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Supramolecular detection of geometrical differences of azobenzene carboxylates

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ABSTRACT

In dynamic combinatorial chemistry, the geometry of a template can be translated into the composition of a library of interchanging components. In this study, such a dynamic combinatorial library was used for the first time to detect and evaluate differences in the geometry of isomers of photoswitchable azobenzene based templates.

The modus operandi of molecular machines consists in utilising switchable moieties which change their geometry when an appropriate stimulus is applied.[1] Among the various triggers that can be used for this purpose, light has unique features that render it particularly useful, i.e. its unmatched spatial resolution and electrically neutral character.[2] Moreover, light-triggered transformations are generally reversible and can easily be fine-tuned to selectively affect only the chosen molecules. The photoactive moieties that are often applied in such transformations include diaryl- and dithienylethene, spiropyrane, and azobenzene (AB) derivatives.[2b,3] Among these, the latter appear to be the most useful owing to their synthetic availability and robustness.[4] One challenging aspect of such light-induced changes in geometry lies in accurately detecting and evaluating them. Simple UV–vis and ^{1}D NMR measurements are typically employed to track such isomerisation, but they do not measure changes in the molecule geometry directly, usually providing information only about chromophore moiety and its close proximity.[5] Such geometrical changes are indeed difficult to spot and quantify, and this is even more troublesome when one isomer is thermodynamically unstable, e.g. *(Z)*-isomer of AB. There are few examples in the literature that deal with the detection of such differences in the geometry of photoisomers, the methods used being limited to NOE[6] and diffusion-based[7] NMR, conducting atomic force microscopy[8] (*c*-AFM), FRES, and in rare cases single crystal X-ray diffraction.[9]

In this Letter we present a novel concept for sensing photochemical isomerisation phenomena using dynamic combinatorial chemistry (DCC).[10] A dynamic combinatorial library (DCL) consists of species that interchange via reversible reactions. The composition of such a DCL is a consequence of the thermodynamic stability of its components, which can be modified through the addition of a template. The template may bind to selected components, resulting in the amplification of their abundances. In general, the content of a library component exhibiting the highest affinity towards the template is increased at the cost of all other DCL members.[11] Binding usually occurs between two compatible groups, enabling weak non-covalent interactions, the most important of these being hydrogen bonds (H-bonds). The strongest binding and therefore amplification are obtained when there is a good geometrical match between the anchoring points in the template and in the DCL member. If the template is a switchable molecule the spatial arrangement of the anchoring groups can be changed upon isomerisation, and different amplification profiles will be obtained for each isomer. Thus, the composition of the DCL can be translated into the geometrical parameters of the template.

Recently, we described a DCL relying on disulfide bond exchange, composed of cyclooligomers ($\mathbf{1_n}$) incorporating dipicolinic acid diamide subunits equipped with H-bond donors suitable for anion complexation (Fig. 1).[12] Under basic conditions these macrocycles are in equilibrium, which can be altered through the introduction of anionic guests. This library proved to be strongly

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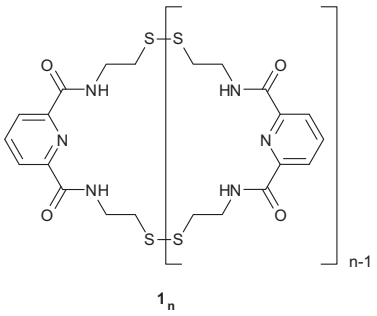


Figure 1. Dynamic combinatorial library $\mathbf{1_n}$.

influenced by the shape and size of the various carboxylates acting as templates. For example, benzene-1,3,5-tricarboxylate predominantly amplifies the tetrameric $\mathbf{1_4}$ whereas structurally related cyclohexane-1,3,5-tricarboxylate increases mainly the abundance of trimeric $\mathbf{1_3}$.

For the present study, we decided to use as template model photoswitchable carboxylates **2**, **3**, and **4** in the form of tetra-*n*-butylammonium (TBA) salts equipped with two, three and four carboxylic groups, respectively (Scheme 1).

The corresponding compounds were synthesised according to known procedures (see ESI for details). Upon irradiation of compounds **2**–**4** with light, a photostationary state (PSS) is established between the near planar *(E)*-isomer and the more compact V-shaped *(Z)*-isomer.

