Selective Synthesis and Kinetic Measurement of 1:1 and 2:2 Cyclic Compounds Containing 1,4,7,10-Tetraazacyclododecane and Azobenzene Units

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1:1 cyclic compounds **8a**−**c** (51−55%) and 2:2 cyclic compounds **9a**−**c** (20−49%) containing 1,4,7,-10-tetraazacyclododecane (cyclen) and azobenzene units were selectively synthesized under UV irradiation (330 nm < λ < 380 nm) and in the dark. Synthesis depended on the wavelength of irradiation light and the length of methylene chains of the linker between the cyclen and azobenzene units. A study of NMR and UV−vis spectra indicated that properties of **8a**−**c** and **9a**−**c** are closely related to their structural flexibility. Rate constants (k) and thermodynamic parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) of **8a**−**c** and **9a**−**c** were studied in nonpolar media (benzene) and polar media (methanol). The cis to trans isomerization rates in the dark for these cyclic compounds increase with ring size or structural flexibility (**8a** < **8c** < **8b** < **9a** < **9b** < **9c**). In principle, $\Delta S^{\ddagger}$ dominates $\Delta G^{\ddagger}$ in cyclic compounds.

Introduction

Trigger-regulated compounds have been extensively applied to molecular devices based on functional/multifunctional regulation,[1a,b] molecular capsules,[1c,d] self-organized supramolecular systems,[1e−g] etc. Photoswitch systems of azobenzene, thiophenefulgide, and nitrospiropyran, for example, have been specially used as sensitive triggers in molecular recognition and assembly chemistry.[2,3] To mimic the enzymatic reaction of metal proteins, we recently synthesized a series of photoswitchable compounds comprising a tetraazacyclododecane (cyclen) as a metal binding site and an azobenzene unit as a light trigger.[4] Cis−trans isomerization of azobenzene upon irradiation by light may change the shape of the ligand molecule, enabling it to change properties of metal complexes. As Shinkai et al. reported on the synthesis of cyclic compounds containing a crown ether and an azobenzene unit, these cyclic compounds were prepared by condensation reaction between acid chlorides and amines or by reduction of two nitro groups followed by diazotization.[2] These cyclization reactions, however, generally gave very low yields. In a previous work,[4] we preliminarily reported the photochemical synthesis of two cyclic compounds 1:1 **8a**−**c** and 2:2 **9a**−**c**. Here we report the synthesis in detail as well as the results of a study of their rate constants and thermodynamic parameters in cis to trans isomerization in the dark.

Results and Discussion

Preparation of Compounds 4 and 7. Compounds **4** and **7** were synthesized as shown in Scheme 1. 4,4′-Dihydroxylazobenzene **1** was prepared based on the method of Willstätter and Benz.[5] Compounds **2a**−**c** were obtained in excellent yields of 95−99% by a reaction of $Br(CH_2)_nNH_2{\cdot}HBr$ (n = 2, 3, and 4) with carbobenzoxy chloride (ZCl). In the process of alternate addition of ZCl and 3.5 M K_2CO_3, the reaction solution was maintained at pH 6−7 to avoid formation of pale yellow byproducts. Protecting groups Z of **3a**−**c** were readily cleaved by treatment with 33% HBr/AcOH yield ammonium salts **4a**−**c**. 1,7-Diprotected cyclen **5** was derived from the reaction of cyclen and ZCl.[6] Diacetic acid **6** was precipitated by adding 6 M HCl and was directly subjected to elemental analysis without further purification. Activation of carboxylic acids of **6** with 1,3-thiazolidine-2-thione (TTH) was done in the presence of DDC or 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSC).

Compounds **1**−**7** were characterized on the basis of ^{1}H and ^{13}C NMR, FAB-MS, and/or TOF-MS and elemental analysis except for **7**, which contained impurities even after purification twice by recrystallization and TLC.

Cyclization Reactions. Cyclization reactions between **4** and **7** were conducted under high-dilution conditions (Scheme 1 and Table 1). A solution of **7** in THF and a solution of 1.0 equiv of **4b** (n = 3) and Et_3N in THF−H_2O were simultaneously added to a large volume of THF at 2 mL/min. The product was isolated by preparative TLC on an alumina plate. When the reaction was conducted under UV irradiation (330 nm < λ < 380 nm),

