A Photochemically Activated Cyclophane

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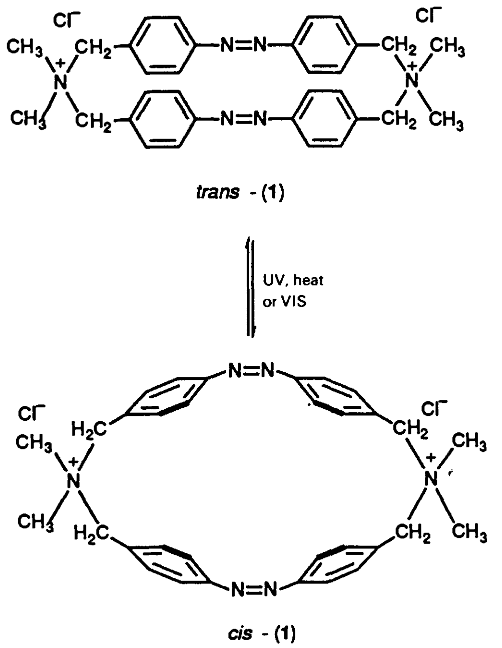
A water-soluble, photoresponsive macrocycle (**1**), composed of two N^+ cations and two azobenzene units, has been synthesized. This cyclophane changes its cavity shape in response to a photoinduced *trans–cis* isomerization of the azobenzene moieties. The photoresponsive association behaviour has been examined for mono- and di-carboxylate guest molecules through spectral studies, thermal *cis*→*trans* isomerization, and electrical conductance measurements. It has been shown that *cis*-(**1**) strongly binds guest molecules having a general structure $^-OOC(CH_2)_nCOO^-$, the driving force for the guest binding being the electrostatic force between two N^+ cations and two carboxylate anions and the hydrophobic force between the *cis*-azobenzene units and a $-(CH_2)_n-$ chain. The results establish that the guest selectivity in host–guest chemistry can be controlled by the enforced change in the cavity shape.

Macrocyclic compounds contain intramolecular cavities delineated by molecular segments and are expected to specifically interact with guest metals and molecules. As the guest selectivity is primarily governed by the size of the intramolecular cavity, one may expect that if the topological ring shape can be reversibly changed, this would lead to control of the guest-binding ability and guest selectivity. In a crown ether compound suitably combined with a photoresponsive azobenzene group, for example, the photochemical *trans–cis* configurational change occurring in the azobenzene moiety can be transferred to the crown ether moiety and enforce its conformational change.[1] As a result, the ion-binding ability and ion selectivity characteristic of crown ether compounds can be controlled by an on-off-type 'light switch'.[1] This concept can be applied to the molecular recognition of organic guest molecules by cyclophanes because a similar recognition pattern based on the size compatability between the guest and the host cavity has frequently been observed. An azobenzenophane would be suitable as a test of this possibility because the cavity shape would be changed reversibly by the photoinduced *trans–cis* isomerism of the azobenzene component. Although azobenzenophanes have been synthesized by several groups,[2–8] a study of the photochemical control of host–guest-type interactions has been very limited.[5,6] In that case, what type of azobenzenophane should be designed in order to accomplish the present research purpose? In order to realize host–guest-type interactions, an aqueous system is recommended in which the hydrophobic force broadly operates on organic guest and host molecules.[9] Thus, a water-soluble azobenzenophane is preferred. This is the primary prerequisite for molecular design. If the azobenzenophane ring is too large, the local *trans–cis* photoisomerization cannot change the cavity shape sufficiently in order to affect the guest selectivity. This tells us that a small ring is preferred so as to realize a drastic change in the topological ring shape. This is a secondary prerequisite. Bearing these considerations in mind we designed a water-soluble azobenzenophane (**1**). We have found that the guest recognition pattern is affected by photoinduced *trans–cis* isomerism in the azobenzene components.

