Photo- and Thermal *cis–trans* Isomerization of [2$_3$](4,4')Azobenzenophane

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Four isomers, *EEE*, *EEZ*, *EZZ* and *ZZZ*, exist for [2$_3$](4,4')azobenzenophane depending on the degree of the isomerization of three azobenzene units. These isomers are stable enough to be separated by reversed-phase liquid chromatography. The compound in methanol exists as the *EEE* form in the dark. Upon irradiation at 366 nm the *EEE* form isomerizes *via* the *EEZ* form and the *EZZ* form to the *ZZZ* form. At the photostationary state at 366 nm, 85% of the compound exists as the *ZZZ* form. From the photostationary state the compound thermally isomerizes gradually to the *EEE* form. The thermal reaction from the *ZZZ* form to the *EEE* form also proceeds in a stepwise fashion. The relative values of the quantum yields for the photoisomerization and the absolute value of the rate for the thermal isomerization have been determined for each step. Both the photo- and thermal processes in the $Z \rightarrow E$ direction show the different efficiencies (or rates) depending on the processes. These experimental results can be explained by supposing that the different degree of ring strain works for ground and (or) excited states of each isomer. In this compound, a certain isomer can be enriched by the combination of external stimuli, such as light or heat. This raises the possibility of synthesizing molecules with more than two functional states.

Among macrocycles, there exist compounds which are able to bind alkali-metal ions or low-molecular-weight organic compounds, as exemplified by crown ethers,[1] cyclodextrins[2] and calixarenes.[3] Studies have also been carried out in which a photosynthetic model is constructed containing electron-donating chromophores and electron acceptors connected within a macrocycle.[4] In these studies, the relation between the relative positions of the acceptors and the donors, which are precisely controlled by the macrocyclic framework, and the efficiency of the electron transfer is clarified in detail. These examples represent how closed, rigid framework of macrocyclic compounds can be used to advantage.

On the other hand, macrocyclic compounds in which the main frame includes photo-responsive units have recently become the focus of interest because it may be possible to change the whole conformation of the macrocycle by means of external stimuli and to attain more than two kinds of functional state. For example, crown ethers including an azobenzene unit,[5] cyclodextrin capped with an azobenzene unit[6] and a compound in which two porphyrin rings are connected in a circular manner with two azobenzene units[7] have been synthesized. In the first two examples, it is reported that the binding abilities of these compounds to alkali-metal ions or toluene, *etc.*, can be changed by isomerization of the azobenzene units. These examples represent dynamic structural change in macrocyclic compounds induced by ring strain. Although these studies, in which isomerization is utilized as a switch for complete conformational change of the molecules, are very interesting, there are few studies in which the relationship between kinetic parameters for the dynamic structural change of macrocyclic compounds and the ring strain are discussed.

We have already reported the synthesis of macrocyclic azobenzene compounds, in which 4,4' positions of two azobenzene units are connected by two carbons each, in which the isomerization at 298 K from the *EZ* form to the *ZZ* form is about 10 000 times faster than from the *ZZ* form to the *ZE* form.[8,9] In these experiments the large differences in the isomerization rates are shown, even though both of the modes are the isomerizations of –N=N– bonds from *Z* to *E* under the same condition except for the ring strain. These experimental results demonstrate not only that ring strain can change the whole conformation of the macrocyclic compounds but also that the degree of the ring strain influences the rate of the conformational change.

In this study we have extended these studies to the isomerization of a macrocyclic compound with three azobenzene units in the frame. Four isomers, *EEE*, *EEZ*, *EZZ* and *ZZZ*, exist for the compound. The rates of photo- and thermal isomerizations between the isomers were determined by liquid chromatographic methods.[10]

Experimental

Materials.—Spectral grade methanol was used as the solvent for kinetic measurements. 1,2,17,18,33,34-Hexaaza-[2$_6$]paracyclophane-1,17,33-triene (**1**) was synthesized by the method described previously.[8]

Photo- and Thermal Isomerization.—Photoisomerization of **1** was carried out at λ = 366 nm with light produced by a 450 W high-pressure mercury lamp and appropriate combinations of glass filters at 25 ± 2 °C. Thermal isomerization was performed in sealed glass tubes equipped in a thermostatically controlled bath (kinetic viscosity bath, TV-5S, Thomas Kagaku Co., Ltd.). The isomerizations were followed by reversed-phase liquid chromatography (Merck Hibar LiChrosorb RP-18, acetonitrile). The absorption spectra of the isomers were measured with a Spectra Multi Channel Photo Detector (Ohtsuka Denshi MCPD 350) after HPLC processing.