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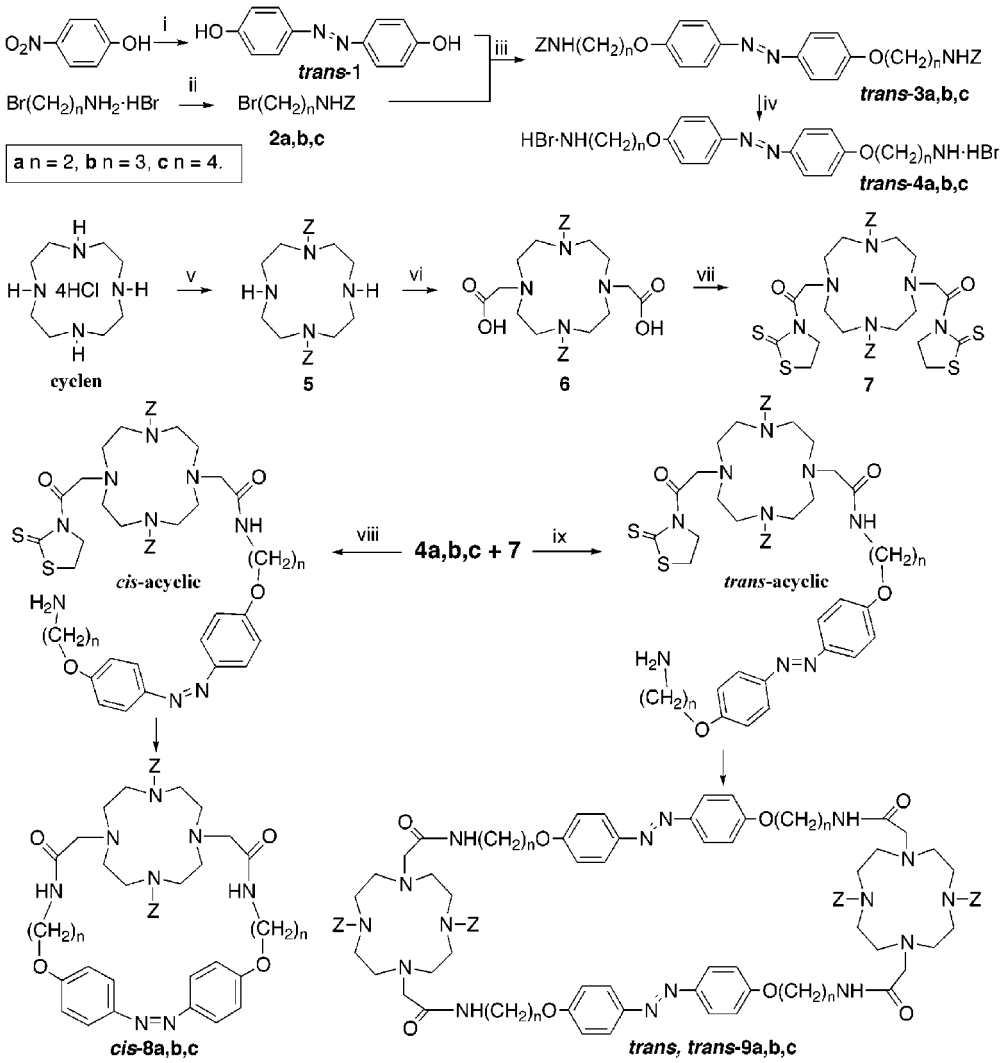
Scheme 1[a]



[a] Key: (i) KOH, 200 °C; (ii) Br(CH$_2$)*n*NH·HBr, ZCl, K_2CO_3, pH 6−7; (iii) (a) NaH, (b) 60 °C; (iv) HBr/AcOH; (v) ZCl, NaOH, pH 2−3; (vi) (a) $BrCH_2COOH$, KOH, (b) **1**, Na_2CO_3, 45−65 °C; (vii) TTH, WSC, DMAP; (viii) 330 nm < λ < 380 nm; (ix) in the dark.

Table 1. Main Products in Reactions of Compounds 4a−c with 7[a]

	UV (330−380 nm)			in the dark		
product	**8a**	**8b**	**8c**	**9a**	**9b**	**9c** + **8c**
yield, %	51	52	55	47	49	20 + 27
m/z[b]	822	850	878	1643	1669	1755
R_f[c]	0.47	0.55	0.57	0.30	0.32	0.33

[a] **a** *n* = 2; **b** *n* = 3; **c** *n* = 4; n is the number of −(CH$_2$)$_n$− (methylene chain linkers). [b] FAB-MS/[M + H]$^+$ (100%). [c] Alumina TLC eluted with 80% EtOAc−MeCN.

