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■ Bistable Switches

Spectroscopic and Theoretical Identification of Two Thermal Isomerization Pathways for Bistable Chiral Overcrowded Alkenes

Jos C. M. Kistemaker⁺, Stefano F. Pizzolato⁺, Thomas van Leeuwen, Thomas C. Pijper, and Ben L. Feringa^{*[a]}

Abstract: Chiroptical molecular switches play an important role in responsive materials and dynamic molecular systems. Here we present the synthesis of four chiral overcrowded alkenes and the experimental and computational study of their photochemical and thermal behavior. By irradiation with UV light, metastable diastereoisomers with opposite helicity were generated through high yielding *E*–*Z* isomerizations. Kinetic studies on metastable 1–4 using CD spectroscopy and HPLC analysis revealed two pathways at higher temperatures for the thermal isomerization, namely a thermal *E*–*Z* isomerization (TEZI) and a thermal helix inversion (THI). These processes were also studied computationally whereby a new strategy was developed for calculating the TEZI barrier

for second-generation overcrowded alkenes. To demonstrate that these overcrowded alkenes can be employed as bistable switches, photochromic cycling was performed, which showed that the alkenes display good selectivity and fatigue resistance over multiple irradiation cycles. In particular, switch 3 displayed the best performance in forward and backward photoswitching, while 1 excelled in thermal stability of the photogenerated metastable form. Overall, the alkenes studied showed a remarkable and unprecedented combination of switching properties including dynamic helicity, reversibility, selectivity, fatigue resistance, and thermal stability.

Introduction

Responsive materials^[1–3] and dynamic molecular systems^[4–10] that change structure and functions as a result of an external input signal are attracting major attention owing to the prospect of smart materials^[11–17] and nanoscale devices.^[18–22] Photochemical switches allow for non-invasive control, reversibility and high spatio-temporal precision.^[5] Overcrowded alkenes have been used in a wide variety of responsive nanoscale systems, such as in a molecular car powered by four unidirectional molecular motors or as multi-state switches featuring dynamic functions of which up to four distinct configurations can be addressed.^[23–25] The large number of structural modifications that has been presented by our group and others has expanded the field of molecular design with three generations of photoswitchable overcrowded alkenes, the majority of which exhibits a strong directional preference and functions as rotary motors.^[7,26–32] Through desymmetrization of our systems, the unidirectionality of the rotary motion has been extensively demonstrated and various stereoisomers have been identified by spectroscopic and chromatographic techniques for each variation in design.^[33–44] A key aspect of these systems is that the photochemical generation of metastable species is followed by thermally induced isomerizations, for which the lifetimes have been tuned through structural changes to range from nanoseconds to years.^[34,38,44,45] Hence, overcrowded alkenes can be defined as either motors or switches depending on the activation energy and therefore speed of the thermal isomerization step (i.e. when the rotation rate is the limiting step). Their propensity to undergo continuous light- and ther-

mal-induced directional rotary motion (motor behavior), however, diminishes their usefulness as switches in applications where thermal stability is desired, for example, in the field of photoswitchable catalysis.^[24,46,47] As such, there is a demand for thermally highly stable alkenes that can be switched photochemically and reversibly between distinct geometrical chiral forms.

Molecular motors of the second generation consist of a symmetric 'lower' half (for *R*=H) and an asymmetric 'upper' half that feature a single stereocenter (Scheme 1).^[30,48]

Scheme 1. General scheme of photochemical *E*–*Z* isomerization and thermal helix inversion of second-generation molecular motors.

Upon irradiation with UV light they can undergo a photochemical *E*–*Z* isomerization, a process that results in a metastable (MS) diastereoisomer which is of the opposite helicity. In this process, the methyl substituent on the stereogenic center has changed from an unhindered outward facing axial orientation to an equatorial orientation in which the methyl faces the lower half, thus creating steric hindrance. This steric strain causes the MS diastereoisomer to be higher in energy with respect to the original configuration. The strain can subsequently be reduced by a thermally activated isomerization in which (usually) the upper half moves around the lower half, again resulting in an inversion of the helicity. In the resulting stable isomer, the upper half has undergone a 180° rotation with respect to the lower half (see Scheme 1, in the case *R*=H, the symmetry in the lower half causes the initial and final states to be chemically identical). In theory, it is possible that the thermal isomerization of the metastable state follows an alterna-

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tive and competing pathway other than thermal helix inversion (THI). Structurally similar stilbene switches are able to undergo thermal *E*-*Z* isomerization (TEZI) from *cis* to *trans*, although the activation energy for this process usually exceeds 150 kJ mol^{-1} .^[49,50] For some overcrowded alkenes though, this barrier has been observed to be significantly lower due to the steric strain in the minimum energy configurations, thus forcing the double bond far from planarity. As an example, bis-fluorenylidene exhibit activation energies for the TEZI of $\sim 105 \text{ kJ mol}^{-1}$.^[51,52] For second-generation motors, in order to positively identify the outcome of the thermal isomerization of the photochemically generated metastable state the lower half has to be desymmetrized. The two-step process starting from the stable-(*Z*) state will then lead either to the opposite isomer stable-(*E*) of the initial configuration, which is indicative of a THI, or back to the initial stable isomer stable-(*Z*), thus indicating a reversible switching process by a TEZI (Scheme 2).