The corresponding *(E)*→*(Z)* and *(Z)*→*(E)* isomerisation for a diluted solution ($5 \cdot 10^{-5}$ M) of templates was completed within 1 min by irradiation with UVA light (368 nm, 60W) or blue light (410 nm, 5W LED), respectively. In UVA light driven PSS, the majority of each template exists in the respective *(Z)*-form. Relevant data describing *(Z)*→*(E)* isomerisation of the templates studied are shown in Table 1.[13] The rates of the thermal *(Z)*→*(E)* isomerisation indicate that the number of carboxylate groups is just as important as their substitution pattern in the arene ring. For example, the symmetrical di-*para*-substituted **2** back-isomerises faster than the unsymmetrical di-*meta*- and *para*-substituted **3**, whereas the symmetrical tetra-meta-substituted **4** is situated in between. Reports in the literature indicate that thermal-isomerisation of

Table 1
Kinetic data for thermal *(Z)*→*(E)*[a]

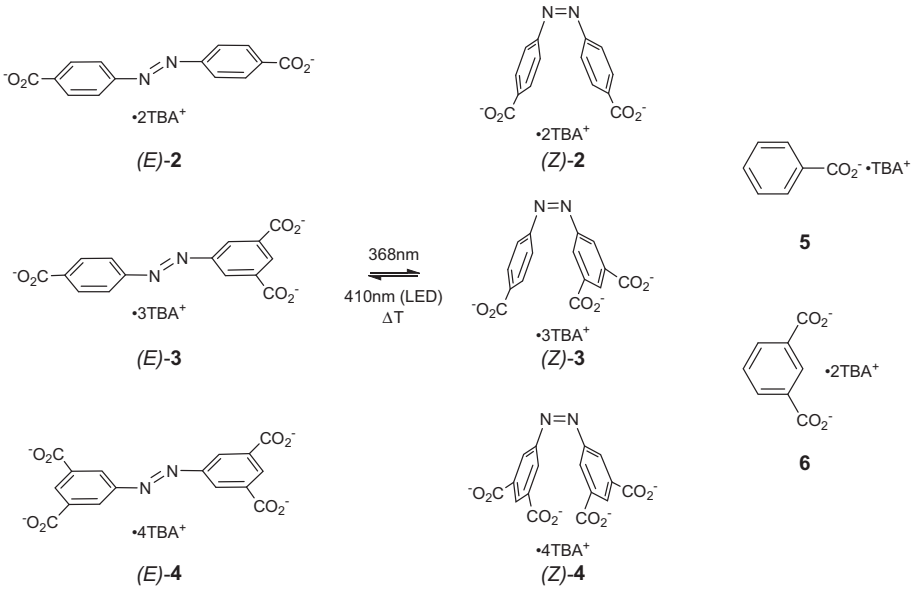
Compound	%$Z_{@PSS}$	$k_{\Delta T} \cdot 10^{-6}$ (s)	$\tau_{1/2}$ (h)
2	85 (68)	8.4	23.0
3	89 (70)	2.7	71.5
4	90 (82)	5.1	37.8

[a] Measured at $T = 298 \pm 0.1$ K; PSS are given for host concentration $5 \cdot 10^{-5}$ M and $5 \cdot 10^{-2}$ M (in parentheses), respectively; $k_{\Delta T}$ was predicted using $\Delta G^{\ddagger}$ derived from thermodynamic data (see ESI‡).

meta-substituted AB derivatives should resemble that of the parent AB, due to weak π-conjugation of substituents with an azo group. Surprisingly, however, template **3** most resembles the parent AB. Notably, the rates of isomerisation $k_{\Delta T}$ for the corresponding carboxylic acids are 2.2–8 times higher (see ESI), which supports the recently published hypothesis that increased electron density in the π-system of the AB scaffold accelerates this process.[14] For our purposes, the rates of thermal isomerisation of all templates are sufficiently low. The degree of thermal *(Z)*→*(E)* isomerisation was negligible ($\tau_{1/2} > 20$ h @ 25 °C) during the templation experiment, since the equilibration of the library takes only 3 h. Templation experiments with a library of $\mathbf{1_n}$ were conducted using tetrabutylammonium (TBA) salts of **2**–**4** in *(E)*-form and their PSS mixtures of *(E)*- and *(Z)*-isomers (further named in the text as *(Z)*-form). TBA salts of benzoic (**5**) and isophthalic acids (**6**), as well as their equimolar mixture, were used as references, as they resemble in terms of their structure the appropriate halves of templates **2**–**4**. Templation experiments were run in DMSO (+0.5% H_2O), with a total concentration of **1** being 0.01 M. Compositions of the library were determined by HPLC analyses. For each template and each library component we calculated a normalised amplification factor (AF_n), a useful parameter introduced recently by Otto and co-workers,[15] which we modified in the range of negative values to limit and normalise its range to −1.