Experimental

Materials.—The preparation of 4,4′-bis(chloromethyl)azobenzene (**2**) has been described previously.[10]



trans -(**1**)

cis -(**1**)

4,4′-*Bis*(N,N-*dimethylaminomethyl*)*azobenzene* (**3**).—Compound (**2**) (1.00 g; 3.60 mmol) was added to a methanol solution (25 cm^3) containing 4 cm^3 of aqueous dimethylamine (50 wt %) and the mixture was stirred at room temperature for 20 h. The completion of the reaction was confirmed by TLC (silica gel, methanol–chloroform 1 : 1 v/v). The solution was concentrated under reduced pressure. The residue was treated with aqueous alkali (0.1 mol dm^{-3} NaOH), collected by filtration, and washed with dil. aqueous ammonia. The solid product was dissolved in ligroin. The solution was mixed with aqueous 0.1 mol dm^{-3} NaOH and treated with activated charcoal. After filtration, the ligroin layer was separated and washed several times with water. Finally, the concentration of the ligroin solution gave compound (**3**) in 83% yield, m.p. 73–76 °C; δ_H($CDCl_3$) 2.27 (12 H, s, CH_3), 3.49 (4 H, s, CH_2), and 7.45 and 7.87 (4 H, and 4 H, d and d, ArH) (Found: C, 73.0; H, 8.1; N, 18.6%. $C_{18}H_{24}N_4$ requires C, 72.94; H, 8.16; N, 18.90%).

Table 1. Influence of added water on the yield of *trans*-(**1**).

Solvent/cm^3		
Chloroform	Water	Yield (%)
35	0	0
35	35	20.2
35	56	30.3
35	80	50.2

Table 2. Spectroscopic and isomerization properties of (**1**) and (**2**) in water at 30 °C.

Property	(**1**)	(**4**)
λ_{max}/nm for *trans* isomer	325	320
ε_{max}/dm^3 mol^{-1} cm^{-1} for *trans* isomer	44 300	20 200
cis % at the photostationary state^a	26.5	44.8
k_0 s^{-1} for thermal isomerization	1.65×10^{-6}	1.31×10^{-6}

^{a} Attained at [(**1**)] = [(**2**)] = 2.50×10^{-5} mol dm^{-3}.

4,4'-Bis(N,N,N-*trimethylammoniomethyl*)*azobenzene Dichloride* (**4**).—A methanol solution (50 cm^3) containing (**2**) (1.40 g, 5.00 mmol) and 4 cm^3 of aqueous trimethylamine (30 wt %) was stirred at 57 °C for 3 h. The completion of the reaction was confirmed by TLC (silica gel, methanol). The solution was concentrated under reduced pressure, and evaporation was ceased before the precipitate formed. The methanol solution was diluted with chloroform, and the crystals were collected by filtration. Yield 92%, m.p. 224–227 °C (decomp.); δ_H(D_2O, internal standard DSS) 3.22 (18 H, s, CH_3), 4.66 (4 H, s, CH_2), and 7.83 and 8.06 (4 H and 4 H, d and d, ArH) (Found: C, 55.5; H, 7.7; N, 12.5; Cl, 16.05%. $C_{20}H_{30}N_4Cl_2 \cdot 2H_2O$ requires, C, 55.43; H, 7.90; N, 12.92; Cl, 16.36%).

Compound (**1**).—Compounds (**2**) (0.56 g, 2.00 mmol) and (**3**) (0.60 g, 2.00 mmol) were dissolved in chloroform (35 cm^3). The solution was heated under reflux in the presence of water (80 cm^3) (in the absence of water, the reaction afforded only polymeric products). The progress of the reaction was followed by TLC (silica gel, hexane–methanol, 2:1 v/v). After 20 h, the aqueous layer was separated, treated with activated charcoal, and salted out with NaCl. The precipitate was recovered by filtration and washed with cold water. Yield 50.2%, m.p. 197–203 °C; δ_H(CD_3OD) 3.10 (12 H, s, CH_3), 3.31 (8 H, s, CH_2), and 7.89 and 8.12 (8 H and 8 H, d and d, ArH) (Found: C, 59.2; H, 6.8; N, 12.7; Cl, 10.9%. $C_{32}H_{36}N_6Cl_2 \cdot 4H_2O$ requires C, 59.35; H, 6.84; N, 12.97; Cl, 10.95%). The IR spectrum gave a broad absorption band at 3300 cm^{-1} and the NMR spectrum gave a single peak at 4.88 ppm, indicating that four water molecules are included.