Scheme 2. General scheme for photochemical and thermal behavior (TEZI vs. THI) of desymmetrized overcrowded alkenes stable-(*Z*) and metastable-(*E*).

Previously, research on molecular motors has to a large extent been supported by computational chemistry.^[31,48,53–55] For example, it has been shown that the energy barrier of the thermal helix inversion can be predicted with reasonable accuracy (within several kJ mol^{-1}) through the use of density functional theory (DFT) at the B3LYP/6-31G(d,p) level.^[31,44,48,53,55] Indeed, this method has been utilized to design new motors in silico by prediction of the helix inversion energy barriers of motors prior to their synthesis to determine whether their rotation rates would be of the desired order of magnitude. However, to date a method has not been available that can accurately predict the energy barrier of the potentially competing TEZI. The reason for the lack of a suitable computational method for investigating the TEZI is that the transition state (TS) involved cannot be accurately described by single determinant methods such as Hartree–Fock and Kohn–Sham DFT. For this reason, a multideterminant method has to be employed instead. One popular multideterminant method potentially capable of providing an accurate description is the CASSCF theory in which the orbitals of interest are treated as in a full configuration interaction (CI) calculation (the active space).^[56] Such an approach can be very effective in describing

the ‘static correlation’ that often cannot be accounted for effectively by a single determinant method. Unfortunately, the use of CASSCF is limited by the number of orbitals that can be treated in this way, since full CI calculations are computationally demanding. In practice, the size of a complete active space is often limited to 14 electrons in 14 orbitals to keep the calculation manageable.^[57] This poses a challenge as the π system of a molecular motor is typically much larger. As such, if CASSCF or a related theory is to be used for studies on molecular motors, it is necessary to limit the number of CSFs in such a way that the accuracy is not significantly impaired.

Herein, we report on the switching behavior of four second-generation overcrowded alkenes, namely 1–4 (Scheme 3). Their photochemical and thermal isomerization processes have been studied by various analytical methods, while the thermal isomerization processes are also studied by computational methods. A strategy for studying the TEZI by computational chemistry will also be presented. We will show that the metastable isomers of 1–4 are able to undergo thermal isomerization through both the THI and TEZI pathways. Finally, we will demonstrate that 1–4 exhibit properties that make them highly useful bistable switches, such as high selectivity, low switching fatigue, and high thermal stability.

Scheme 3. Reaction conditions: i) methacrylic acid, NEt_3 , THF, Δ , 16 h; ii) $(\text{COCl})_2$, DMF, DCM, rt, 1 h; iii) AlCl_3 , DCM, 0°C , 1.5 h, 80% (over 3 steps); iv) $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$, $\text{Sc}(\text{OTf})_3$, EtOH, Δ , 16 h, 68%; v) 8–10 $\rightarrow$ 1–3: 1) BTI, DMF, -40°C , 1 min; 2) 12, DMF, DCM, -40°C - rt, 1 h; 3) HMPT, toluene, 65°C , 16 h; 11 $\rightarrow$ 4: 1) P_4S_{10} , toluene, 70°C , 3 h; 2) 13, toluene, Δ , 16 h; 3) PPh_3 , toluene, Δ , 16 h; 1 45% *Z*:*E* 1:1.1, 2 50% *Z*:*E* 1:1.3, 3 62% *Z*:*E* 1:1, 4 24% *Z*:*E* 1:1.

Results and Discussion

Design

As mentioned above, the bridging units (X and Y, see Scheme 1) included in the rings connected by the tetrasubsti-

tuted alkene play an important role in the structure's flexibility, thermal stability, and switching properties. Previous studies on overcrowded alkenes with symmetrical lower halves have shown the effect of the size of the rings connected to the bridging alkene bond on the activation barrier of the thermal relaxation step.^[48] In particular, the combination of a five-membered ring in the lower half (fluorene) with a sulfur- or oxygen-containing six-membered ring in the upper half (Scheme 1, benzo[f]thiochromene ($X=S$, $Y=-$) and benzo[f]chromene ($X=O$, $Y=-$), respectively) resulted in distinctive high energy activation barriers for the thermal relaxation step and consequently long half-lives of the metastable species ($\Delta^\ddagger G^\circ = 109 \text{ kJ mol}^{-1}$, $t_{1/2}$ at room temperature (rt) = 35 days ($X=S$) and $\Delta^\ddagger G^\circ = 106 \text{ kJ mol}^{-1}$, $t_{1/2}$ at rt = 9.4 days ($X=O$), respectively). Due to the lack of asymmetry in the lower half, the two aforementioned competing thermal pathways, that is, THI and TEZI, could not be distinguished, as they would give access to the two undistinguishable products. Therefore, we decided to extend our investigation by synthesizing four overcrowded alkenes of the second generation with an asymmetric substitution pattern in the lower half (1–4, Scheme 3), expecting these systems to display thermal bistability.