$$AF_n = \begin{cases} \frac{A_n - A_0}{A_{max} - A_0} & \text{for} \quad A_n > A_0 \\ \frac{A_0 - A_n}{A_0} & \text{for} \quad A_n < A_0 \end{cases}$$

where A_0 is the concentration of library component, A in the absence of template, A_n – in the presence of template, and Amax



Scheme 1. Structures of templates **2**–**6** and isomerisation of **2**–**4**.

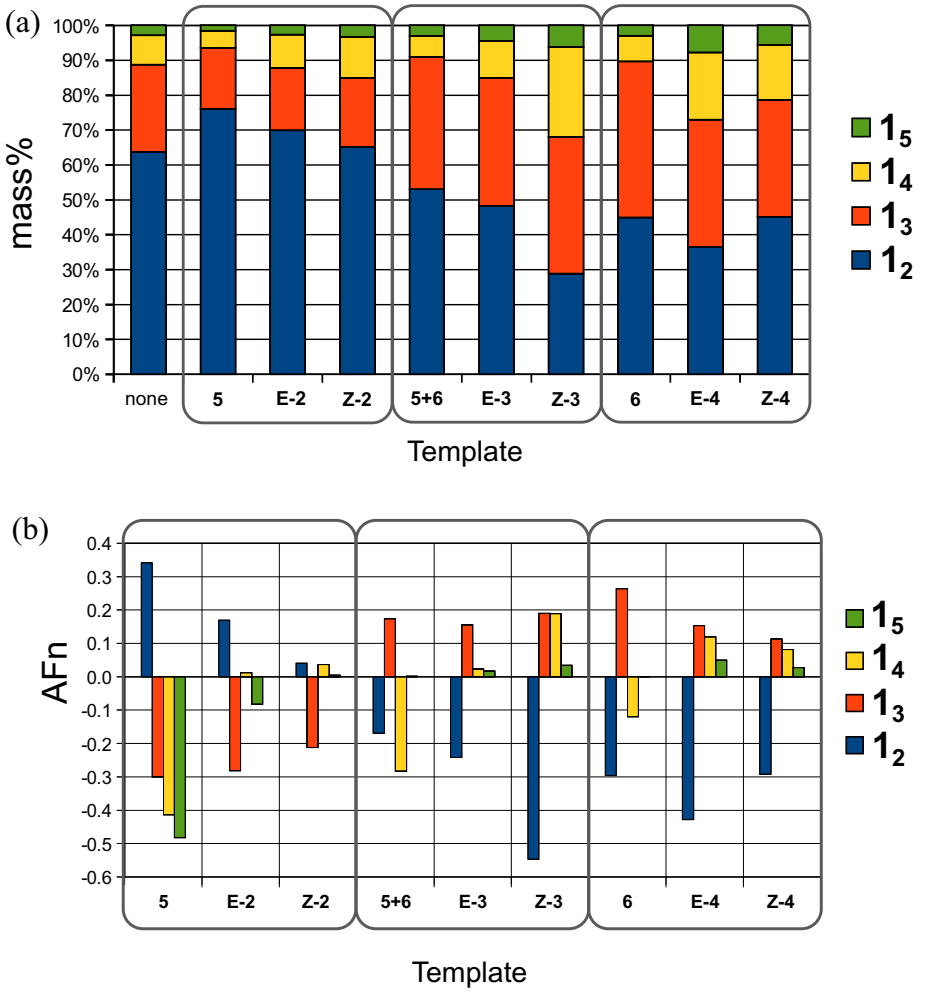


Figure 2. Distribution of components in templated DCLs. (a) $\%_{mass}$ of oligo-macrocycles, (b) normalised amplification factors induced by templates.

is the maximum possible concentration of component A. AF_n ranges from −1 to 1. Positive values indicate amplification of the given component, while negative values mean the reduction of its abundance. The extreme values of −1 and 1 indicate a total absence of the component and the maximum attainable concentration, respectively. The library compositions in the templation experiments and amplification profiles are presented in Figure 2.