Photo- and Thermal Isomerization.—*trans*→*cis* Photoisomerization was carried out using a 200 W high-pressure mercury lamp with a coloured glass filter [Toshiba UV-D35 (330 nm < λ < 380 nm)]. *cis*→*trans* Photoisomerization was carried out using the same mercury lamp with a coloured glass filter [Toshiba Y-46 (λ > 460 nm)]. The kinetic measurements for the thermal *cis*→*trans* isomerization were followed spectroscopically at 30 °C by monitoring the increase in the absorption maxima of the *trans* isomers. To obviate possible photoisomerization (*trans*→*cis*) by light from the spectrophotometer, we measured the absorbance for several seconds per minute. The details of the method have been described previously.[10,11]

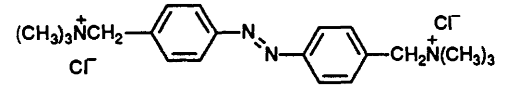
Results and Discussion

Comments on the Synthesis Methods.—We first attempted the reaction of (**2**) and (**3**) in several solvents (methanol, chloroform, *N,N*-dimethylformamide, *etc.*) under high-dilution conditions. However, the products we isolated were all polymeric and even a trace amount of cyclic *trans*-(**1**) could not be detected. The examination of Corey–Pauling–Koltun (CPK) molecular models suggests that the ring of *trans*-(**1**) is considerably strained because two planar azobenzene units are linked by short $-CH_2-N^+-CH_2-$ straps. In a sense, the ring strain in *trans*-(**1**) is equivalent to that in [3.3]paracyclophanes. Thus, the intermolecular reaction proceeds in preference to the intramolecular cyclization.

In this case we noticed that the two starting materials are soluble in organic solvents whereas the product [*trans*-(**1**)] and the intermediate ($ClCH_2$–azobenzene–$CH_2N^+Me_2CH_2$–azobenzene–CH_2NMe_2) are water-soluble. For example, when a chloromethyl group in (**2**) reacts with a *N,N*-dimethylaminomethyl group in (**3**), the intermediate becomes water-soluble. If the reaction is carried out in a two-phase mixture of chloroform and water, the intermediate is transferred into the aqueous phase where neither (**2**) nor (**3**) exists. As a result, the intramolecular cyclization occurs under the ideal high-dilution conditions (Figure 1). As expected, the reaction in a two-phase system gave the product [*trans*-(**1**)] in moderate yields. As summarized in Table 1, the yield increases with increasing water volume. Probably, the concentration of the cationic intermediate in the water phase decreases and the more ideal high-dilution condition is accomplished.

It is clear that in the present method, the high-dilution conditions are attained by extracting the reaction intermediate into the aqueous phase. This two-phase method may be applicable more widely to the synthesis of hindered cyclophanes.

Photo- and Thermal Isomerization.—The spectroscopic properties of compound (**1**) and its noncyclic analogue (**4**) are summarized in Table 2. The typical absorption spectra are illustrated in Figure 2. The CPK molecular models suggest that the ring of *trans*-(**1**) is considerably strained. This is scarcely reflected by the spectroscopic data, however: λ_{max} for *trans*-(**1**) shifts only by 5 nm to longer wavelength and ε_{max} is *ca.* 2 × that of *trans*-(**4**) (*i.e.*, the extinction coefficients are almost the same). The *trans* isomers were isomerized to the *cis* isomers by UV light irradiation. The percentage of *cis*-(**1**) in the photo-stationary state was significantly lower than that of (**4**). This suggests that the ring of *cis*-(**1**) is also strained.



trans - (**4**)