Determination of the Concentration of the Isomers.—Relative concentrations of the isomers were determined by a normalization method using the HPLC peak areas monitored at λ = 284 nm. It was impossible to isolate the isomers of **1** preparatively; however, the response factors at λ = 284 nm for the isomers were determined from eqn. (1) which should be satisfied for any samples of the same total concentration but different isomer ratio;

$$A_{EEE}/f_{EEE} + A_{EEZ}/f_{EEZ} + A_{EZZ}/f_{EZZ} + A_{ZZZ}/f_{ZZZ} = K \quad (1)$$

where A is peak area of the isomers; f is the response factor of the isomers and K is a constant. Thus, the peak areas of HPLC, monitored at 284 nm for 17 solutions whose isomer ratios were

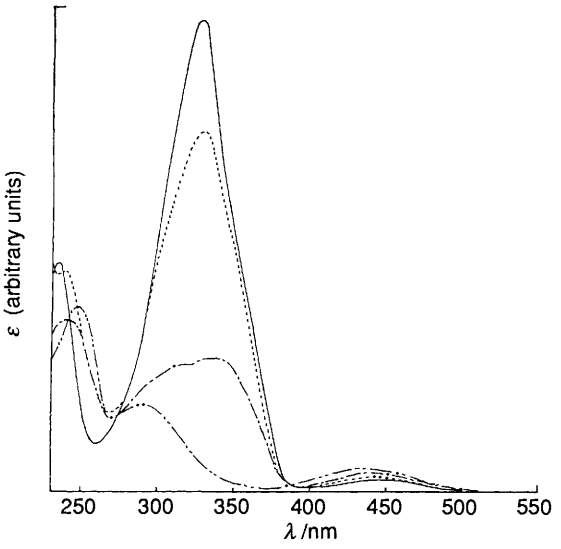


Fig. 1 Absorption spectra of *EEE* isomer, ——; *EEZ* isomer, – – – –; *EZZ* isomer, — — —; *ZZZ* isomer, — — — — of **1**

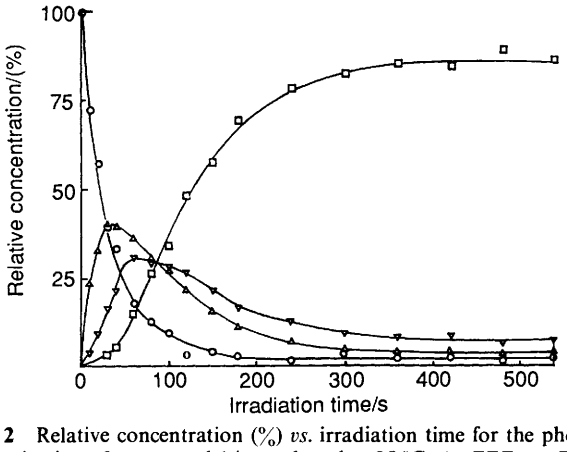


Fig. 2 Relative concentration (%) *vs.* irradiation time for the photoisomerization of compound **1** in methanol at 25 °C: ○, *EEE*; △, *EEZ*; ▽, *EZZ*; □, *ZZZ*.

changed by changing the irradiation time, were substituted into eqn. (1), and the best fitted values of the response factors were determined. When the response factors fit the relation, $f_{EEE} = f_{EEZ}/0.99 = f_{EZZ}/0.80 = f_{ZZZ}/0.72$, the coefficient of variation for K was the smallest (3.7%). This variation coefficient for the sum of the four peaks is not as large as HPLC data obtained by the weighing method.[11] This fact supports the reliability of this method for obtaining response factors in this study.

Results

Identification of the Four Isomers.—The absorption spectrum in methanol before photo-irradiation has a strong band at 329 nm and a broad band at *ca.* 440 nm which are characteristic of *E*-4,4′-dialkyl-substituted azobenzenes. By reversed-phase chromatography, it was confirmed that the solution contained only one kind of compound. Therefore, it is concluded that [2$_3$](4,4′)azobenzenophane exists as the *EEE* form in solution in the dark.

