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An Incremental System To Predict the Effect of Different London Dispersion Donors in All-*meta*-Substituted Azobenzenes

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Abstract: Predictive models based on incremental systems exist for many chemical phenomena, thus allowing easy estimates. Despite their low magnitude in isolated systems London dispersion interactions are ubiquitous in manifold situations ranging from solvation to catalysis or in biological systems. Based on our azobenzene system, we systematically determined the London dispersion donor strength of the alkyl substituents Me, Et, *i*Pr up to *t*Bu. Based on this data, we were able to implement an incremental system for London dispersion for the azobenzene scheme. We propose an equation that allows the prediction of the effect of change of substituents on London dispersion interactions in azobenzenes, which has to be validated in similar molecular arrangements in the future.

Chemical processes are in general governed by the interactions between all participating entities. Established models help to predict these interactions and, hence, the outcome of, for example, a reaction. Despite the development of computational methods and the ever-increasing accuracy, such intuitive models are still the basis for the design process of molecular scientists. One very successful concept in this regard is the frontier molecular orbital (FMO) theory,[1] which allows straightforward analysis of transformations simply with pen and paper. Weaker interactions, such as van der Waals and in particular the attractive part, London dispersion, are much more difficult to predict. Therefore, it is not surprising that the concept is rarely covered in basic organic textbooks as it is reverse to the concept of steric repulsion.[2]

Although the theory behind London dispersion was proposed more than 80 years ago,[3] efforts to quantify this effect have only recently been intensified.[4] Experimentally, different molecular systems have been designed to address the challenge of "measuring" such small interactions, such as London dispersion. Torsion balances applied by Wilcox[5] or Cockroft[6] use the reversible rotation around a single bond to compare the interactions of different entities. The conformational preference controlled by dispersion interactions between different groups is also the principle for systems based on cyclooctatetraene[7] or thiobarbiturate.[8] Alternatively, dissociative concepts such as the proton-bound N-heterocyclic dimers by Chen[9] or equilibrating titanium complexes[10] also allow the strengths of different London dispersion donors to be compared.

In our group, we established the azobenzene molecular switch as efficient tool to quantify these small-energy interactions. Therewith, we could show that the larger the substituents on the azobenzene, the larger the attraction due to London dispersion.[11] However, with longer *n*-alkyl chains, entropy counteracts the effect and an ideal length of four carbons (*n*-butyl) to maximize London dispersion interactions was determined.[12] Furthermore, we screened various alkane solvents and could qualitatively show their effect on the London dispersion interactions.[13]

Although the general attractive effect of London dispersion donors is accepted, their application as design parameters for chemical processes is still hampered by the lack of a handy scale, which would allow a structural alteration on London dispersion to easily be predicted. One reason why such a scale is still missing can be assigned inter alia to the high distance dependency of dispersion forces. However, the azobenzene, with its standardized distance in combination with the easy synthetic accessibility, is ideally suited to provide the necessary data, allowing such an incremental system to be established for London dispersion.

The systematic independent variation of the substituents at either phenyl ring allows the interdependence of structural changes of each group to be determined (Scheme 1). This

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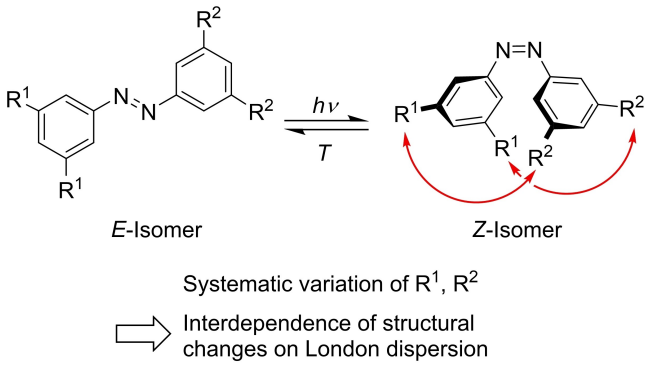
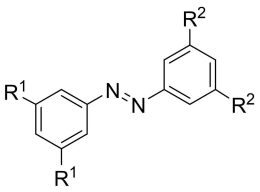


Scheme 1. Concept for the establishment of an incremental system as a London dispersion scale.