Synthesis

Hydrazone **8** was synthesized from commercially available 2,5-dimethylbenzenethiol in four steps with a 54% overall yield. Compounds **9–11** with a naphthyl moiety were prepared following modified literature procedures (see Supporting Information material).^[58,59] A Barton–Kellogg coupling of thioketone **12** and the diazo species, obtained by the in situ oxidation of the corresponding hydrazones **8–10** with [bis(trifluoroacetoxy)iodo]benzene (BTI), afforded mixtures of isomers of episulfides with varying *E/Z* ratios. The mixtures were separated by flash column chromatography and subsequently desulfurized to obtain the corresponding overcrowded alkenes. A Barton–Kellogg coupling of the diazo species **13** and the thioketone, obtained by thiation of the corresponding ketone **11**, provided a mixture of alkenes and episulfides which were directly desulfurized, yielding the desired overcrowded alkenes. The *E/Z* isomers were separated by column chromatography and assigned by the difference in chemical shift of the absorptions corresponding to the methoxy substituent and the protons in position 1 or 8 at the lower half in the ^1H NMR spectra (for example: stable-(*Z*)-**1** $\delta = 3.42 \text{ ppm}$ ($\text{CH}_3\text{O}-$), stable-(*E*)-**1** $\delta = 3.93 \text{ ppm}$ ($\text{CH}_3\text{O}-$); for full details see the section Characterization, irradiation experiments and Eyring analysis in the Supporting Information). The enantiomers of **1–4** were separated by preparative chiral HPLC (Figure 1, Figure 2 and Supporting Information for full details).

Photochemical and thermal isomerizations

Single enantiomers of each overcrowded alkene were subjected to circular dichroism (CD) spectroscopy to assign absolute stereochemistry as well as to perform a qualitative analysis. The isolated enantiomers of compounds **1–4** displayed strong

Figure 1. CD spectra of **1–4**. Black: experimental CD spectra of (*Z,P,S*)-**1**, (*Z,P,S*)-**2**, (*Z,P,R*)-**3**, and (*Z,M,R*)-**4** (heptane, $1.0 \times 10^{-5} \text{ M}$). Blue: theoretical ECD spectra calculated with TD-DFT, normalized and shifted by 30 nm (B3LYP/6-31+G(d,p) applying Gaussian shapes (line width = 0.3 eV) to 30 discrete transitions) used to assign enantiomers. Red: CD spectra of PSS mixtures of **1** (312 nm), **2** (365 nm), **3** (312 nm), and **4** (365 nm). Irradiation conditions: the PSS mixtures were obtained starting from the above-mentioned solutions (heptane, $1.0 \times 10^{-5} \text{ M}$, black curves) after irradiation (indicated wavelength) at room temperature over 2 min.

Cotton effects in the area of $\sim 250\text{--}320 \text{ nm}$ and slightly smaller Cotton effects of opposite sign at higher wavelengths ($> 320 \text{ nm}$) with the exception of compound **3** which lacked such a longer wavelength absorption band (Figure 1).

The presence of such strong Cotton effects around 400 nm is indicative of the helical shape of these overcrowded alkenes, while the lack of this band for compound **3** could be due to the absence of a heteroatom in its core structure (which is present in the other compounds).

To assign absolute stereochemistry, experimentally obtained CD spectra were compared to the calculated CD spectra. Potential energy surfaces of **1–4** were investigated with the semi-empirical PM3 method and the geometries of the resulting minima and transition states were refined by using DFT (B3LYP/6-31G(d,p) (vide infra). Time-dependent (TD) DFT with the B3LYP functional and a 6-31+G(d,p) basis set provided theoretical CD spectra of **1–4** and allowed the assignment of the absolute stereochemistries of **1–4** (Figure 1). Due to the existence of multiple conformations (e. g. of the methoxy group) and the uncertainty in the calculated Boltzmann distribution used to proportionate the spectra of the individual conformations, the calculated spectra were not expected to display a complete match with the experimental data. However, the match is sufficient to allow the discrimination between the two possible enantiomers and is therefore suitable for the assignment of the absolute stereochemistry of **1–4**.^[31,40,55,60]

The chiral descriptors for each species described in this work (e. g. (*Z,P,S*)-**1**, Figure 1) indicate respectively: the configurational isomer of the tetrasubstituted alkene (*E* or *Z*), the configura-

tional helicity of the molecule (*P* or *M*), and the absolute stereochemistry of the stereogenic center (*R* or *S*).