1:1 cyclic compound **8b** was the predominant product isolated in a 52% yield. In the dark,[7] however, **8b** was not detected on TLC and both 2:2 cyclic compound **9b** at 49% and 1:1 "acyclic" product [R_f = 0.18 MeCN/MeOH/Et_3N (8:1:0.1), *m*/*z* (FAB) 868.0 (M + H)$^+$] at 8% were obtained. Analogous results were obtained in the reaction of **4a** (*n* = 2) and **7**. UV−vis spectra of the acyclic product (*n* = 3) showed that the cis form was produced under UV irradiation and converted to the trans form in the dark. The cis-acyclic compound (Scheme 1) readily closed the ring to give **8a** or **8b**. However, the trans-acyclic compound is in a disadvantageous configuration to conduct the 1:1 intramolecular cyclization reaction. Both 2:2 cyclic compounds **9a** and **9b** were primarily obtained, although intramolecular cyclization is generally preferential to intermolecular reaction in a high dilution. The CPK model examination predicts that 1:1 intramolecular cyclization can proceed even in the trans-acyclic compound if methylene chain linkers are long enough. Actually, in contrast to **4a** and **4b** (*n* = 2 and 3), compound **4c** (*n* = 4) reacted with **7** in the dark to yield both **8c** at 27% and **9c** at 20% (Table 1). Under UV irradiation, it yielded **8c** at 55%.

Reaction Conditions for Cyclization. Yields of **8b** and **9b** under different reaction conditions are shown in Table 2. All reactions were conducted in high dilution at 0.1 mmol (reactant)/200 mL (solvent) at room temperature. Products were isolated by preparative TLC. Typical results are shown in entries 1 and 2. Under UV irradiation (entry 1), **8b** was yielded at 52% and traces of **9b** were observed on TLC. ^{1}H NMR spectra for the *cis*-**4b** showed small characteristic signals of *trans*-**4b**; namely, trans to cis isomerization was not complete under UV

(7) To completely convert the cis form to the trans form, solutions were irradiated under light (λ > 460 nm) for 5 min and allowed to stand in the dark at 30 °C for 8 h, or allowed to stand in the dark for 24 h at 30 °C before a solution of **4** was added in the dark. UV−vis spectra showed that the trans form absorption intensity increased slightly in the dark after visible irradiation (λ > 460 nm).

Table 2. Yields of 8b and 9b under Different Reaction Conditions

		reaction conditions			product (%)	
entry	method[a]	reactant	Et_3N (equiv)	light[b]	**8b**	**9b**
1	I	**4b** + **7**	1	UV	52	trace
2	I	**4b** + **7**	1	dark	N.D.[c]	49
3	I	**4b** + **7**	1	vis	5	40
4	I	**4b** + **7**	1	W.L.	5−13	8−23
5	I	**4b** + **7**	1.5	UV	44	trace
6	I	**4b** + **7**	1.5	dark	N.D.	36
7	II	**10**[d] + **7**		UV	53	trace
8	II	**10** + **7**		dark	N.D.	52
9	III	**4b** + **6**		W.L.	N.D.	N.D.
10	III	**4b** + **6**		UV	7	trace
11	III	**4b** + **6**		dark	N.D.	trace

[a] Method: (I) a solution of **4b** + Et_3N and of **7** were simultaneously added to THF−H_2O; (II) same procedure as (I) using THF instead of THF−H_2O; (III) WSC was used for the coupling reaction in DMF. [b] Irradiation under 330 nm < λ < 380 nm (UV) and under λ > 460 nm (vis); in the dark (dark); white light of common laboratory illumination (W.L.). [c] No compound was detected by TLC. [d] Compound **10** is a free amine derived in advance from ammonium salt **4b**.

irradiation. This accounts for the formation of traces of **9b**. Under visible irradiation (λ > 460 nm), about 10% of **4b** was present in the cis form judging from UV−vis spectra of **4b**. Consistent with this prediction, under visible irradiation (entry 3), both **9b** (40%) and **8b** (5%) were obtained rather than only **9b** (49%) as observed in the dark (entry 2). When the reaction was conducted under common laboratory illumination (entry 4), compounds **8b** and **9b** were not selectively synthesized and yields were rather low. Because of **4b** solubility, solvent THF−H_2O and base Et_3N were used for reactions. However, the use of excess Et_3N (entries 5 and 6) lowered yields of **8b** and **9b**, particularly for **9b**, to 36% from 49%, since **7** was easily hydrolyzed in alkaline solution. To improve the reaction by method II of increasing reactant solubility and limiting the effect of hydrolysis, free amine **10** derived from ammonium salt **4b** and THF as solvent were used. As shown in entries 7 and 8, however, the yields of **8b** and **9b** hardly changed. In addition, ca. 30% of **4b** was lost in preparing **10**. We attempted to synthesize compound **8b** by direct treatment of diacid acid **6** with **4b** in the presence of Et_3N and WSC (entry 9), but the desired products **8b** and **9b** were scarcely obtained (entries 9−11). This indicates that compound **7** bearing the TTH-amide group is a suitable compound for the reaction.[8]