Upon irradiation with UV light, the band at 329 nm is decreased and that around 440 nm is increased. After irradiation for an arbitrary length of time, four peaks 1, 2, 3 and 4 (V_R = 3.6, 5.2, 8.4, 16.4 cm^3, respectively) appeared on the HPLC chromatograms (Merk Hibar LiChrosorb RP-18; acetonitrile). The absorption spectra of the isomers that give rise to these peaks were measured with a Spectra multi-channel photodetector equipped with a data processor (Ohtsuka Denshi MCPD 350). The ratio of absorbance of the isomers at 329 nm (λ_{max} of the spectrum due to $\pi\pi^*$ of the initial solution) to that at 440 nm decreases in the peak order 4, 3, 2 and 1. It is well known for polyazo compounds that the isomers with more *Z* conformations have a higher dipole moment and thus smaller R_f value on reversed-phase HPLC.[12] The larger absorbance around 440 nm and smaller absorbance around 330 nm in comparison with the *E* conformers are the characteristics of *Z* conformers of 4,4′-dialkyl-substituted azobenzene derivatives. Hence, peaks 1, 2, 3 and 4 can be identified as the *ZZZ*, *EZZ*, *EEZ* and *EEE*, respectively. Fig. 1 shows the absorption spectra of the four isomers.

Photoisomerization.—Fig. 2 shows the change in relative concentration against irradiation time. Upon irradiation at 366 nm the *EEE* isomer concentration decreases rapidly, and at the same time the *EEZ* isomer increases. The increase in the *EZZ* and the *ZZZ* isomer concentrations follows the change of the *EEZ*. In the early stage *EEZ* and *EZZ* attain maximum concentrations and then decrease gradually. At the photostationary state λ = 366 nm, 85% of the compound exists in the *ZZZ* form. This concentration change demonstrates qualitatively that the photoisomerization proceeds consecutively, *i.e.*, *EEE* ⟶ *EEZ* ⟶ *EZZ* ⟶ *ZZZ*.

Differential equations for the rate processes of isomers introduced from Scheme 1 are expressed as eqns. (2)–(5). Each

$$\frac{d[EEE]}{dt} = -1000\varphi_1 \frac{\varepsilon_{EEE}[EEE]lI_0(1-10^{-D})}{D} + 1000\varphi_4 \frac{\varepsilon_{EEZ}[EEZ]lI_0(1-10^{-D})}{D} - k_1[EEZ] \quad (2)$$

$$\frac{d[EEZ]}{dt} = -1000\varphi_2 \frac{\varepsilon_{EEZ}[EEZ]lI_0(1-10^{-D})}{D} + 1000\varphi_5 \frac{\varepsilon_{EZZ}[EZZ]lI_0(1-10^{-D})}{D} - k_1[EEZ] - 1000\varphi_4 \frac{\varepsilon_{EEZ}[EEZ]lI_0(1-10^{-D})}{D} + 1000\varphi_1 \frac{\varepsilon_{EEE}[EEE]lI_0(1-10^{-D})}{D} + k_2[EEZ] \quad (3)$$

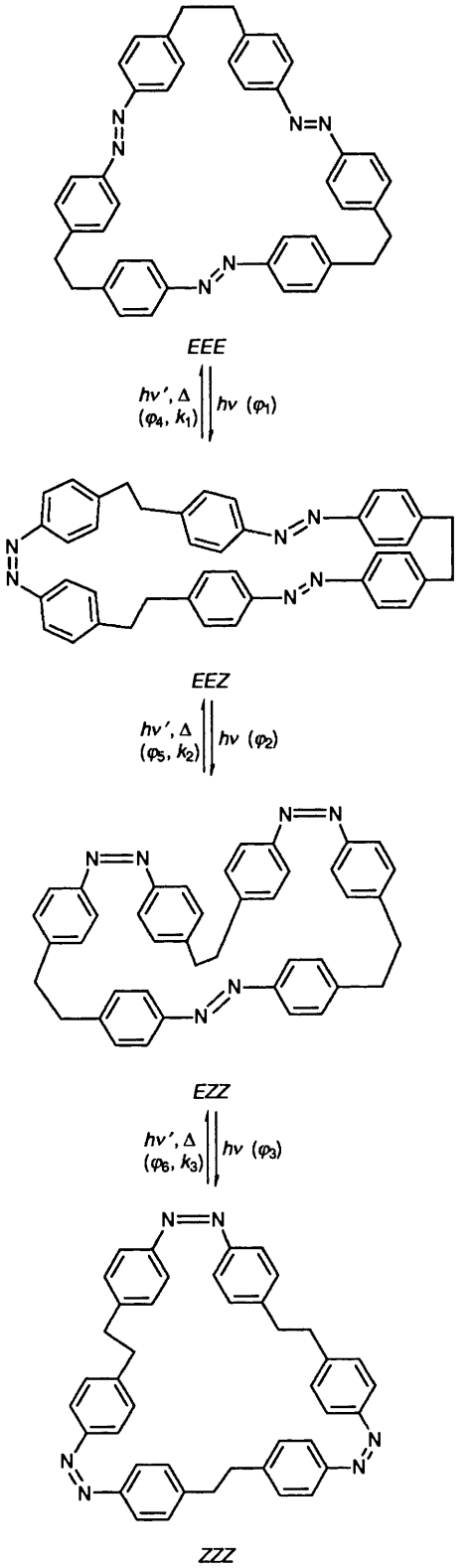
$$\frac{d[EZZ]}{dt} = -1000\varphi_3 \frac{\varepsilon_{EZZ}[EZZ]lI_0(1-10^{-D})}{D} + 1000\varphi_6 \frac{\varepsilon_{ZZZ}[ZZZ]lI_0(1-10^{-D})}{D} - k_2[EZZ] - 1000\varphi_5 \frac{\varepsilon_{EZZ}[EZZ]lI_0(1-10^{-D})}{D} + 1000\varphi_2 \frac{\varepsilon_{EEZ}[EEZ]lI_0(1-10^{-D})}{D} + k_3[ZZZ] \quad (4)$$