The correlation between the Cotton effect and the helicity agrees with the results of Cnossen et al. in which the same correlation was observed for four different overcrowded alkenes.^[55] Compounds with a positive helicity display a negative Cotton effect for the longest wavelength absorption band and vice versa, with the exception of **3** as this species lacks a strong CD absorption band in the 350–450 nm region (vide supra).

UV irradiation of solutions in heptane (312 or 365 nm, see Figure 1 for details) of each of the *Z* isomers of **1–4** resulted in the inversion of the major bands in their CD spectra. This is indicative of an inversion in helicity and shows that the photochemical *Z–E* isomerization of the stable-(*Z*)-**1–4** to the metastable-(*E*)-**1–4** has taken place. The presence of the metastable-(*E*) isomers was further confirmed by chiral HPLC analysis (Figure 2) and ¹H NMR spectroscopy (illustrated for **1** in Figure 3, see Supporting Information for further details). The ratio between the *E* and *Z* isomers at the photostationary state (PSS) in heptane solution was determined by chiral HPLC analysis (*E:Z* ratio: (*S*)-**1** 95:5, (*S*)-**2** 96:4, (*R*)-**3** 97:3, and (*R*)-**4** 99:1), showing an almost quantitative photoswitching process towards the metastable diastereoisomer for all four compounds, with remarkably high ratios for this class of overcrowded alkene based switches.

Heating the irradiated samples allowed them to undergo thermal isomerization (for conditions, see Figure 4), which resulted in major changes in their CD spectra. HPLC chromato-

Figure 2. Chiral HPLC traces of **1–4**. Top: HPLC traces (heptane/2-propanol) of pure enantiomers separated by preparative chiral HPLC (structures of stable-*Z* isomers depicted in Figure 1) as assigned by CD absorption spectroscopy: (*Z,P,S*)-**1** (Chiralcel OD-H, 98:2), (*Z,P,S*)-**2** (Chiralpak AD-H, 97:3), (*Z,P,R*)-**3** (Chiralcel OD-H, 98:2), and (*Z,M,R*)-**4** (Chiralcel OD, 99.3:0.7). Middle: HPLC traces of the PSS mixtures of **1–4** (identical conditions). Bottom: HPLC traces after subsequent thermal isomerization of **1–4** (identical conditions). For irradiation and thermal isomerization conditions, see Figure 1 and Figure 4.

Figure 3. ¹H NMR spectra of the switching process of **1**. a) ¹H NMR spectra of stable-(*Z*)-**1** (~3 mg in CDCl₃, 0.8 mL); b) ¹H NMR spectra after irradiation of stable-(*Z*)-**1** (312 nm) to the metastable state affording a PSS mixture in CDCl₃ of stable-(*Z*)-**1**:metastable-(*E*)-**1** = 16:84 (note: PSS ratios are known to be affected by nature of solvent, vide supra).

Figure 4. Decay curves (top/left axes) and Eyring plots (bottom/right axes) of metastable **1–4**. Decay curves of: (*E,M,S*)-**1** recorded by HPLC taking aliquots from a hexanol solution (131–152 °C); (*E,M,S*)-**2** recorded by HPLC taking aliquots from a dodecane solution (112–132 °C); (*E,M,R*)-**3** recorded by CD in dodecane (95–105 °C); (*E,P,R*)-**4** recorded by CD in dodecane (84–105 °C). Least-squares analysis on the original Eyring equation for **1–4** with error bars of 3σ. (heptane, 1.0 × 10^{−5} M). Thermal decay conditions: the PSS mixtures (hexanol or dodecane, 1.0 × 10^{−5} M) were heated at fixed temperatures starting from the above-mentioned solutions (black curves) after irradiation with UV light (indicated wavelength) at room temperature over 2 min under stirring.

grams of the resulting samples showed a partial reversal of the metastable-(*E*) isomer to the initial, stable-(*Z*) isomer which is observed together with the appearance of a new peak attributed to the stable-(*E*) isomer (Figure 2). These results signify: i) that the photochemical *Z* to *E* isomerization results in the formation of a highly stable diastereoisomer that is able to relax measurably only at high temperatures, and ii) that relaxation can take place via two competing pathways, one leading to the initial isomer through TEZI and the other leading to the corresponding *E* isomer through THI (Scheme 2).