The rate of thermal *cis*→*trans* isomerization was determined by monitoring the increase in the absorbance, *A*, for the *trans* isomers. Plots of log ($A_0 - A_t$) *vs.* time were linear for up to three half-lives, indicating that the isomerization obeys first-order kinetics. Basically, the isomerization of *cis*-(**1**) to *trans*-(**1**) consists of two steps, *cis–cis*→*cis–trans*→*trans–trans*. We confirmed that it is impossible to make a molecular model for the *cis–trans* isomer. This implies that in (**1**), the thermal isomerization proceeds directly from *cis–cis* [(*i.e.*, *cis*-(**1**)] to *trans–trans* [(*i.e.*, *trans*-(**1**)]. In other words, two *cis*-azobenzene units isomerize simultaneously to *trans*-azobenzene units.[12] As shown in Table 2, the first-order rate constant (k_0) for (**1**) is not so different from that for (**4**). Thus, the possible ring strain is not reflected by the thermal isomerization rate. Presumably, the initial state for *cis*-(**1**) is destablized because of ring strain, but

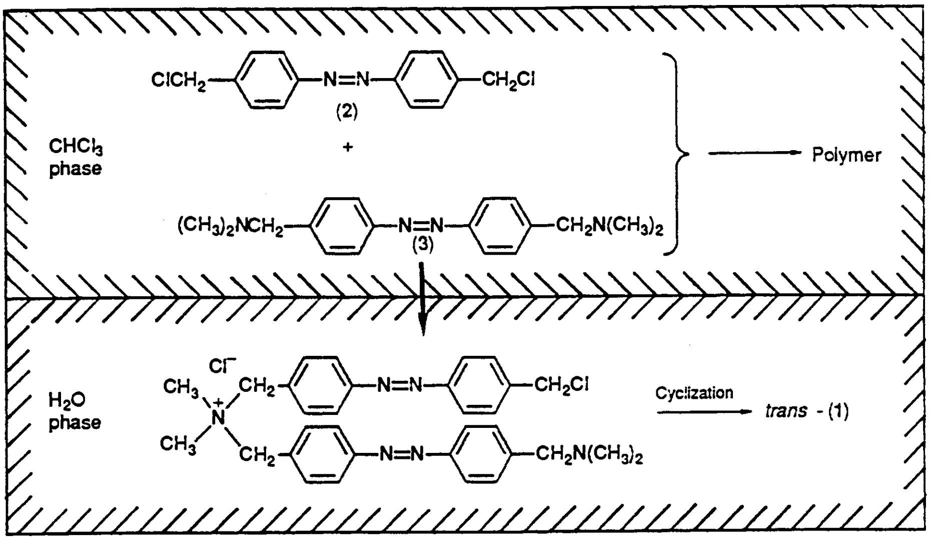


Figure 1. Schematic representation of the cyclization step under two-phase high-dilution conditions.

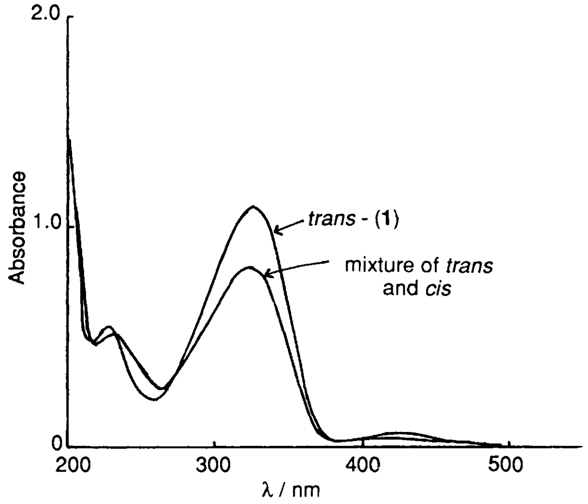


Figure 2. Absorption spectra for *cis-trans* isomerization of (**1**) (2.50×10^{-5} mol dm^{-3}) in water at 30 °C.

the transition state is also destabilized. As a result, the $\Delta G^{\ddagger}$ value for the thermal isomerization of *cis*-(**1**) is not so different from that of *cis*-(**4**).

