Noncovalent Interactions

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Attraction or Repulsion? London Dispersion Forces Control Azobenzene Switches

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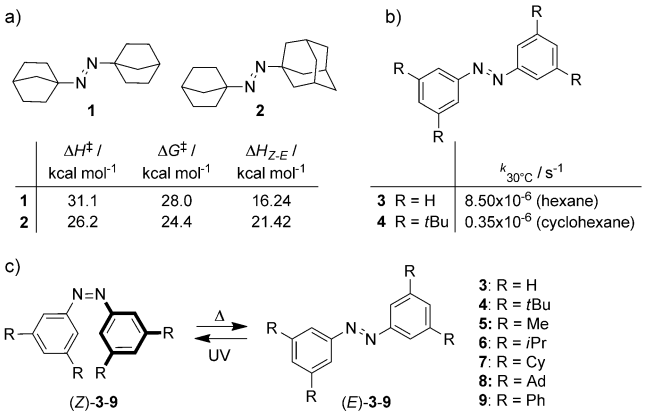
Abstract: *Large substituents are commonly seen as entirely repulsive through steric hindrance. Such groups have additional attractive effects arising from weak London dispersion forces between the neutral atoms. Steric interactions are recognized to have a strong influence on isomerization processes, such as in azobenzene-based molecular switches. Textbooks indicate that steric hindrance destabilizes the Z isomers. Herein, we demonstrate that increasing the bulkiness of electronically equal substituents in the meta-position decreases the thermal reaction rates from the Z to the E isomers. DFT computations revealed that attractive dispersion forces essentially lower the energy of the Z isomers.*

Every first-year chemistry student is taught that the larger an alkyl group is, the stronger is its steric repulsion. This concept is the basis for rationalizing the higher stability of *trans* versus *cis* isomers[1] as well as the higher stability of equatorial versus axial substitutents in cyclohexanes.[2] Recent studies, however, point out that attractive interactions were underestimated in discussions on repulsive steric hindrance in chemistry.[3] Namely, London dispersion interactions, which are part of the van der Waals forces, were seen as extremely weak or neutralized in solution.[4] Nonetheless, during the last few years it was demonstrated that intramolecular London dispersion forces have a strong impact, for example, on the thermodynamic stability[5] and the conformation[6] of molecules, on chemical reactions such as cycloadditions,[7] biochemical processes,[8] as well as in coordination chemistry.[9] It could be shown that London dispersion forces were responsible for the stability of extremely sterically crowded molecules with long C–C bonds such as aryl ethanes[10] or adamantyl dimers.[11]

An essential process in organic chemistry in which steric interactions play an important role is the $E \leftrightarrow Z$ isomerization of double bonds. Herein, the azobenzene scaffold has an exceptional position, as it can be isomerized upon irradiation with light.[12] Hence, it is not surprising that a wide range of applications exploit the isomerization properties as a molecular switch in areas ranging from material science[13] to bio-[14] and medicinal chemistry.[15] The growing interest led to a large increase in the number of publications on the effects of substituents on the thermal isomerization from the thermodynamically unstable *Z* to the stable *E* isomer.[16] Typically, variations in the electronic nature of the substituents were described. The incorporation of azo units into macrocyclic structures has also been shown to influence the isomerization properties.[17] In addition, integration into foldamers[18] and polymers[19] were presented. Small intermolecular interactions, such as van der Waals forces, are essential in the case of solid-state switching.[20] Nonetheless, hardly any attention has been given to the intramolecular effect of substitution with electronically neutral substituents such as alkyl groups on azobenzenes. The reason might be found in the well-accepted conclusion that steric effects have a strong destabilizing influence on the *Z* isomer.

At first glance this prediction is supported by the observation of Rüchardt and co-workers, who investigated the stability of aliphatic azo compounds by varying the size of the alkyl substituents (Scheme 1 a).[21] Increasing the bulkiness of the alkyl group leads to a decrease in the stability of the corresponding *Z* isomer and to a faster thermal back reaction to the *E* isomer. However, a comparison of known literature *k* values for the thermal *Z* to *E* isomerization of unsubstituted azobenzene **3**[22] with 3,3′,5,5′-tetra-*tert*-butylazobenzene (**4**)[16a] (Scheme 1 b) shows the more crowded *tert*-butyl-substituted derivative to be kinetically more stable.