To investigate the kinetic behavior of the two thermal isomerization pathways, samples of alkenes **1–4** were irradiated to PSS at room temperature after which their thermal relaxation was monitored over time. For alkenes **3** and **4**, thermal relaxation was followed in real-time using CD spectroscopy at the specific wavelength (381 nm and 395 nm, respectively) which showed the largest difference between the initial stable-(Z) isomer and the PSS mixture (Figure 4). However, for alkenes **1** and **2** this setup was not suitable as the thermal relaxation of these alkenes, in order to become observable, required temperatures that are above the temperature range of the temperature controller of the CD spectrophotometer employed. Instead, solutions of (Z,P,S)-**1** and (Z,P,S)-**2** in hexanol and dodecane, respectively, were irradiated to PSS and placed in a temperature-controlled oil bath. Aliquots were then taken regularly and analyzed by chiral HPLC. A least squares analysis of the HPLC integrals of the major diastereoisomers of **1** and **2** versus time and the change in CD absorption for **3** and **4** versus time provided the reaction rates (k_{total}) for the thermal isomerization process at various temperatures. The observed rate is the sum of the individual rates for TEZI and THI (k_{TEZI} and k_{THI}) and these are related as given in Equation (1),

$$\frac{k_{\text{TEZI}}}{k_{\text{THI}}} = \frac{[\text{stable} - (Z)]}{[\text{stable} - (E)]} \quad (1)$$

where the final ratio between the stable-(Z) and stable-(E) isomers is obtained from HPLC after correction for the initial concentration of the stable-(Z) isomer at PSS. A least-squares analysis of the rates versus the temperature on the original Eyring equation (2),

$$k = \frac{k_B T}{h} e^{\left(\frac{\Delta^\ddagger S^\circ}{R}\right)} e^{\left(\frac{\Delta^\ddagger H^\circ}{RT}\right)} \quad (2)$$

with appropriate weighing ($1/k^2$) afforded the entropies and enthalpies of activation. The standard errors (σ) were obtained from a Monte Carlo error analysis on the linearized Eyring equation (3),

$$T \cdot \ln\left(\frac{k}{T}\right) = T \cdot \left(\ln\left(\frac{k_B}{h}\right) + \frac{\Delta^\ddagger S^\circ}{R} \right) - \frac{\Delta^\ddagger H^\circ}{R} \quad (3)$$

from forty thousand samples using calculated standard errors on rates and estimated standard errors on temperatures. The results of the Eyring analysis are summarized in Table 1. From the fitting curves in Figure 4 it is evident that the increase in temperature is accompanied by a decrease in accuracy. This is expected for these experiments and therefore an extensive error analysis has been performed to assure the validity of the results from the Eyring analysis. While the error on the derived enthalpy ($\Delta^\ddagger H^\circ$) and entropy ($\Delta^\ddagger S^\circ$) of activation are appreciable, the error on the Gibbs free energy of activation ($\Delta^\ddagger G$) remains small particularly when it is calculated for a temperature in or near the range of temperatures in which the thermal relaxation was observed.

Table 1. Kinetic parameters determined by the direct Eyring analysis (Figure 4), with standard errors obtained from a Monte Carlo analysis for thermal isomerizations (TEZI and THI) of metastable **1–4**.

	(E,M,S)- 1	(E,M,S)- 2	(E,M,R)- 3	(E,P,R)- 4
$t_{1/2}$ at rt [years] ^[a]	75 ± 35	4.3 ± 4.2 × 10 ⁴	1.3 ± 0.6	1.3 ± 0.2
T at $t_{1/2} = 1$ h [°C]	138.2 ± 0.4	121.3 ± 0.3	116.0 ± 0.7	99.1 ± 0.2
$\Delta^\ddagger H^\circ_{\text{TEZI}}$ [kJ mol ⁻¹]	110 ± 5.4	184 ± 8.1	86.6 ± 4.1	108 ± 2.6
$\Delta^\ddagger S^\circ_{\text{TEZI}}$ [J K ⁻¹ mol ⁻¹]	-51.3 ± 13	147 ± 21	-98.5 ± 11	-30.9 ± 7.1
$\Delta^\ddagger G^\circ_{\text{TEZI}}$ [kJ mol ⁻¹] ^[b]	129 ± 0.6	129 ± 0.5	123 ± 0.1	120 ± 0.5
$\Delta^\ddagger H^\circ_{\text{THI}}$ [kJ mol ⁻¹]	118 ± 5.7	208 ± 9.2	99.4 ± 4.6	96.5 ± 2.4
$\Delta^\ddagger S^\circ_{\text{THI}}$ [J K ⁻¹ mol ⁻¹]	-53.2 ± 14	182 ± 23	-72.8 ± 12	-68.0 ± 6.6
$\Delta^\ddagger G^\circ_{\text{THI}}$ [kJ mol ⁻¹] ^[b]	138 ± 0.6	140 ± 0.6	127 ± 0.1	122 ± 0.5

[a] Room temperature (rt): 20 °C. [b] Standard conditions: 100 °C and atmospheric pressure.