^{1}H *NMR Spectra.*—Guest inclusion into hosts composed of aromatic compounds is conveniently evidenced by ^{1}H NMR spectra because they induce the up-field shift of guest peaks because of the aromatic ring current. To perform this experiment we must photo-isomerize *trans*-(**1**) in an NMR tube (the concentration must be $> 10^{-3}$ mol dm^{-3}). We found that the photo-isomerization of *trans*-(**1**) to *cis*-(**1**) (2.50×10^{-3} mol dm^{-3}) scarcely proceeds, even though the photo-irradiation is continued for a long period (*ca.* 1 h). We thus spread the D_2O solution on a glass plate and photo-irradiated the thin layer by UV light. We then obtained a D_2O solution containing 14% of *cis*-(**1**). The solution was transferred into an NMR tube and then subjected to the measurement.

trans-(**1**) in D_2O gave δ_H 3.03 ppm for Me and 7.74 and 7.97 ppm for aromatic protons. The *trans–cis* mixture (86:14) gave several additional peaks attributable to *cis*-(**1**): δ_H 2.96 ppm for Me and 6.97, 7.10, 7.32 and 7.43 ppm for aromatic protons. The result indicates that aromatic protons in *cis*-(**1**) are more shielded than those in *trans*-(**1**). We then added disodium adipate [(**5**; $n = 4$) 2.50×10^{-3} mol dm^{-3}] to these solutions. The $(CH_2)_4$ protons of (**5**; $n = 4$) gave two peaks at δ_H 1.53 and 2.17 ppm in D_2O in the absence of (**1**). In the presence of (**1**) these peaks moved to higher magnetic field: δ_H 1.22 and 1.85 ppm in the presence of *trans*-(**1**) and 1.25 and 1.86 ppm in the presence of the *trans–cis* mixture (86:14). These NMR data suggest that dianionic adipate interacts with dicationic (**1**) in D_2O to undergo the effect of the ring current. Here, it seemed difficult to obtain further insight into host-guest-type interaction using an NMR method. We thus examined the influence of added (**5**; n = 1, 4 and 8) on the rate of thermal *cis*→*trans* isomerization in detail.

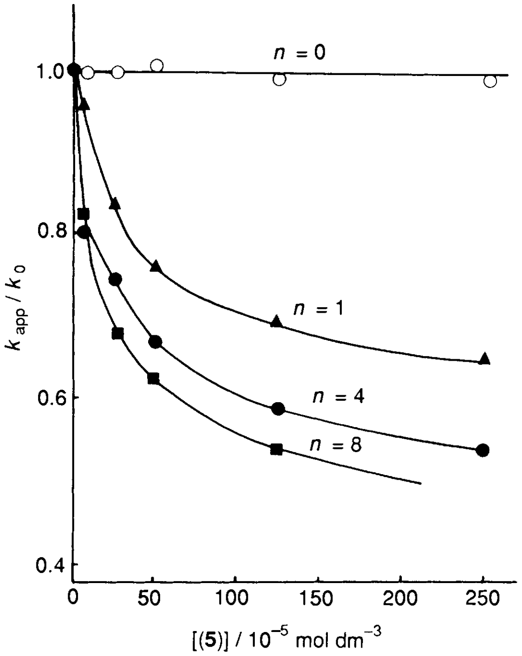


Figure 3. Influence of added (**5**) on the rate of thermal *cis*→*trans* isomerization of (**1**): 30 °C, [(**1**)] = 2.50×10^{-5} mol dm^{-3}.

$$NaO_2C(CH_2)_nCO_2Na$$

(**5**)

cis→trans *Thermal Isomerization.*—As shown in Figure 3, the apparent first-order rate constants (k_{app}) for thermal isomerization of (**1**) decreased with increasing concentration of (**5**)

Table 3. Association constants (K) and first-order rate constants (k_c) for thermal *cis*-to-*trans* isomerization of (**1**)·(**5**) complexes at 30 °C.