Scheme 1. a) Kinetic and thermodynamic data for the thermal *Z* to *E* isomerization of two aliphatic azo compounds in mesitylene. b) *k* values of two *meta*-substituted azobenzenes for the thermal *Z* to *E* isomerization. c) The thermal *Z* to *E* isomerization of seven differently substituted azobenzenes investigated in this study (Ad = adamantyl, Cy = cyclohexyl).

To investigate this phenomenon seven differently substituted azobenzenes were prepared (Scheme 1 c, for the synthesis of azobenzenes **3**–**9** see the Supporting Information)

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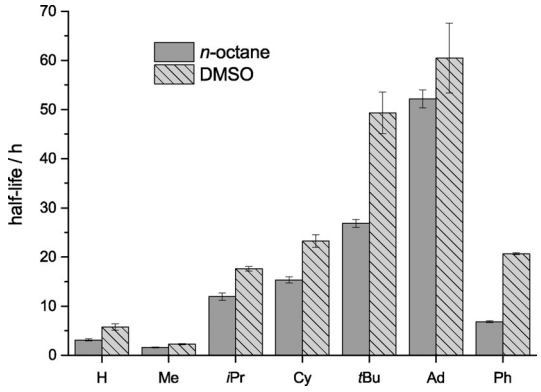


Figure 1. Half-lives of azobenzenes **3**–**9** measured in *n*-octane and DMSO at 53 °C.

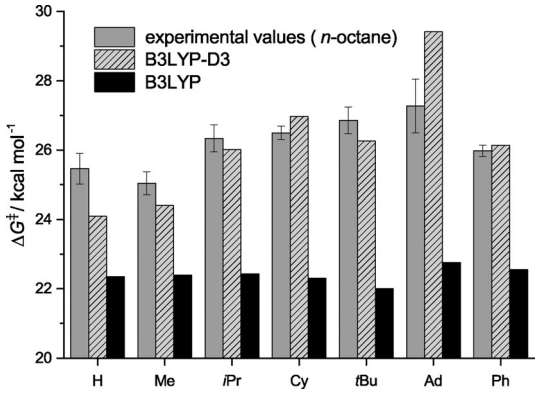


Figure 2. Experiment versus computation with a 6-311G(d,p) basis set (55 °C).

and the rates of $Z \rightarrow E$ isomerization were determined by temperature-controlled UV/Vis spectroscopy. In contrast to the common opinion, the experimentally measured half-lives at 53 °C in *n*-octane demonstrated that larger substituents lower the reaction rates of the thermal *Z* to *E* transformation dramatically (Figure 1). The unsubstituted azobenzene (**3**) and the phenyl-substituted azobenzene (**9**) have a slightly different electronic structure than the alkyl-substituted derivatives. The isomerization was measured in different solvents (6×10^{-5} M *n*-octane and DMSO; chlorinated solvents were avoided to exclude protonation effects under irradiation[23]) and showed a comparable trend. The data determined on samples at higher dilution (1×10^{-5} M in both solvents) resulted in the same trend (see Supporting Information), thereby excluding the influence of intermolecular interactions.

Measurements at temperatures between 39 °C and 67 °C allowed the extraction of the $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and $\Delta S^{\ddagger}$ values (Table 1). The experimentally determined $\Delta G^{\ddagger}$ values in *n*-octane represent the measured half-lives, and increase as expected from the methyl-substituted azobenzene (**5**) to adamantyl-substituted (**8**). Interestingly, the activation enthalpy increases from Me to *t*Bu substitution, but drops again for adamantyl, while the entropy follows the opposite trend. Solvation might be a dominant factor in this case.

Table 1: Experimental kinetic data of the thermal $Z \rightarrow E$ isomerization of **3**–**9** in *n*-octane.