The reason for this is that extrapolation of these parameters to room temperature spans over hundred degrees Celsius for some examples thus magnifying the uncertainty. This is notably observed for the half-life at room temperature, an often reported feature. For example, the standard error determined for the half-life of **2** is as large as the half-life itself. Therefore we report a more appropriate characteristic of the first-order reaction, namely the 'hour half-life temperature' which is the temperature at which the half-life equals one hour. This property is not an extrapolation but usually falls within or close to the range of measured temperatures and is derived from the Eyring equation by the use of the Lambert W function^[61] as in Equation (4).

$$T_{t_{1/2}=1\text{h}} = \Delta^\ddagger H^\circ \cdot \left(R \left(\frac{3600 \cdot k_B \cdot \Delta^\ddagger H^\circ \cdot e^{\frac{\Delta^\ddagger S^\circ}{R}}}{h \cdot \ln(2)} \right) \right)^{-1} \quad (4)$$

The error on the parameters discussed for different processes is reduced to less than a percent of the parameter. Moreover, the temperature at which the half-life equals one hour is a much more chemically intuitive feature, particularly when the half-lives at room temperature of the processes under investigation are over a year or even exceeding forty thousand years (as for (E,M,S)-**2**).

Going from oxygen in **4** (X=O), carbon in **3** (X=C), to sulfur in **2** (X=S), the hour half-life temperature increases from 99 to 116 and 121 °C, indicating an increase in stability of the metastable diastereoisomer. Furthermore, substituting the naphthalene moiety in **2** for the xylene moiety in **1** increases the hour half-life temperature even further to 138 °C. From the Gibbs free energy of activation for the two possible pathways it is clear that under standard conditions the TEZI pathway is preferred over the THI pathway.

Plotting the Gibbs free energy versus temperature (Figure 5), hereby assuming that the enthalpy and entropy are temperature independent, reveals that for the entire temperature range under investigation (experimental temperature range: 85–152 °C) the barrier for the TEZI is lower than that for the THI for all alkenes **1–4**. A difference in the entropy of activation for the two processes logically leads to the existence of

a point at which the rates for the two processes are expected to be equal. Such a point would signify the inversion of the two processes, because beyond this temperature the barrier of the THI will be lower than that of the TEZI. For alkenes **3** and **4**, these points are found at relevant temperatures (37.8 °C and 226 °C, respectively), while for **1** and **2** the inversions would take place either far outside of the experimentally significant temperature range or never at all (411 °C and < 0 K, respectively).

Figure 5. Gibbs free energy of activation for the TEZI and the THI processes plotted versus temperature for the metastable diastereoisomers of alkenes **1–4**. The experimental temperature range is marked by gray vertical lines (85–152 °C), inversion points for the two processes are marked for **3** and **4** by a dot.

Computational results

The experimental study of the thermal behavior of the metastable diastereoisomers (*E*)-**1–4** was accompanied by a computational study of the potential energy surface of overcrowded alkenes **1–4**. As indicated above, a semi-empirical scan of the PES (PM3) provided minima and transition states which were refined by using DFT with the B3LYP functional and a 6-31G(d,p) basis set.^[62–69] However, while Kohn–Sham DFT theory is adequate for studies into the THI pathway, studies into the TEZI pathway require the use of a method capable of accounting for static correlation. The reason for this is that the TS of the TEZI has strong biradicaloid character which cannot be properly described with a single-determinant method.^[53] As such, calculations on the TEZI pathway were performed by using CASSCF and MRMP2 theories.

Initial TEZI TS geometries were obtained at the GVB-PP(1) level (which gives results identical to CASSCF(2,2)) using the 3-21G basis set. The initial geometries were subsequently refined at the CASSCF(10,10)/6-31G(d) level. In cases where more than one transition state geometry was found, subsequent calculations were performed for all geometries to determine their energies. Each optimized geometry was subjected to a vibrational analysis to verify whether it truly corresponds to a minimum on the PES (or first-order saddle point in the case of a TS ge-

ometry). From these calculations, thermochemical corrections (at $T = 373.15$ K and $p = 1$ atm) to the calculated energies were also obtained. The CASSCF(10,10)/6-31G(d)-optimized geometries were finally used to calculate energies at the MRMP2/CASSCF(14,14)/6-31G(d) level (Figure 6), to which the thermochemical corrections were subsequently added. It should

Figure 6. a) Active space used in CASSCF(14,14) and MRMP2/CASSCF(14,14) calculations. π bonds included are indicated with red circles. b) Correlation between X-ring size and thermal relaxation energy barrier.

hereby be noted that energy calculations at the MRMP2/CASSCF(14,14)/cc-pVTZ level were attempted as well, but were found to display a larger deviation from experimental results. This observation, combined with the use of an active space which excludes part of the π system as well as lone pairs of heteroatoms, suggests that the predictive accuracy of the presented method (see Table 3) is in part due to a favorable cancellation of errors. A more detailed discussion of the computational approach used is presented in the Computational Study into the Thermal *E–Z* Isomerization Pathway section in the Supporting Information.