A monofunctional template (benzoate) amplifies the smallest library component (the dimer) at the expense of all other macrocycles. The changes induced by *(E)*-**2** are quite similar to that of benzoate, the dimer being the most amplified macrocycle, though the AF_n is far lower. Yet unlike benzoate, *(E)*-**2** also exhibits a slight amplification of the tetramer, which seems to be the smallest host to interact with both distant anchoring points of **2**. The binding is quite weak and, according to simple modelling, the supermolecule's formation requires the host to adopt an unfavourable expanded conformation. Amplification of larger hosts, which may accommodate *(E)*-**2** more easily, is not observed since binding of just two anionic groups does not provide enough enthalpy to overcome the negative entropy of the formation of higher oligomers. The distribution of macrocycles induced by photoisomerised *(Z)*-**2** is characterised by a negligible amplification of the dimer, but stronger amplification of the tetramer. This means that *(Z)*-**2** with a shorter distance between carboxylate groups is a better suited template for $\mathbf{1_4}$ and binding does not require the aforementioned receptor stretching. The weak amplification of $\mathbf{1_2}$ indicates that in the *(Z)*-form of template **2** the two binding points are less likely to act independently.

In the case of template **3**, as a reference we employed an equimolar mixture of benzoate and isophthalate (**5** + **6**). This mixture induced changes very similar to those seen with **6** alone, with the trimer as the only amplified guest. Since photoswitchable host **3** in its *(E)*-form amplifies mainly the trimer, we attribute this to the interaction of the guest with the isophthalic part of the host. However, compared with the reference mixture **5** + **6**, *(E)*-**3** also amplifies to some extent $\mathbf{1_4}$ and $\mathbf{1_5}$, which definitely requires cooperation of all three anchoring points. DCL templated with photoisomerised guest *(Z)*-**3** possesses quite a different distribution of oligomers. Tetramer, having a significantly higher contribution (25 vs 10 mass%), seems to be the optimal host for the contracted *(Z)*-**3**. Concurrently, the amount of dimer is reduced from 47 to 28 mass%. In addition, the amount of the trimer remains virtually the same regardless of the geometry of template **3** applied. The amplification factors for $\mathbf{1_3}$ and $\mathbf{1_4}$ with *(Z)*-**3** are nearly the same. This means that the tetramer possesses higher affinity towards the template than the trimer, since the higher oligomers are much more difficult to amplify due to entropic reasons.[11c,12a]

The last template examined, namely tetra-anionic **4** in *(E)*-form, in contrast to the reference isophthalate (**6**) is capable of effective amplification of the trimer, tetramer, and pentamer. Amplification of the trimer, which engages only one half of the template, is less pronounced than for model **6**. The significant amplification of $\mathbf{1_4}$ and $\mathbf{1_5}$ is a result of the cooperation of the four carboxylate groups. Quite surprisingly, the *(Z)*-**4** mixture exhibits all amplification factors more weakly than the *(E)*-isomer. We expected the anion