1: $R^{1,2}$ = Me
2: R^1 = Me; R^2 = Et
3: $R^{1,2}$ = Et
4: R^1 = Me; R^2 = *i*Pr
5: R^1 = Et; R^2 = *i*Pr
6: R^1 = Me; R^2 = *t*Bu
7: $R^{1,2}$ = *i*Pr
8: R^1 = Et; R^2 = *t*Bu
9: R^1 = *i*Pr; R^2 = *t*Bu
10: $R^{1,2}$ = *t*Bu

Scheme 2. Compounds synthesized for data acquisition.

analysis is based on the Arrhenius equation [Eq. (1)], by which we can correlate the relative changes in the activation barrier for different all-*meta* alkyl substituted azobenzenes with the interaction strength of the groups attached.

$$k = A \cdot e^{-\frac{E_A}{RT}} \quad (1)$$

The electronic structure of these azobenzenes is not significantly altered, neither does the isomerization mechanism change for this special type of compounds, as we could demonstrate by an Exner plot in a previous study.[11] Therefore, we can assume a constant pre-exponential factor *A*, allowing the relative changes to be related to a standard compound with the following equation [Eq. (2)] at a constant temperature *T*.

$$\frac{\ln(k_1)}{\ln(k_2)} = \frac{E_{A1}}{E_{A2}} \quad (2)$$

With a known activation energy of one of the compounds, all the others could be estimated for a given temperature. 3,3′,5,5′-Tetramethylazobenzene (**1**) should serve as the reference compound. The experimental value for $\Delta G^{\ddagger}$ for the thermal *Z*→*E* isomerization determined in previous studies, for example, for **1** can easily be adjusted to other temperatures.

To obtain the necessary data, the groups R^1 and R^2 were varied from Me to Et to *i*Pr to *t*Bu, as shown in Scheme 2. The synthesis was done according to the established routes (see the Supporting Information for details). With the compounds in hand the kinetic measurements were performed. In order to compare the results with previous studies in our lab and to realize a reasonable backreaction rate the measurements were conducted at 40 °C in *n*-octane. By using time resolved UV-Vis spectroscopy at a constant temperature, the rate constants and half-lives for the *Z*→*E* isomerization of the synthesized azobenzenes were determined.

As expected from previous studies,[11,12] the results clearly show the slower thermal *Z*→*E* isomerization for the investigated azobenzenes **1**–**10** with increasing size of the substituents (Figure 1). It is also evident that for the asymmetric derivatives

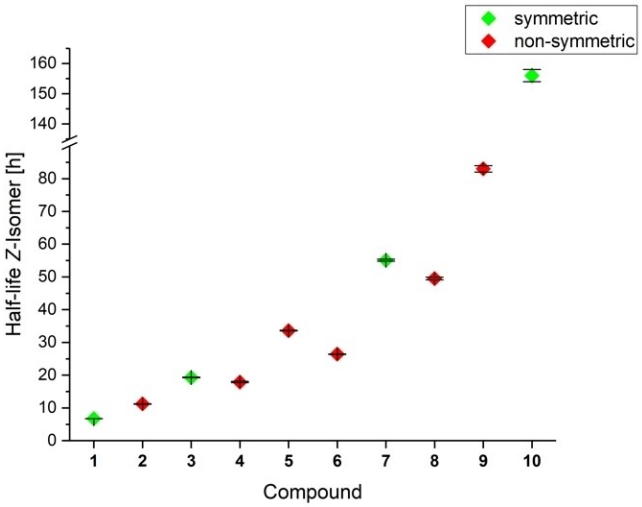


Figure 1. Half-lives of Z isomers of azobenzenes **1**–**10** in *n*-octane at 40 °C. The values for **1**, **3** and **10** were implemented from a previous study.[12]