The calculated Gibbs free energies are summarized for alkenes **1–4** in Table 2 and the obtained geometries for (*S*)-**2** are depicted in Figure 7 as an example. The geometries of **1**, **3**, and **4** do not differ significantly in general appearance from those of **2**, although they naturally do differ in specific bond angles and lengths. Going from alkene **4** to alkene **3** to alkene **2**, the size of the bridging atom X in the upper half increases, which is accompanied by an increase in the size of that ring and thus forces the aryl moiety towards the lower half (Figure 6b, Table 2). The increase in steric hindrance is alleviated by additional folding of the six-membered ring, as can be seen

Table 2. Relative Gibbs free energies of **1–4** calculated at the DFT-B3LYP/6-31G(d,p) level or MRMP2/CASSCF(14,14)/6-31G(d)//CASSCF(10,10)/6-31G(d) level indicated by * (373.15 K, 1 atm, in kJ mol^{−1}).

	(<i>S</i>)- 1	(<i>S</i>)- 2	(<i>R</i>)- 3	(<i>R</i>)- 4
stable-(<i>Z</i>)	0	0	0	0
TS TEZI*	165	150	146	138
metastable-(<i>E</i>)	22.2	23.1	27.2	24.9
TS THI	163	165	151	146
stable-(<i>E</i>)	0.94	1.74	1.89	1.46
MS-(<i>E</i>) X-ring size [pm] ^[a]	961	958	901	875
MS-(<i>E</i>) dihedral angle [°] ^[b]	46.7	47.6	42.6	41.4

[a] Summed lengths of the bonds making up the six-membered ring in the upper half (Figure 6b). [b] Dihedral angle made up by atoms **1**, **2** and the central alkene as indicated in Figure 6a.

Figure 7. Calculated geometries of (S)-2 (X=S). Left: top view with the upper half on top, the alkene on the z-axis and the fluorene in the x-z plane, right: front view with the alkene on the y-axis and the fluorene in the x-y plane.

from the dihedral angle made up by atoms 1, 2, and the central alkene (as indicated in Figure 6a for the metastable-(E) isomer). Both **1** and **2** are bridged by a sulfur atom and therefore hardly differ in ring size, although the difference between the aryl and xyllyl moieties is to a small extent reflected by their dihedral angles (see 'dihedral angle' in Table 2). The barrier for the THI increases with an increase in the degree of folding of the upper half, as is seen from the dihedral angle. A similar increase is observed for the calculated barrier for the TEZI, with the exception of **1** which exhibits a significantly higher barrier without an increase in folding with respect to **2**. A rationale for this difference in activation energy is that the six-electron π -system of the xyllyl moiety of **1** is less effective in stabilizing the biradicaloid character of the TS geometry com-

pared to the larger 10-electron π -system of the naphthyl moiety of **2** (see the Computational Study into the Thermal E-Z Isomerization Pathway" section in the Supporting Information).

Table 3 provides an overview of the experimentally determined and calculated Gibbs free energies of activation for the TEZI and THI pathways for alkenes **1–4**. The calculated barriers for the THI agree strongly with those found experimentally, differing by no more than 3 kJ mol⁻¹. The calculated barriers for

Table 3. Comparison of experimental and theoretical barriers for TEZI and THI of **1–4**.^[a]

Metastable:	(E)-1	(E)-2	(E)-3	(E)-4
$\Delta^\ddagger G^\circ_{\text{TEZI}}$ [kJ mol ⁻¹]	129 ± 0.6	129 ± 0.5	123 ± 0.1	120 ± 0.5
$\Delta^\ddagger G^{\text{calc}}_{\text{TEZI}}$ [kJ mol ⁻¹]	142	127	119	113
$\Delta^\ddagger G^\circ_{\text{THI}}$ [kJ mol ⁻¹]	138 ± 0.6	140 ± 0.6	127 ± 0.1	122 ± 0.5
$\Delta^\ddagger G^{\text{calc}}_{\text{THI}}$ [kJ mol ⁻¹]	141	142	124	121

[a] Standard conditions: 100 °C and atmospheric pressure.

the TEZI deviate more from the experimentally determined barriers. The barriers of **2** and **3** correspond well, whereas the barrier of **1** is overestimated and the barrier of **4** is slightly underestimated. The slight underestimation of the TEZI barrier for **4** still allows a reasonable prediction of the behavior of the overcrowded alkene, however, the overestimated barrier of **1** suggests almost equal rates for the THI and TEZI processes, while experimental results show the TEZI pathway to be significantly faster than the THI pathway. This could imply that the computational approach used herein may not be as accurate for overcrowded alkenes with xylene-derived upper halves as it is for those with naphthalene-derived upper halves. Nonetheless, these computational methods provide valuable insight into how the thermal isomerization behavior relates to the geometric changes in these second-generation overcrowded alkenes.

Photoswitching process

It was found that the increased thermal stability of the metastable states of alkenes **1–4** makes them very suitable candidates for use as bistable photoisomerizable switches. The switching properties of **1–4** were monitored by UV/Vis absorption spectroscopy (Figure 8) and ¹H NMR spectroscopy (vide supra). Solutions of stable **1–4** (heptane) in quartz cuvettes were irradiated at room temperature for a few minutes towards either the metastable state using UV light (312 or 365 nm) or the stable state using visible light (420 or 450 nm). Using UV/Vis absorption spectroscopy, the reversible photochemical E-Z isomerizations were found to be characterized by clear isosbestic points, indicating the absence of side reactions, as well as bathochromic shifts of the major absorption bands in the metastable state of about 30–80 nm.