Spectroscopic Study. Cyclic compounds **8a**−**c** and **9a**−**c** were characterized on the basis of ^1H and ^{13}C NMR, FAB-MS or TOF-MS, elemental analysis, and UV−vis spectra. NMR signals of **8b** and **9b** were assigned from 2D-NMR spectra of $^1H-^1H$ COSY and HMQC. The wavelengths of electronic absorption maximum (λ_{max}) for **8a**−**c** and **9a**−**c** are listed in Table 3 and typical UV−vis spectra (**8a** and **9a**) are shown in Figure 1. Isomerization of the azobenzene unit for **8a**−**c** and **9a**−**c** quickly reached a photostationary state under visible irradiation (λ > 460 nm) for cis to trans and under UV irradiation (330 nm < λ < 380 nm) for trans to cis within 10 min at room temperature. Even after visible irradiation (λ > 460 nm) for 10 min, cis forms (*cis*-**8a**, *cis*, *cis*-**9a**) were not completely converted to trans forms (*trans*-**8a**-vis, *trans*-**9a**-vis) (Figure 1). When solutions were allowed to stand

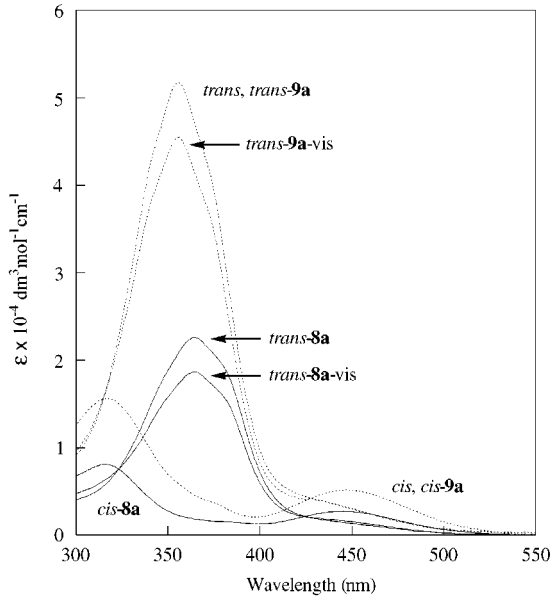


Figure 1. UV−vis spectra for **8a** and **9a** in MeOH at 25 °C. Trans-vis and cis spectra were measured after visible (λ > 460 nm) and UV (330 nm < λ < 380 nm) irradiation for 10 min. *trans*-**8a** and *trans*,*trans*-**9a** spectra were measured after reaching the thermal-stationary state in the dark.

in the dark for 5−16 h at 60 °C, absorption intensities slowly increased and reached a thermal-stationary state (*trans*-**8a**, *trans*,*trans*-**9a**). Isomerization at 25 °C for **8a**−**c** and **9a**−**c** was neglected.

Especially noteworthy (Table 3) is that some spectroscopic properties of *trans*-**8a**−**c** (smaller ring) differ from those of *trans*,*trans*-**9a**−**c** (larger ring), whereas those of all cyclic compounds in the cis form corresponded well to linear compound **10** (data not shown). These spectroscopic characteristics are summarized below.

(1) Each ^1H NMR spectrum of *trans*-**8a**−**c** showed that 3,3′,5,5′-H (meta protons to azo) gave a broad signal in $CDCl_3$ at 25 °C, whereas 2,2′,6,6′-H (ortho protons) gave a doublet (Figure 2). With linear compound **10** and large ring compounds **9a**−**c** in the trans,trans form, both 3,3′,5,5′-H and 2,2′,6,6′-H protons appeared as sharp doublets. At a higher temperature (55 °C), 3,3′,5,5′-H of **8b** turned into a doublet at 6.97 ppm due to the magnetic equivalence of these protons. At a lower temperature (−20 °C), however, it became 3 doublet signals (6.83, 6.95, and 7.08 ppm with 1:2:1 intensity ratio). 2,2′,6,6′-H protons also gave 3 doublet signals (7.81, 7.84, and 7.92 ppm) at −20 °C. Namely, aromatic protons of the azobenzene unit are not magnetically equivalent at a lower temperature, and 3,3′,5,5′-H is subjected to a larger effect than 2,2′,6,6′-H. This clearly indicates that *trans*-**8b** has a rigid conformation. Restricted rotational movement of the azobenzene unit causes nonequivalence of 3,3′,5,5′-H resulting in the broad signal at 25 °C. CPK model studies support this conclusion. Note that signals of the methylene linker protons between the cyclen and azobenzene unit split into two spin systems in $^1H-^1H$ COSY spectra of *trans*-**8b** at −20 °C, suggesting that the whole molecular shape deviates from C_2 symmetry.