the *Z*→*E* isomerization proceeds faster than for their constitutional isomers with a symmetrical substitution pattern. This can clearly be seen by the comparison of **3** to **4** or **7** to **8**. Also, for the derivatives **5** and **6**, which are also constitutional isomeric azobenzene, a longer half-life is observed for compound **5** with a more similar sized substitution pattern (Et↔*i*Pr vs. Me↔*t*Bu). In general, our results show that methyl groups are having the smallest impact on stabilizing London dispersion interactions. With the above presented equation, the Gibbs activation energies for the *Z*→*E* isomerization were calculated (Table 1). The differences in the calculated Gibbs activation energies of **3** and **4**, **5** and **6** or **7** and **8** vary between 0.2 and 0.6 kcal mol^{-1}. These results illustrate the increased stabilizing contributions in symmetrical azobenzenes due to higher attraction of the pairwise increased London dispersion interactions. If a CH_2 group in a symmetric azobenzene is formally swapped from one substituent to one on the opposing phenyl ring, it will be positioned at a larger distance from the center of the molecule. Although the substituents can rotate, in average the interaction distance is slightly increased, leading to less attractive dis-

Table 1. Rate constants k and activation energies ($\Delta G^{\ddagger}_{Z\text{-}E}$) of the thermal $Z \rightarrow E$ isomerization of compounds **1**–**10** in *n*-octane and comparison with computed thermodynamic parameters ($\Delta H_{Z\text{-}E}$, $\Delta G_{Z\text{-}E}$). Energies and enthalpies are given in kcal mol^{-1} and k values in s^{-1}.

Cpd	Experimental $k_{Z\text{-}E}$[a]	$\Delta G^{\ddagger}_{Z\text{-}E}$[a]	Computed $\Delta H_{Z\text{-}E}$[b]	$\Delta G_{Z\text{-}E}$[b]
1	$2.857\times10^{-5}\pm2\times10^{-8}$	24.9 ± 0.3	10.40	10.30
2	$1.72\times10^{-5}\pm1\times10^{-7}$	26.1 ± 0.4	9.39	9.89
3	$9.98\times10^{-6}\pm4\times10^{-8}$	27.4 ± 0.4	8.31	10.42
4	$1.073\times10^{-5}\pm9\times10^{-8}$	27.2 ± 0.4	9.55	9.88
5	$5.74\times10^{-6}\pm2\times10^{-8}$	28.7 ± 0.4	8.20	9.54
6	$7.29\times10^{-6}\pm2\times10^{-8}$	28.1 ± 0.4	9.28	9.39
7	$3.49\times10^{-6}\pm2\times10^{-8}$	29.8 ± 0.4	7.98	9.08
8	$3.89\times10^{-6}\pm3\times10^{-8}$	29.6 ± 0.4	7.70	9.40
9	$2.32\times10^{-6}\pm3\times10^{-8}$	30.8 ± 0.4	7.71	8.78
10	$1.23\times10^{-6}\pm2\times10^{-8}$	32.3 ± 0.5	7.44	8.63

[a] At 40 °C; [b] Computed with the lowest-energy conformer at the [DLPNO-CCSD(T)/def2-TZVP//PBE0-D3BJ/def2TZVP] level[14,15,16] at 25 °C.

persion interactions and, therefore, to a faster thermal $Z \rightarrow E$ isomerization for the asymmetric azobenzenes.

This distance dependency can also be illustrated by the comparison of the half-lives of **7** and **10** with their constitutional isomers with *n*-propyl and *n*-butyl substituents. The compounds **7** and **10** with the more compact substituents have half-lives of 55.1 and 156 h, whereas the ones with the flexible linear *n*-alkane chains have half-lives of 26.6 and 30.47 h,[13] respectively. In an *iso*-propyl or a *tert*-butyl group, the carbon atoms are in average closer to each other. Hence, the dispersion interactions show less anisotropic behavior between the branched alkyl chains (*i*Pr, *t*Bu) than for the corresponding linear chains (*n*Pr, *n*Bu).