$$\frac{d[ZZZ]}{dt} = -1000\varphi_6 \frac{\varepsilon_{ZZZ}[ZZZ]lI_0(1-10^{-D})}{D} + 1000\varphi_3 \frac{\varepsilon_{EZZ}[EZZ]lI_0(1-10^{-D})}{D} - k_3[ZZZ] \quad (5)$$

where $D = (\varepsilon_{EEE}[EEE] + \varepsilon_{EEZ}[EEZ] + \varepsilon_{EZZ}[EZZ] + \varepsilon_{ZZZ}[ZZZ])l$

I_0 = photons cm^{-2}.

term corresponds to one photo- or thermal process. In the cases of $d[EEE]/dt = 0$ (at t = 500 s), $d[EEZ]/dt = 0$ (at t = 30 and 500 s), $d[EZZ]/dt = 0$ (at t = 60 and 500 s), and $d[ZZZ]/dt = 0$ (at t = 500 s), respectively, the differential



Scheme 1

equation for the rate processes gives the eqns. (6)–(9) where φ_1, φ_2, φ_3, φ_4, φ_5 and φ_6 are the quantum yields for *E*–*Z*

$$\varepsilon_{EEE}\varphi_1[EEE] = \varepsilon_{EEZ}\varphi_4[EEZ] \quad (6)$$

$$\varepsilon_{EEZ}\varphi_2[EEZ] + \varepsilon_{EEZ}\varphi_4[EEZ] = \varepsilon_{EZZ}\varphi_5[EZZ] + \varepsilon_{EEE}\varphi_1[EEE] \quad (7)$$

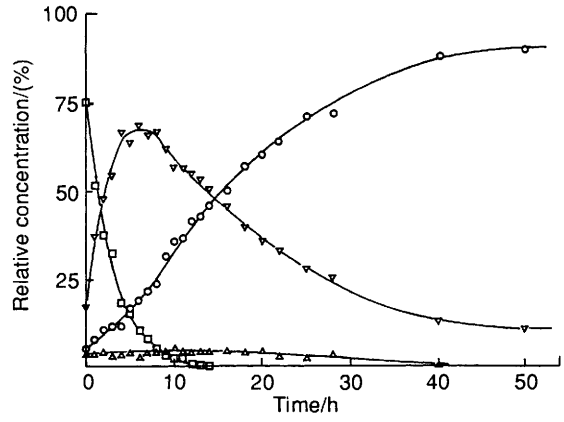


Fig. 3 Relative concentration (%) *vs.* time for the thermal isomerization in the dark of compound **1** in methanol at 50 °C: ○, *EEE*; △, *EEZ*; ▽, *EZZ*; □, *ZZZ*

$$\varepsilon_{EZZ}\varphi_5[EZZ] + \varepsilon_{EZZ}\varphi_3[EZZ] = \varepsilon_{ZZZ}\varphi_6[ZZZ] + \varepsilon_{EEZ}\varphi_2[EEZ] \quad (8)$$

$$\varepsilon_{ZZZ}\varphi_6[ZZZ] = \varepsilon_{EZZ}\varphi_3[EZZ] \quad (9)$$

photoisomerization (see Scheme 1), ε_{EEE} and $[EEE]$, respectively, are the molar coefficient and the relative concentration of *EEE* (ε and [ ] for other isomers are defined similarly).