This is in full agreement with the calculated structural change and concomitant change in the HOMO–LUMO gap. Upon the formation of the metastable state the overcrowded

Figure 8. UV/Vis spectra of the switching process of **1–4**. Experimental UV/Vis absorption spectra in black of (*Z,P,S*)-**1**, (*Z,P,S*)-**2**, (*Z,P,R*)-**3**, (*Z,M,R*)-**4** (heptane, 1.0×10^{-5} M). Irradiation of **1** (312 nm), **2** (365 nm), **3** (312 nm), and **4** (365 nm) to the metastable state affords a PSS shown in red with two intermediate moments in the process shown as well in red (*E:Z* ratio: (*S*)-**1** 95:5, (*S*)-**2** 96:4, (*R*)-**3** 97:3, and (*R*)-**4** 99:1). Irradiation using a longer wavelength of **1** (420 nm), **2** (450 nm), **3** (420 nm), and **4** (450 nm) allowed the reversed *E–Z* isomerization towards the stable state affording a new PSS shown in blue with two intermediate moments in the process shown as well in blue (*Z:E* ratio: (*S*)-**1** 64:36, (*S*)-**2** 82:18, (*R*)-**3** 97:3, (*R*)-**4** 70:30). Inserts display irradiation cycles between the two PSS's for each compound.

alkene experiences an increase in twist as is illustrated in the calculated structures in Figure 7. This twisting increases the energy of the HOMO by an average 23 μeV for **1–4**, while at the same time lowering the LUMO by an average 246 μeV , which together significantly reduces the HOMO–LUMO gap. This is opposite to the observations of Cnossen et al. for second-generation molecular motors with six-membered rings in both the upper as well as lower half in which the twist over the double bond was lowered in the metastable state and a hypsochromic shift was observed.^[55] The bathochromic shift upon formation of the metastable **1–4** allows a highly selective photochemical switching process in which both states can be addressed by the use of light of an appropriate wavelength (Figure 8, Scheme 4). None of the overcrowded alkenes showed any noticeable degradation over multiple switching cycles, thus exhibiting an excellent fatigue resistance of this family of molecular switches.

The PSS ratios for the stable-*Z* to metastable-*E* isomerizations obtained upon irradiation with UV light were determined

Scheme 4. General scheme for reversible highly selective photoswitching of stable (*Z*)-**1–4** and metastable (*E*)-**1–4**.

by HPLC and were all found to yield $\geq 95\%$ of the metastable-*E* state for the forward isomerization (vide supra). The reverse reaction using visible light afforded varying PSS ratios (*Z:E* ratio; (*S*)-**1** 64:36, (*S*)-**2** 82:18, (*R*)-**3** 97:3, (*R*)-**4** 70:30),^[70] as determined by HPLC and/or UV/Vis (see Supporting Information). Alkene **3** hereby displayed the most efficient photoswitching, producing 97% of the opposite diastereoisomer in both directions, and would therefore be the most suitable candidate for use as a bistable photocontrolled switch. With respect to thermal stability, overcrowded alkene **1** exhibits the most favorable behavior, possessing an hour half-life temperature of 138 °C. This is over 22 °C higher than that of **3** and the TEZI of **1** yields the starting isomer almost exclusively ($> 94\%$), making it remarkably bistable as well as selective during the thermal isomerization.

Conclusion

Four overcrowded alkenes have been synthesized and investigated experimentally and computationally. The calculated CD spectra of **1–4** agree well with the experimental spectra which allowed their absolute stereochemical assignments. Irradiation with UV light allowed high-yielding *E–Z* isomerizations providing metastable diastereoisomers. Kinetic studies on metastable **1–4** using CD and HPLC identified two pathways at high temperatures for thermal isomerization. The thermal *E–Z* isomerizations and helix inversions were studied computationally and a new strategy was developed for calculating the TEZI barrier for second-generation overcrowded alkenes. By including the most important π bonds in the active space, the method is able to provide energy barriers for the TEZI process that are in good agreement with those observed experimentally. Furthermore, the calculated THI barriers were found to be in close agreement with those observed experimentally. To show the value of these overcrowded alkenes as bistable switches, photochemical switching cycles were performed which proved the alkenes to be excellent switches. Switch **3** showed the best performance as a photo-switch, while **1** excelled in thermal stability, both exhibiting highly selective isomerizations. These favorable switching properties offer attractive prospects for the design of novel photoresponsive systems.

Experimental Section

Experimental procedures, supporting characterization data, supporting irradiation and kinetic experiments, computational details, and copies of the ^1H and ^{13}C NMR spectra are presented in the Supporting Information.

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