(2) A downfield shift (0.36−0.41 ppm) of O-CH_2 protons (azobenzene-O-CH_2−) was observed for *trans*-**8a**−**c** compared to corresponding protons of *trans*,*trans*-**9a**−**c**, indicating that O-CH_2 protons tend to exist near a plane of the azobenzene ring. The deshielding effect of the

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Table 3. Typical Data on NMR and Absorption λ_{max} of UV−Vis Spectra

		1:1 cyclic compound			2:2 cyclic compound			linear
		8a	**8b**	**8c**	**9a**	**9b**	**9c**	**10**[b]
				NMM[a] (ppm)				
3,5-H	trans	7.07 br	6.98 br	6.95 br	6.91 d	6.80 d	6.81 d	6.89 d
2,6-H	trans	7.86 d	7.85 d	7.79 d	7.74 d	7.73 d	7.73 d	7.86 d
O−CH_2	trans	4.38 br	4.28 br	4.29 br	4.02 br	3.89 br	3.88 br	4.01 br
3,5-C	trans	118	116.8	116.6	114.6	114.5	114.4	114.4
O-CH_2	trans	69.2	67.7	67.2	65.8	65.6	65.6	65.2
				UV−vis, λ_{max}[c] (nm)				
MeOH	trans	364	362	363	356	356	356	355
	cis	446	448	449	447	448	447	445
C_6H_6	trans	366	365	366	358	358	359	360
	cis	445	447	446	447	447	447	447

[a] In $CDCl_3$; br = broad, d = doublet, J_H = 8.3−8.9 Hz; 3,5-H (C) and 2,6-H to azobenzene unit; O−CH_2 of azobenzene-O-CH_2; after reaching a thermal-stationary state in the dark, spectra were recorded at 25 °C for the trans (*trans*-**8a**−**c** and *trans,trans*-**9a**−**c**); and after UV irradiation (330 < λ < 380 nm) for 10 min for the cis form (*cis*-**8a**−**c** and *cis,cis*-**9a**−**c**). [b] Linear compound **10** is a free amine derived from ammonium salt **4b**. [c] Another cis-λ_{max} at 310−312 nm in C_6H_6 and one at 315−318 nm in MeOH are omitted for clarity.

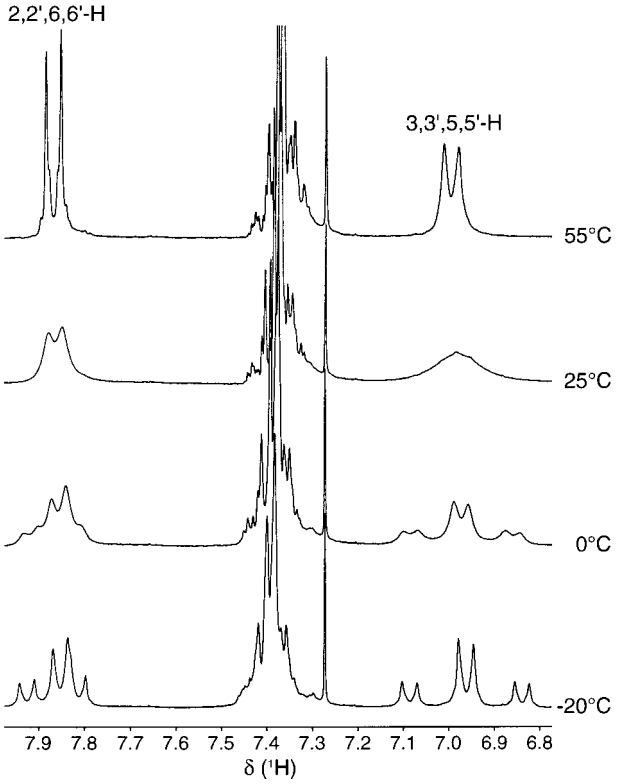

Figure 2. Temperature dependence of 3,3′,5,5′-H and 2,2′,-6,6′-H ^{1}H NMR signals of **8b** in the trans,trans form.

azobenzene ring current results in the downfield shift of O-CH_2 protons. The NOE difference spectrum (1-D) of **8a** in the trans form at room temperature showed that irradiation of O-CH_2 protons clearly enhanced the signal of 3,3′,5,5′-H on the azobenzene ring and irradiation of latter protons also enhanced O-CH_2 protons. These results support the concept that O-CH_2 protons are located near 3,3′,5,5′-H. The same proton enhancements were not observed for **8a** in the cis form or **9a** in the trans,trans form. The interaction of O-CH_2 protons with 3,3′,5,5′-H was also observed in the NOESY spectrum (2-D) of *trans*-**8b** at 0 °C. Spectra (2-D) did not show any interaction of Z group protons with other protons, indicating that the effect of Z groups on the azobenzene unit is precluded.