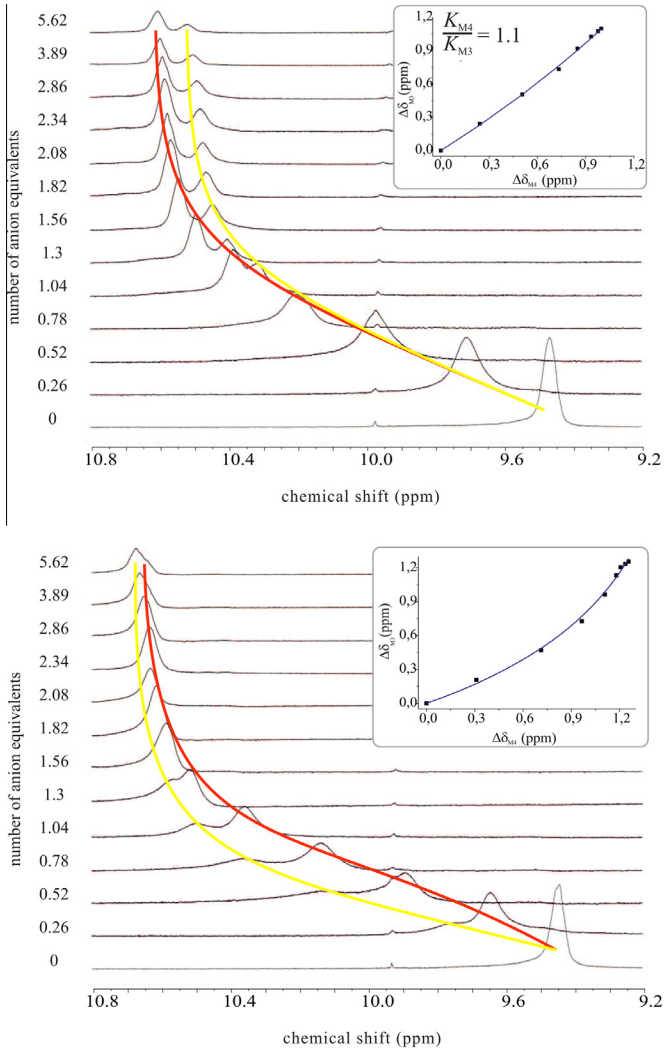


Figure 3. Changes in the chemical shift ($\Delta\delta$) of amide protons of $\mathbf{1_3}$ (red) and $\mathbf{1_4}$ (yellow) upon addition of template *(E)*-**3** (top) and *(Z)*-**3** (bottom) in DMSO-d_6. Corresponding correlations between $\Delta\delta$ for both macrocycles (inset).

in the *(Z)*-form to be particularly effective in the amplification of the tetramer. A possible explanation for this observation may involve the formation of a strong ion pair between tetraanionic *(Z)*-**4** and the TBA cation, which hampers any interactions with the macrocyclic hosts. This assumption is, however, not supported by NMR experiments.

In order to provide further confirmation of the differences in affinities of the photoisomers towards macrocyclic hosts we performed an NMR competitive titration.[16] Such an experiment is particularly useful in determining the ratio of two association constants – the selectivity. We carried the measurement on a mixture of $\mathbf{1_3}$ and $\mathbf{1_4}$ with *(E)*- and *(Z)*-**3** as guests in two separate experiments (see ESI for details). Under neutral conditions there was no disulfide bond exchange, the composition remained constant during the course of titration. The changes of chemical shifts ($\Delta\delta$) of amide protons are presented in Figure 3. For *(E)*-**3** the correlation between the $\Delta\delta$ of the two macrocycles is nearly linear, which indicates that both hosts possess similar affinity towards the anions guest. In the case of photoisomerised *(Z)*-**3** the correlation line is bent which indicates that host $\mathbf{1_4}$ binds the introduced guest more efficiently than host $\mathbf{1_3}$.[17] These results are in perfect agreement with the observed amplification in DCL. Additionally, titration of pure $\mathbf{1_3}$ with *(E)*-**3** provided an association constant at the level of $>10^4\ M^{-1}$, which indicates a strong binding of the templates by the macrocyclic hosts.

In the next step, we attempted to employ light as a factor influencing the composition of the DCL with the templates as mediators. So far, there is only one paper by Waters and co-workers[18] describing light induced changes in a DCL in which the library substrate is based on an azobenzene core. The equilibrated mixtures of $\mathbf{1_n}$ and one of the templates **2**–**4** in the *(E)*-form were irradiated with 368 nm light and PSSs were reached, as indicated by UV–vis analyses. We expected the library to modify the distribution of macrocycles according to aforementioned templation experiments. However, for all anions we observed no change in composition, even 12 h after irradiation – the library was "frozen". Analogous freezing was observed for *(Z)*→*(E)* isomerisation of compounds **2** and **3** with blue light. This effect was never observed when $\mathbf{1_n}$ and templates were irradiated individually before mixing them. We eventually found that it is possible to influence the library composition by light stimulus when 5 mol% of unoxidised monomer $\mathbf{1\text{-}H_2}$ (dithiol) was added to the mixture of DCL and photoswitchable template **3** (see ESI). The complex behaviour of this system requires further investigation.

In summary, for our three model anionic templates having switchable functionality, the differences in the geometry of the isomers can be detected and semi-quantitatively evaluated by analysing their templation effects on the dynamic combinatorial library. Information about the template's geometry is, in such an experiment, translated into the composition of the DCL. In addition, we proved that it is possible to modify the composition of a DCL by a light stimulus via the photoswitchable template acting as a mediator.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.043.

