined in this study is very similar to the population of the a-p form of the tetramethyl bridge-substituted DAE 4a, determined to be 81% by VT 1H NMR spectroscopy,
whereas simultaneously exhibiting a photocyclization quantum yield of $\Phi_{ac} = 0.83$. The comparatively lower photocyclization quantum yield of $\Phi_{ac} = 0.6$ for compound 1, while maintaining the same level of population of the a-p conformer around 80%, therefore might stem from additional effects beyond the scope of this work.

As we had hoped to find a more immediate relation of the a-p conformer population and the photocyclization quantum yield, we re-investigated the tetramethyl bridge-substituted DAE 40. When trying to reproduce the non-linear shifting of resonances previously observed in the VT $^1$H NMR experiments, we were unable to find any non-linear shift. All resonances show a slight linear (but no non-linear) shift upon cooling of the sample. This is in contrast to the previously published data and may be explained by incorrect temperature calibration of the spectrometer in the previous work. However, from the changes in the signal pattern of the $^1$H NMR spectra at different temperatures, we expect only the pseudo-C$_2$-symmetric a-p conformer form to be populated at RT. This is based on the number of signals expected for the two protons in the five-membered bridge: the a-p conformation would lead to a pseudo-C$_2$-symmetry and the two protons become homotopic, whereas the p conformation would be pseudo-C$_2$-symmetric and the two protons should be diastereotopic and give distinct NMR signals. As we only observe a single, sharp resonance over the whole temperature range, we rule out a significant population of the p conformation. Unless there is incidental isochronicity of resonances, we therefore presume the a-p conformation of compound 40 to be exclusively populated at RT. We tried to corroborate this result by NOE measurements as detailed above for compound 10. Although we were able to quantify the NOE of interest from the bridge methyl groups to the thienyl proton, we were unable to reliably quantify another NOE correlation as reference. Without this reference, we were unable to estimate the population based on NOEs. The indications from the number of signals observed for compound 40 in combination with expected symmetry point towards an exclusive population of the a-p conformation in compound 40. Performing DFT calculations as described above, we estimate a Boltzmann population of 92% of the a-p conformer versus 8% of the p conformer of compound 40. Thus, the trend observed for the photocyclization quantum yields goes into the same direction as the population of the a-p conformation in compounds 10 and 40.

**Conclusion**

By combining different analytical methods, namely, UPLC-MS, X-ray crystallography, NOE, VT $^1$H NMR spectroscopy, and RDC measurements, we could gain unprecedented insight into the stereoselective switching behavior of bridge-substituted dithienylethenes. X-ray crystallography on a distinct derivative revealed that the major helically pre-oriented form in the crystalline state is a-p (P*,S*,S*) form suggesting (S*,S*,R*,R*) being the most prevalent form in the ring-closed form. RDC studies of compound 10 revealed a similar conformation for the major open form as a-p (P*,S*,S*). This is consistent with the NOE measurements, in which the distance between the single protons of the cyclopentene and thiophene rings fits well with the predicted average distance of the computed a-p conformer ensemble. Combined with DFT calculations, these results suggest that the a-p (P*,S*,S*) form is the thermodynamically more stable and thus major conformer in the ground state as compared to the minor a-p (M*,S*,S*) conformer. We attribute this to the steric repulsion between the β-thienyl protons and the alkyl substituents in the cyclopentene bridge moiety. However, the thermal barrier for their respective interconversion at room temperature was found to be small and hence the ratio of both conformers remains constant throughout the cyclization process. In view of the comparable photokinetic factors (product of the quantum yield and the molar absorptivity at the irradiation wavelength) of both ring-opened conformers, the ratio of the formed ring-closed diastereomers, that is, (S*,S*,R*,R*)/all-(S*), should also remain constant throughout the cyclization process. Therefore, the degree of diastereoselectivity is indeed predetermined by the conformer ratio of their ring-opened precursors as schematically depicted by a stylized potential energy diagram in Scheme 3.

However, as the ring-opening processes of the ring-closed diastereomers proceed at unequal rates due to dissimilar photokinetic factors caused by different absorption spectra, a net shift of the overall de in the irradiated solution could be induced over multiple switching cycles. By this means, we demonstrate for the first time that the ratio of two diastereomers can be controlled by employing subsequent irradiation cycles with UV and visible light.

Furthermore, it is quite intriguing that the conformer population in the ground state could be nicely correlated to

![Scheme 3. Potential energy diagram for the interconversion of the a-p helically pre-oriented conformers of DAEs 10–30 and subsequent photoinduced cyclization to their respective closed-form diastereomers.](image-url)

the trends seen in the observed cyclization quantum yields of DAEs 1–4 and thus reinforces the insight that only the α-p conformation can be regarded as photoactive.

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