(**5**)	$K/\text{dm}^3\ \text{mol}^{-1}$	k_c/s^{-1}
(**5**; n = 0)	0	1.60×10^{-6}
(**5**; n = 1)	7.95×10^{3}	8.80×10^{-7}
(**5**; n = 4)	1.74×10^{4}	7.30×10^{-7}
(**5**; n = 8)	1.03×10^{4}	1.61×10^{-7}

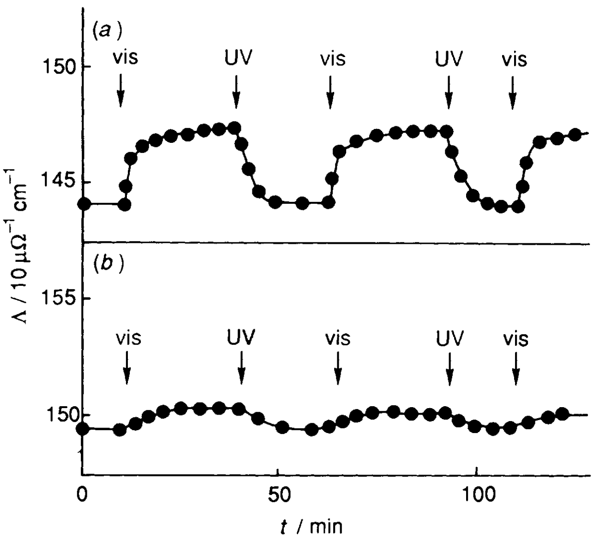
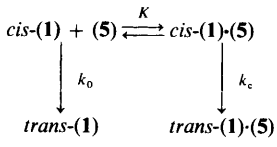


Figure 4. Influence of photoirradiation on the conductance: solvent, CH_3OH-H_2O (2000:1 v/v); 30 °C, [(**1**)] = [(**5**)] = 2.5×10^{-5} mol dm^3; (*a*) (**1**) and (**5**; n = 4); (*b*) (**1**) and (**5**; n = 0).

[except for (**5**; n = 0)]. This implies that the isomerization of (**1**) is suppressed by the association with (**5**). On the other hand, the rate of thermal isomerization of a noncyclic analogue (**4**) is scarcely influenced by added (**5**; n = 4) (0–2.5×10^{-3} mol dm^{-3}). We also found that neither sodium valerate (monoanionic guest) nor hexane-1,6-diol (non-ionic guest) changes the rate of thermal isomerization of (**1**) (guest concentration, 0 – 2.5×10^{-3} mol dm^{-3}). These results consistently support the view that the rate suppression occurs characteristically in a combination of cyclic (**1**) and dianinic (**5**). Strangely, disodium terephthalate and disodium oxalate (**5**; n = 0) exerted no effect on the thermal isomerization of (**1**) although they are dianionic species. The examination of CPK molecular models reveals that in *trans*-(**1**) two *trans*-azobenzene units are so close to each other that it is impossible for guest molecules to be inserted between these two azobenzene units, whereas in *cis*-(**1**) a small intramolecular cavity is composed of two *cis*-azobenzene units. This cavity is too small to accept a phenyl group but large enough to complex an aliphatic –$(CH_2)_n$– chain. This is why compounds (**5**) are effective while disodium terephthalate is ineffective. In (**5**; n = 0) the distance between two negative charges is too short to interact with two positive charges in *cis*-(**1**). Furthermore, it has no hydrophobic methylene group. Thus, this dicarboxylate is weakly bound to *cis*-(**1**).

The foregoing considerations provide a possible binding mode between *cis*-(**1**) and (**5**): compounds (**5**) are bound to *cis*-(**1**) not only through electrostatic interactions at two points but also through hydrophobic interactions between the cavity and the –$(CH_2)_n$– chain. As mentioned above, the NMR data indicate that (**5**; n = 4) is 'bound' to *trans*-(**1**). However, the intramolecular cavity of *trans*-(**1**) is closed. Presumably, the interaction between *trans*-(**1**) and (**5**; n = 4) takes place on the surface of *trans*-(**1**) through the electrostatic attraction. This suggests that the association with *trans*-(**1**) is much weaker than that with *cis*-(**1**).