(3) Similar to ^{1}H NMR, ^{13}C NMR signals of 3,3′,5,5′-C on the azobenzene ring and O-CH_2 carbons in *trans*-**8a**−**c** showed downfield shifts (2.2−3.4 ppm and 1.6−3.2 ppm) compared to corresponding carbons of *trans,trans*-**9a**−**c**. As chemical shifts in ^{13}C NMR are generally dominated by electron density on carbon atoms, the above results suggest a decrease of the electron density on 3,3′,5,5′-C and O-CH_2.

(4) λ_{max} values of *trans*-**8a**−**c** were larger by 6−8 nm (viz., red shift) than those of *trans,trans*-**9a**−**c** both in benzene (359 nm) and in methanol (356 nm, Figure 1). λ_{max} values of all cyclic compounds in the cis form and *trans,trans*-**9a**−**c** were close to those of linear compound **10**. As mentioned above, due to the restricted conformation of *trans*-**8a**−**c**, the p-orbital of nonbonding electrons of the adjacent oxygen overlaps more efficiently with the π-orbitals of the azobenzene. The resulting "additional conjugation" causes a red shift. The red shift was also supported by INDO/1 calculation (ZINDO of the CAChe system, Oxford Molecular Group).

Thus, these interesting properties of NMR and UV−vis spectra are closely related to the structural flexibility of cyclic compounds. Structural flexibility is reconsidered below to interpret cis−trans isomerization kinetics.

Kinetic Measurement and Thermodynamic Parameters Calculation. Here we focus on thermal isomerization from cis to trans in the dark (Figure 1). We measured rate constants (k) and derived free energy ($\Delta G^{\ddagger}$), enthalpy ($\Delta H^{\ddagger}$), and entropy ($\Delta S^{\ddagger}$) of activation in the formation of *trans*-**8a**−**c** and *trans,trans*-**9a**−**c** in a polar solvent (methanol) and a nonpolar solvent (benzene). k values were determined from the increase in the absorption maximum of trans forms. The final absorbance of the trans form at 60 °C was used as the value corresponding to 100% conversion. It was also confirmed that back-transformation from trans to cis by the light of the spectrophotometer was negligible during our measurement time. In the case of the 2:2 products **9a**−**c**, there are two azobenzene moieties in a molecule. The molar extinction coefficient for azobenzene moieties was nearly double that of corresponding 1:1 products **8a**−**c** (Figure 1). ^{1}H NMR spectra for **9c** on the halfway through isomerization clearly showed 4 doublets of aromatic protons whose chemical shifts [6.63 (d), 6.79 (d), 6.88 (d), 7.78 (d)] were different from those of corresponding signals for all-cis [6.66 (d), 6.81 (d)] and all-trans isomers [6.81 (d), 7.73 (d)]. The intensity of these signals was increased after heating of all-cis isomer, and then decreased with an increase of all-trans isomer. No further spectral changes were observed in NMR and electronic absorption spectra of compounds **9a**−**c** after UV irradia-

Table 4. First-Order Rate Constants (k) for Isomerization from Cis to Trans

	$k \times 10^5$, s^{-1}													
	in benzene							in MeOH						
	1:1 cyclic compound			2:2 cyclic compound			linear	1:1 cyclic compound			2:2 cyclic compound			linear
T (°C)	**8a**	**8b**	**8c**	**9a**	**9b**	**9c**	**10**[a]	**8a**	**8b**	**8c**	**9a**	**9b**	**9c**	**10**
40	1.91	5.09	3.39	6.55	7.80	8.21	12.3	2.15	8.20	6.95	8.67	10.6	11.0	13.3
50	5.47	15.9	10.4	20.6	24.5	26.1	36.6	6.64	25.6	20.9	26.8	32.7	34.5	40.1
60	14.0	44.0	30.0	59.0	70.6	75.3	104	19.4	67.0	60.1	77.3	95.0	100	112

[a] Linear compound **10** is a free amine derived from ammonium salt **4b**.

tion (converted to all-cis isomers) or heating (to all-trans isomers). These indicated that cis, trans isomers should exist during the isomerization from all-cis (cis, cis) to all-trans (trans, trans) isomers. Note that all of kinetic data for compounds **9** described in the following discussion are based on one azobenzene moiety. The isomerization obeyed first-order kinetics in both solvents (Table 4). $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from linear plots (Figure 3, $r >$ 0.998) of $\Delta G^{\ddagger}$ against T. The resulting values for **8a**−**c**, **9a**−**c**, and **10** are summarized in Table 5 and shown in Figure 4. Benzene is a nonpolar solvent (viz., no permanent dipole moment), although it can be polarized by an outer electric field. The solvation of benzene should be much lower than that of methanol since the donor number (DN) is 0.1 and the acceptor number (AN) of benzene is 8.2, whereas the DN of methanol is 19 and the AN of methanol is 41.3.[9] The kinetic properties of a benzene solution are thus considered to be more dominated by intrinsic structures, whereas those of a methanol solution are assumed to reflect both intrinsic molecular characteristics and solvation.