R	k_{Z-E} [s^{-1}][a]	$\Delta H^{\ddagger}_{Z\text{-}E}$ [kcal mol^{-1}]	$\Delta S^{\ddagger}_{Z\text{-}E}$ [cal K^{-1} mol^{-1}]	$\Delta G^{\ddagger}_{Z\text{-}E}$ [kcal mol^{-1}][b]
H	$6.20 \times 10^{-5} \pm 4.72 \times 10^{-6}$	22.17 ± 0.22	−10.04 ± 0.68	25.46 ± 0.44
Me	$1.24 \times 10^{-4} \pm 1.23 \times 10^{-5}$	21.03 ± 0.17	−12.20 ± 0.51	25.04 ± 0.33
*i*Pr	$1.62 \times 10^{-5} \pm 1.05 \times 10^{-6}$	22.99 ± 0.19	−10.20 ± 0.60	26.34 ± 0.39
Cy	$1.25 \times 10^{-5} \pm 5.13 \times 10^{-7}$	23.18 ± 0.10	−10.11 ± 0.30	26.50 ± 0.20
*t*Bu	$7.18 \times 10^{-6} \pm 2.12 \times 10^{-7}$	24.15 ± 0.19	−8.26 ± 0.59	26.86 ± 0.39
Ad	$3.69 \times 10^{-6} \pm 1.01 \times 10^{-7}$	23.12 ± 0.39	−12.65 ± 1.2	27.27 ± 0.78
Ph	$2.81 \times 10^{-5} \pm 7.54 \times 10^{-7}$	22.21 ± 0.08	−11.49 ± 0.25	25.98 ± 0.16

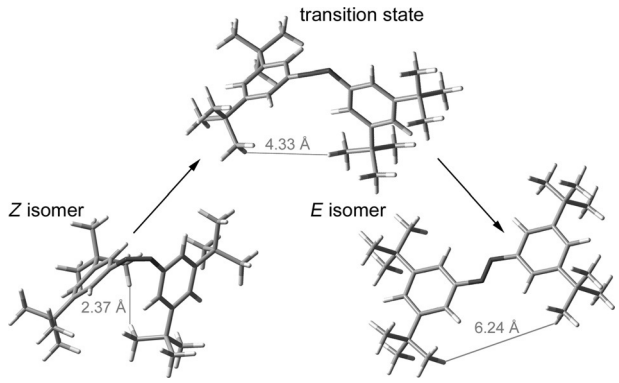
[a] At 53 °C. [b] At 55 °C.

A detailed mechanistic study was conducted to explain the measured decrease in the reaction rates with increasing bulkiness of substituents. For the herein-discussed electronically neutral azobenzenes, an inversion mechanism is commonly accepted.[16a,22] An isokinetic plot[24] ($\Delta H^{\ddagger}$ versus $\Delta S^{\ddagger}$) as well as an Exner plot[25] (log $k_{39\,^{\circ}C}$ versus log $k_{67\,^{\circ}C}$) supported this assumption and demonstrated that the mechanism is equal for all examples **3**–**9** (see the Supporting Information).

Further insights into the processes were gained by DFT computations.[26] Attempts to reproduce the measured kinetic trend at a B3LYP[27] level with a 6-311G(d,p)[28] basis set in the gas phase were not successful (Figure 2). The computed $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ values did not reflect the size of the substituent, but resulted in the same values for all azobenzenes **3**–**9**. Computing the kinetic values at the dispersion-corrected B3LYP-D3 level of Grimme et al.[29] allowed simulation of the experimentally measured trend (Figure 2). The methyl-substituted (**5**) displays the smallest and the adamantyl-substituted azobenzene (**8**) the largest $\Delta G^{\ddagger}$ value. The latter was overestimated by the dispersion correction, probably as a result of the missing solvation contributions and the large number of possible interactions. In addition, the same outcome was obtained when single-point computations were conducted at a TPSSTPSS[30] level with a def2-TZVP[31] basis set, thus eliminating functional-specific effects of B3LYP (see the Supporting Information).

Geometry optimization of the *tert*-butyl derivative (**4**) showed that the distance between the two closest hydrogen atoms of two substituents on different benzene units is 2.37 Å in the *Z* isomer, 4.33 Å in the transition state, and 6.24 Å in the *E* isomer (Scheme 2). Hence, the dispersion effect should mainly occur in the *Z* isomer, thereby explaining the kinetic behavior of the thermal isomerization of azobenzene.