Additionally, we correlated the structural parameters of the *Z* isomer with the thermal isomerization to the *E* isomer. The results partly reproduce the observed kinetics. Because only the most stable conformers were computed by our approach (for details see the Supporting Information), derivatives with substituents with a low rotational barrier show higher deviations from the kinetic results. Due to the interlocked structure of the *Z* isomer, rotational relaxation after isomerization to the *E* state provides an additional energy gain, leading to the higher $\Delta G_{Z\text{-}E}$ in combination with a too low $\Delta H_{Z\text{-}E}$.

This is especially the case for the compounds with methyl or ethyl substituents and gets pronounced for compound **3**. The intramolecular attraction is overestimated, which can be seen by the short distance between the carbon atoms directly bound to the azo group of only 2.725 Å. This distance is with 2.782 Å the largest for **1** and reaches a plateau between 2.732 and 2.736 Å for **8** and **7**, **9**, **10** Although the intramolecular attractions in **10** are much stronger, which is clearly indicated by the low $\Delta H_{Z\text{-}E}$ of only 7.44 kcal mol^{-1}, the C–C distance has been computed to be the same as for **7** (Figure 2).

At a certain point, not only attractive interactions but also repulsive ones play a role with increasing size oft he substituents; this prevents any further approach of the opposing aryl rings. Therefore, attractive long-range interactions from the more remote areas of the molecule become more important for its stabilization.

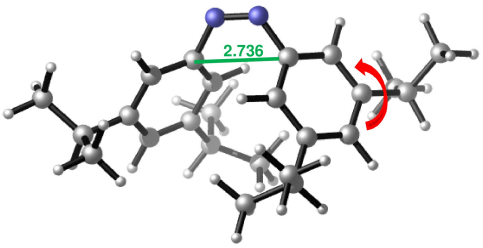


Figure 2. Computed structure of the lowest-energy conformer of the *Z* isomer of **7** at the PBE0-D3BJ/def2TZVP[15,16] level. Illustrated with CYLview.[17] The green line shows the distance between the carbon atoms directly connected to the azo group. To a certain degree this distance reflects the attraction between the substituents at opposing aryl rings. The substituents can rotate as indicated by the red arrow.

Additionally, a local energy decomposition (LED) analysis has been performed. Also here, the contribution of London dispersion interactions increases with increasing number of CH_2 units relatively to other contributions such as exchange energy or electrostatics (Figure 3).

A correlation of the activation energies for the $Z \rightarrow E$ isomerization of the azobenzenes **1**–**10** with the number of C–H contacts of a constant substituent R^2 with varying R^1 allows us to extrapolate the stabilizing contributions for each CH_2 group added to the substituent R^1 (Figure 4). These results show a high linear correlation and provide a possibility to actually assign a value for each dispersion energy donor in this azobenzene system. In this way, we can deduce from the slope of this graph that each C–H contact with a *tert*-butyl group contributes about ~0.70 kcal mol^{-1} to the stabilization of the *Z* isomer (Table S3 in the Supporting Information). The same procedure can be repeated for an *iso*-propyl, ethyl or methyl group as reference leading to expected lower stabilizing contributions of 0.61, 0.60, and 0.54 kcal mol^{-1}, respectively.

As, apart from alkyl–alkyl interactions, alkyl–aryl interactions also play a significant role for the stabilization of these *meta*-

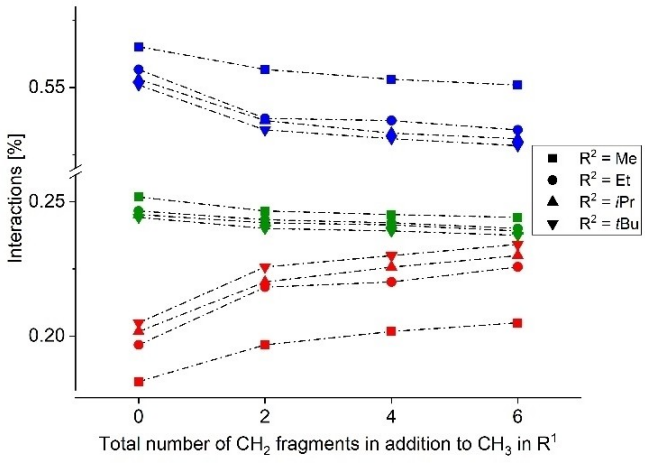


Figure 3. Relative distribution of bond energies between dispersion energy (red), exchange energy (green), and electrostatics (blue).