Kinetics in Benzene. In benzene solution, k of cyclic compounds tends to increase with the ring size (**8a** < **8c** < **8b** < **9a** < **9b** < **9c**) (Table 4), i.e., $\Delta G^{\ddagger}$ tends to decrease with ring size, meaning that isomerization is easier for more flexible compounds. To reveal what factor dominates the reaction rate, we estimated the individual contribution of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ to $\Delta G^{\ddagger}$ (Figure 4). The change of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ is relatively monotonic similar to $\Delta G^{\ddagger}$. The dependence of $\Delta G^{\ddagger}$ on the ring size appears to be governed by $T\Delta S^{\ddagger}$ for cyclic compounds, since both $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ tend to increase with ring size. This result on $T\Delta S^{\ddagger}$ is reasonable, because the increase in structural restriction of transition states based on ground states is expected to be less in larger-ring compounds than in smaller-ring compounds and therefore $T\Delta S^{\ddagger}$ is assumed to move positively as the ring size increases (Figure 4). In other words, the rate acceleration of **9a**−**c** compared to **8a**−**c** is attributable to their $\Delta S^{\ddagger}$ terms, which are less negative than those of **8a**−**c** (Table 5), since the larger 2:2 ring is more flexible than the smaller 1:1 ring. The length of the methylene chain (n = 2, 3, 4) also affects isomerization (Table 5). The magnitudes of $\Delta S^{\ddagger}$ terms are in the order **8a** < **8b** < **8c** for 1:1 compounds and **9a** < **9b** < **9c** for 2:2 compounds. These orders are consistent from the standpoint of structural flexibility. It is also intriguing to compare $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values between cyclic (**8a**−**c** and **9a**−**c**) and linear (**10**) molecules, which may correspond to a cyclic compound with an infinite ring size. Compound **10** gives the largest reaction rate of all compounds, caused by a decrease in $\Delta H^{\ddagger}$ (Figure 4 and Table 4).

(9) (a) Gutmann, V.; Wychera, E. *Inorg. Nucl. Chem. Lett.* **1966**, *2*, 257−260. (b) Mayer, U.; Gutmann, V. *Adv. Inorg. Chem. Radiochem.* **1975**, *17*, 189−230.