The fact that both ε_{EEZ} and ε_{EZZ} are the sum of the molar extinction coefficients originating in the *E*- and in the *Z*-parts of the molecule makes the calculations of φ complicated. The assumption, however, that the azobenzene units absorb nearly independently is a valid one for the isomers. Therefore, we assumed that the *E* part of ε_{EEZ} is $\frac{2}{3}$ ε_{EEE} and the *Z* part of ε_{EEZ} is $\frac{1}{3}$ ε_{ZZZ} (similarly the *E* part of ε_{EZZ} is $\frac{1}{3}$ ε_{EEE} and the *Z* part of ε_{EZZ} is $\frac{2}{3}$ ε_{ZZZ}) and calculated the quantum yields for photons absorbed by the appropriate part of the molecules. Substituting the relative concentrations at 500 s into eqns. (8)–(11), at 30 s into eqn. (7) and at 60 s into eqn. (8) from Fig. 1 and using the relation involving the molar extinction coefficient mentioned above, gives the relation $\varphi_1 = \varphi_2 = \varphi_3$ and $0.02\ \varphi_4 = 0.3\ \varphi_5 = \varphi_6$.

Thermal Isomerization.—Fig. 3 shows the thermal isomerization from the photostationary state at 50 °C in the dark. It is noticeable that the concentration of *EEZ* doesn't increase so much. This fact can be explained by two possibilities. One is that the rate of thermal isomerization *EEZ* ⟶ *EEE* is much faster than that of *EZZ* ⟶ *EEZ*, and the other is that a direct route *EZZ* ⟶ *EEE* exists. By monitoring the thermal concentration change of the isomers after 70 s of irradiation (where the concentration of the *EEZ* isomer is rather high) the first-order rate of disappearance of *EEZ* can be determined almost independently (2.4×10^{-4} s^{-1} at 50 °C) since the rate is fast enough not to be affected by the thermal reaction of *EZZ*. The first-order rate of disappearance of *EZZ* in the dark (1.42×10^{-5} s^{-1} at 50 °C) can also be determined independently from the HPLC data after the *ZZZ* isomer completely disappears. The fact that the rate of thermal disappearance of *EEZ* is 17 times larger than that of *EZZ* supports the former explanation, explaining the slight change of concentration of the *EEZ* form from the photostationary state. The rate constants and the thermodynamic parameters of **1** in methanol are listed in Table 1.

Discussion

The *Z* ⟶ *E* photo- and thermal isomerization rates of one azobenzene unit is dependent on the conformations of the other

Table 1 Rate constants and thermodynamic parameters for the thermal isomerization in the dark of **1** in methanol

Isomerization mode	$k/10^{-5}$ s^{-1}			ΔE_a/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}
	30 °C	40 °C	50 °C		
ZZZ ⟶ *EZZ*	1.02	3.13	9.03	21.2	−13.2
EZZ ⟶ *EEZ*	0.121	0.442	1.42	23.9	−8.7
EEZ ⟶ *EEE*	2.15	7.11	24.0	23.5	−4.4

parts of the macrocycle. It is difficult to explain this dependence by electrical effects, since the three azobenzene units in the macrocycle are separated from one another by ethylenic linkages. It is reasonable to attribute the dependence, in large part, to the difference in ring strain in the four isomers. It is well known that the distances between 4,4′ positions and the angle of two benzenes in azobenzene are changed from the *E* form to the *Z* form.[13] The variation in the thermodynamic parameters for each isomerization process can be attributed to the different degree of the steric effect in both the *Z* form and (or) its transition state. The result of the photoisomerization, where the quantum yield of *Z* ⟶ *E* becomes larger as the number of the *E* azobenzene units increases while that of *E* ⟶ *Z* is not changed, is explained by supposing that the ring strain works in different ways in the excited *E* azobenzene unit and the excited *Z* azobenzene unit.[14] We have not yet been able to estimate steric energies for the four isomerizations by molecular mechanics calculations because the molecule is too large.

Interestingly, the thermal isomerization of *EZZ* ⟶ *EEZ* at room temperature is much slower than any of the other thermal processes. Therefore, an appropriate thermal isomerization from the photostationary state produces an *EZZ* enriched condition (about 70% of isomers exist in the *EZZ* form). Moreover, a *ZZZ* enriched (85%) and an *EEE* enriched (100%) condition is attained by irradiation at 366 nm and refluxing of the solution, respectively. While reports on a tris(azo)macrocyclic[15] or a tetra(azo)macrocyclic[7] compound have appeared, we are not aware of any studies that have determined their rates of isomerization and demonstrated the enrichment of certain isomers by external stimuli. Although further efforts to add binding ability are needed, our findings constitute a step towards the construction of the enzyme model systems which have more than two different binding abilities.

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