References and notes

1. Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem. Int. Ed.* **2000**, *39*, 3348–3391.
2. (a) Balzani, V.; Credi, A.; Venturi, M. *Chem. Soc. Rev.* **2009**, *38*, 1542–1550; (b) Dürr, H.; Bouas-Laurent, H. *Photochromism: Molecules and Systems: Molecules and Systems*; Elsevier Science, 2003.
3. (a) Szymański, W.; Beierle, J. M.; Kistemaker, H. A. V.; Velema, W. A.; Feringa, B. L. *Chem. Rev.* **2013**, *113*, 6114–6178; (b) Brieke, C.; Rohrbach, F.; Gottschalk, A.; Mayer, G.; Heckel, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8446–8476.
4. (a) Bandara, H. M. D.; Burdette, S. C. *Chem. Soc. Rev.* **2012**, *41*, 1809–1825; (b) Beharry, A. A.; Woolley, G. A. *Chem. Soc. Rev.* **2011**, *40*, 4422–4437; (c) Merino, E. *Chem. Soc. Rev.* **2011**, *40*, 3835–3853.
5. For example, blue shift of π–π^* band of the azo chromophore as well as large shielding of the protons adjacent to the N=N linkage are observed upon *(E)*→*(Z)* isomerisation of the ABs in UV–vis and ^{1}H NMR spectra, respectively.
6. (a) Ulysse, L.; Cubillos, J.; Chmielewski, J. *J. Am. Chem. Soc.* **1995**, *117*, 8466–8467; (b) Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **1999**, *121*, 1397–1398; (c) Chen, X.; Hong, L.; You, X.; Wang, Y.; Zou, G.; Su, W.; Zhang, Q. *Chem. Commun.* **2009**, 1356–1358.
7. Nguyen, T.-T.-T.; Türp, D.; Wagner, M.; Müllen, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 669–673.
8. Mativetsky, J. M.; Pace, G.; Elbing, M.; Rampi, M. A.; Mayor, M.; Samorì, P. *J. Am. Chem. Soc.* **2008**, *130*, 9192–9193.
9. Note that majority of them is stabilised in the macrocyclic scaffold or by direct interaction of the N=N bond with the metal cation.
10. (a) Reek, J. N.; Otto, S. *Dynamic Combinatorial Chemistry*; John Wiley & Sons, 2010; (b) Miller, B. L. *Dynamic Combinatorial Chemistry: In Drug Discovery, Bioorganic Chemistry, and Materials Science*; John Wiley & Sons, 2009; (c) Lehn, J.-M. *Chem. Soc. Rev.* **2007**, *36*, 151–160; (d) Otto, S.; Furlan, R. L. E.; Sanders, J.

K. M. *Drug Discovery Today* **2002**, *7*, 117–125; (e) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R.; Sanders, J. K.; Stoddart, J. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 898–952; (f) Lehn, J.-M.; Eliseev, A. V. *Science* **2001**, *291*, 2331–2332; (g) Lehn, J. M. *Chem. Eur. J.* **1999**, *5*, 2455–2463.

11. (a) Corbett, P. T.; Sanders, J. K.; Otto, S. *Chem. Eur. J.* **2008**, *14*, 2153–2166; (b) Ludlow, R. F.; Otto, S. *J. Am. Chem. Soc.* **2008**, *130*, 12218–12219; (c) Corbett, P. T.; Sanders, J. K.; Otto, S. *J. Am. Chem. Soc.* **2005**, *127*, 9390–9392; (d) Corbett, P. T.; Otto, S.; Sanders, J. K. M. *Org. Lett.* **2004**, *6*, 1825–1827; (e) Severin, K. *Chem. Eur. J.* **2004**, *10*, 2565–2580; (f) Grote, Z.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3821–3825.
12. a) Ulatowski, F.; Sadowska-Kuziola, A.; Jurczak, J. *J. Org. Chem.* **2014**, *79*, 9762–9770; b) Ulatowski, F.; Lichosyt, D.; Jurczak, J. *Org. Biomol. Chem.* **2015**, *13*, 10451–10455.
13. For additional data for corresponding carboxylic acids as well as thermodynamic data see ESI.
14. Dabrowa, K.; Niedbala, P.; Jurczak, J. *Chem. Commun.* **2014**, 15748–15751.
15. Hamieh, S.; Saggiomo, V.; Nowak, P.; Mattia, E.; Ludlow, R. F.; Otto, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 12368–12372.
16. Whitlock, B.; Whitlock, H. *J. Am. Chem. Soc.* **1990**, *112*, 3910–3915.
17. (Z)-3 stands for a PSS mixture of photoisomers, therefore during titration a mixture of four components is obtained (two hosts and two guests) and so the exact value of ratio of association constants cannot be calculated.
18. Ingerman, L. A.; Waters, M. L. *J. Org. Chem.* **2008**, *74*, 111–117.