The rate data in Figure 3 were analysed according to the Scheme, where k_c and K denote the first-order rate constant for



Scheme.

thermal isomerization of a *cis*-(**1**)·(**5**) complex and the association constant, respectively. The kinetic situation can be expressed by the equation, which features a linear relationship between $1/(k_0-k_{app})$ and $[(5)]^{-1}$. From the plots were determined the slope and the intercept by a least-squares procedure (r > 0.99). The results are summarized in Table 3.

$$[k_0-k_{app}]^{-1} = [(k_0-k_c)K]^{-1}\cdot[(5)]^{-1} + (k_0-k_c)^{-1}$$

According to CPK molecular models of (**5**) with a linearly extended $(CH_2)_n$ chain, the distance between two COO^- charges is 3.6 Å for (**5**; n = 1), 7.2 Å for (**5**; n = 4) and 12.4 Å for (**5**; n = 8). The distance between two N^+ charges in *cis*-(**1**) is 9.6 Å. Hence, (**5**; n = 4) best fits the cavity of *cis*-(**1**) allowing both the electrostatic and hydrophobic interactions, and the next best fit is (**5**; n = 8) which would be bound to *cis*-(**1**) in an induced-fit manner. As expected, the K values in Table 3 are in the order of (**5**; n = 4) > (**5**; n = 8) > (**5**; n = 1). On the other hand, the k_c values decrease with increasing chain length.

Conductance Measurements.—Through thermal isomerization studies we have substantiated the complexation of *cis*-(**1**) with (**5**). In contrast, it is rather difficult to substantiate the complexation of *trans*-(**1**) with (**5**) although the chemical shifts for (**5**; n = 4) moved to higher magnetic fields. Previously, we have examined the association of azobis(benzo-18-crown-6) (**6**) and polymethylenediammonium cations $H_3N^+(CH_2)_mNH_3^+$ (**7**).[13] *trans*-(**6**) and (**7**) tended to polymerize owing to the intermolecular NH_3^+ ••• crown association, whereas *cis*-(**6**) and (**7**) tended to form pseudo-macrocycles owing to the 1:1 association. The photoresponsive change in the association mode could be conveniently monitored by a conductive method[13,14]: *i.e.*, the *trans*-(**6**) system gave a low conductance (because of the low mobility of the polymers) whereas the *cis*-(**6**) system gave a high conductance (because of the high mobility of the low molecular-weight pseudo-macrocycles). We applied this method to the present system. Since the association of (**1**) with (**5**) provides a neutral complex, the conductance should be decreased when the association takes place.

The aqueous solution containing (**1**) and (**5**; n = 4) was first irradiated by UV light which mediates *trans*→*cis* isomerization. After the photostationary state had been attained, the solution was irradiated by visible light which mediates *cis*→*trans* photoisomerization. As shown in Figure 4(*a*), the conductance was increased. When the solution was irradiated by UV light, the conductance was decreased. This indicates that (**1**) and (**5**; n = 4) form more neutral complexes under UV light irradiation: *i.e.*, *cis*-(**1**) binds (**5**; n = 4) more strongly than *trans*-(**1**). A similar experiment was repeated for (**1**) and (**5**; n = 0). As shown in Figure 4(*b*), a perceptible change in conductance was not detected. This means that (**5**; n = 0) is bound neither to *trans*-(**1**) nor to *cis*-(**1**).

Conclusions

The present study has demonstrated that in an azobenzene-based cyclophane such as (**1**), the framework of the cavity can be easily changed by photoinduced *trans–cis* isomerization of the azobenzene components. By using this structural change one can control the guest selectivity which is usually governed by the geometrical compatability between the guest and the host cavity. The concept is readily applicable to dynamic guest-binding systems such as solvent extraction and membrane transport: *i.e.*, facile and reversible inclusion and removal of guest molecules to and from inclusion host molecules will improve the efficiency in these dynamic processes.

Acknowledgements

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12 A similar phenomenon has been noticed with small azobenzenophane rings: for example, in [3,3](4,4′)-azobenzenophane the rate for *cis–trans*→*trans–trans* is faster by 1000-fold than that for *cis–cis*→*cis–trans*.[3]

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