A noncovalent interaction analysis (NCI) was performed to investigate the nature of the interactions occurring.[32] Weak van der Waals forces are indicated with a green surface. The outcome of the NCI analysis supported our previous



Scheme 2. Geometry optimization of the *Z* and the *E* isomers and the transition sate of the thermal isomerization of *tert*-butylazobenzene **4** [B3LYP-D3/6-311G(d,p)].

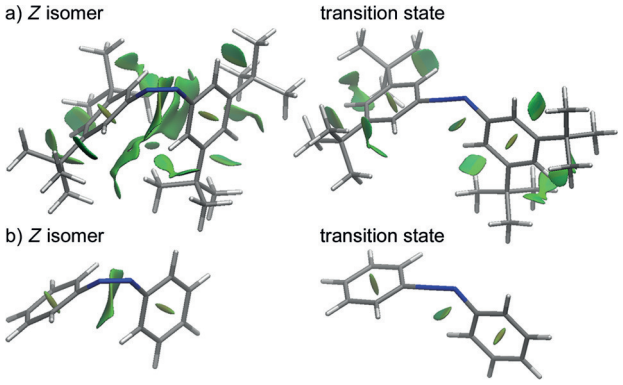


Figure 3. NCI analysis of the optimized [B3LYP-D3/6-311G(d,p)] *Z* isomers and transition states of *tert*-butyl derivative **4** (a) and azobenzene **3** (b), visualized using VMD.[33]

assumptions: weak interactions were mainly detected in the *Z* isomers and only to a minor extent in the transition states (Figure 3a). Interestingly, dispersion forces also influence the kinetics of the unsubstituted azobenzene (**3**; Figure 3b).

The computed dispersion-corrected data revealed that stabilization of the *Z* isomers was the reason for the lower reaction rates as the bulkiness increased, in accordance with the Bell–Evans–Polanyi principle[21] (Table 2). The transition state was hardly influenced by the different substitution ($\Delta H^{\ddagger}_{E\text{-}Z}$ for the thermal conversion of **3**–**9** from the *E* to the *Z* isomer is constant) even for the cyclohexyl (**7**) and adamantyl derivatives (**8**), where the large size of the substituents allowed weak attractive interactions to a small extent in the transition states.

Table 2: Computed thermodynamic parameters [B3LYP-D3/6-311G(d,p)] at 55 °C ($\Delta H_{Z\text{-}E}$, $\Delta G_{Z\text{-}E}$) and the computed activation energy ($\Delta H^{\ddagger}_{E\text{-}Z}$) of the thermal conversion from *E* to *Z*.

R	$\Delta H_{Z\text{-}E}$ [kcal mol^{-1}]	$\Delta G_{Z\text{-}E}$ [kcal mol^{-1}]	$\Delta H^{\ddagger}_{E\text{-}Z}$ [kcal mol^{-1}]
H	12.91	13.34	37.82
Me	12.43	13.59	37.60
*i*Pr	10.02	11.46	37.43
Cy	7.43	10.70	37.11
*t*Bu	9.43	10.76	37.90
Ad	5.44	7.80	37.67
Ph	8.61	11.08	37.40

In conclusion, the rates of the thermal *Z* to *E* isomerization of azobenzenes decrease as the bulkiness of the substituents increase. We propose that the isomerization is influenced by attractive London dispersion interactions stabilizing the *Z* isomers. Although, the differences in the activation enthalpies are small, they have a dramatic influence on the half-lives of the *Z* isomers. We could thus demonstrate that electronically neutral and chemically inert substituents can also influence the switching behavior of azobenzenes. Even unsubstituted azobenzene is influenced by attractive dispersion interactions, which illustrates that these effects should be considered when investigating azo switches and *E* to *Z* isomerizations in general. Further investigations are directed at quantifying the stabilization energy for various substituents, specifying the effects of entropy and different solvents, as well as applying the concept to the design of novel molecular switches.

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