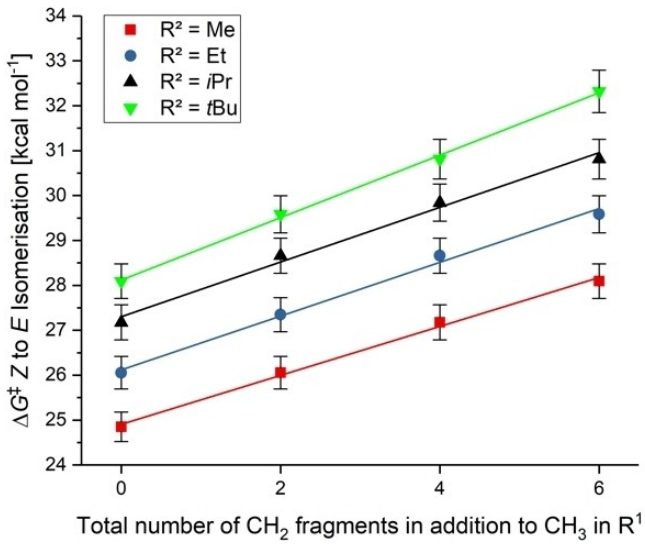


Figure 4. Linear interpolation of the activation energy for the thermal *Z*→*E* isomerization of **1**–**10** against the total number of additional CH_2 groups in the alkyl substituent R^1 for different substituents R^2.

substituted azobenzenes, increasing one substituent already leads to longer half-lives. If ethyl instead of methyl is chosen as R^2, we observe an additional increase of 0.06 kcal mol^{-1} of the activation barrier for each CH_2 group added to R^1. For an *iso*-propyl group as R^2, only a marginal increase is detected. This can be attributed to the rotatability of these substituents. If a CH_3 group of the *iso*-propyl substituent on one side is positioned closer to the center of the molecule, the CH_3 groups on the other part will give way by rotation (Figure 2). For *tert*-butyl as R^2, this effect is eliminated due to its symmetry, leading to a total of 0.16 kcal mol^{-1} increase of the activation barrier for each CH_2 group added to R^1. This would mean an additional stabilizing contribution by alkyl–alkyl interactions in the range of about 0.05 kcal mol^{-1} per added CH_2 group.

By combining all this information, the following equation [Eq. (3)] for an incremental system for this specific molecular arrangement can be formulated to estimate the activation energy $\Delta G^{\ddagger}_{Z\text{-}E}$:

$$\Delta G^{\ddagger}_{Z\text{-}E} \approx 25\ \text{kcal mol}^{-1} + 0.6\ \text{kcal mol}^{-1} \times 2\,(X^1 + X^2) \qquad (3)$$

Here, X^1 is the number of CH_2 fragments in addition to CH_3 in R^1, and X^2 is the number of CH_2 fragments in addition to CH_3 in R^2.

Each additional CH_2 fragment adds ~0.6 kcal mol^{-1} stabilization energy relative to the reference compound **1** ($R^1 = R^2 = CH_3$). As each phenyl unit in the azobenzene test system bears two R groups, this term is multiplied by 2. This equation delivers approximate values, which are [with one exception (Me/*t*Bu)] all within experimental error.

Conclusion

Herein, we have formulated for the first time an incremental system to estimate the strength of different London dispersion donors based on the azobenzene system. The scale originates from a systematic measurement of the thermal *Z*→*E* isomerization of differently substituted (Me, Et, *i*Pr, *t*Bu) azobenzenes. The observed linear relationship of the half-lives with increasing size of the substituents allowed a proposal for an equation proving a reasonable assessment of the London dispersion interactions of these substituents. Such a system will be of great value for all scientists relying on the reciprocal effects of different molecular entities and will have to be validated for other arrangements in the future.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: azobenzene · kinetics · London dispersion · molecular switches · weak interactions

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