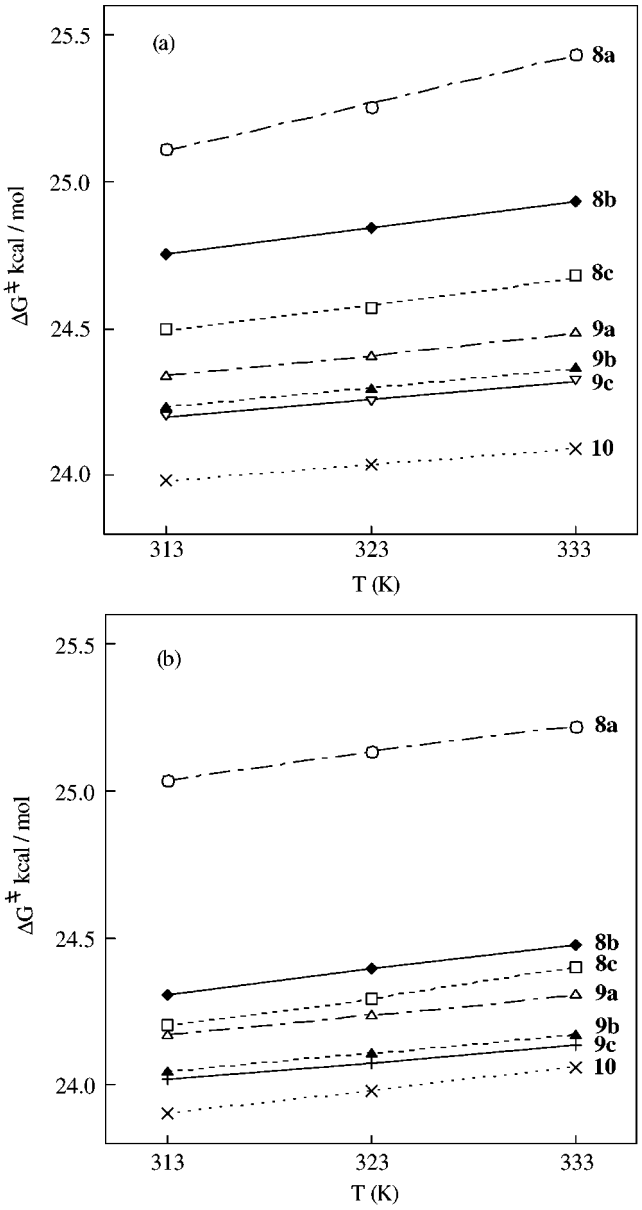

Figure 3. $\Delta G^{\ddagger}$ vs T in (a) benzene and (b) MeOH. Linear compound **10** is a free amine derived from ammonium salt **4b**.

Kinetics in Methanol. In a polar solvent like methanol, the effect of solvation is considerable and may appreciably influence the reaction rate. In a methanol solution, k of cyclic compounds tends to increase with ring size as in a benzene solution (Table 4), i.e., $\Delta G^{\ddagger}$ tends to decrease with ring size. One point different from the benzene system is that the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values of **8a** deviate from monotonic curves (Figure 4). Clearly, however, the dependence of k on ring size is dominated by

Table 5. Enthalpy ($\Delta H^{\ddagger}$) and Entropy ($\Delta S^{\ddagger}$) of Activation for Isomerization from Cis to Trans in Benzene and MeOH

	in benzene							in MeOH						
	1:1 cyclic compound			2:2 cyclic compound			linear	1:1 cyclic compound			2:2 cyclic compound			linear
	8a	**8b**	**8c**	**9a**	**9b**	**9c**	**10**	**8a**	**8b**	**8c**	**9a**	**9b**	**9c**	**10**
$\Delta H^{\ddagger}$ (kcal/mol)	20.0	21.7	21.9	22.1	22.2	22.3	21.7	22.1	21.1	21.7	21.9	22.1	22.2	21.4
$\Delta S^{\ddagger}$ (eu)	−16.2	−8.99	−8.87	−7.21	−6.61	−6.02	−6.80	−9.17	−9.82	−8.32	−6.94	−6.19	−5.79	−7.9

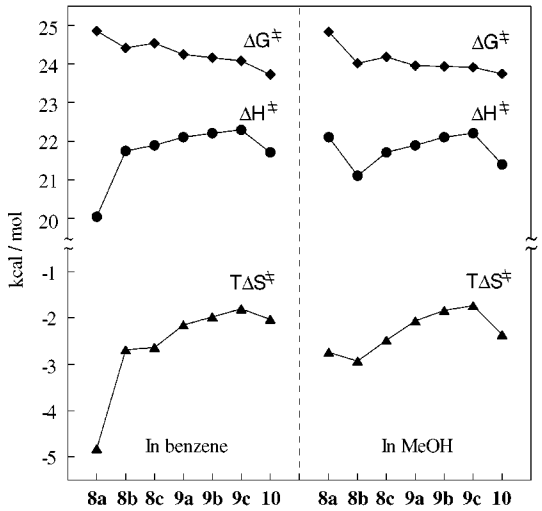

Figure 4. $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $T\Delta S^{\ddagger}$ vs compounds in benzene and MeOH (T = 298 K).

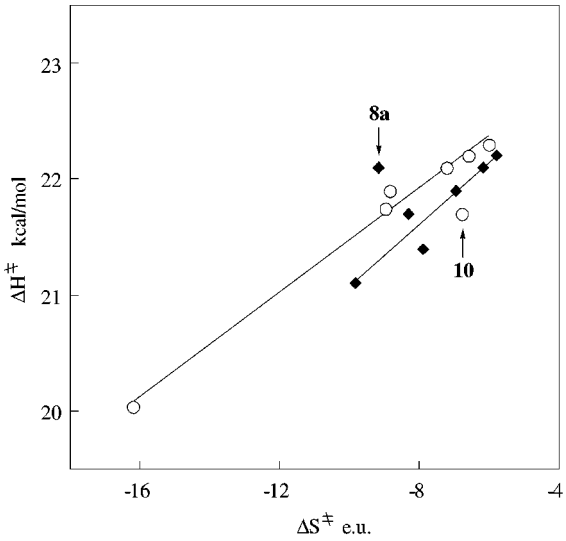

Figure 5. Compensation relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in (○) benzene and (◆) MeOH.

$\Delta S^{\ddagger}$ such as for a benzene solution, except for **8a**, whose reaction rate is governed by $\Delta H^{\ddagger}$ rather than $\Delta S^{\ddagger}$. As observed in benzene, **10** also gives the largest rate of all compounds in methanol (Table 4) due to the decrease in $\Delta H^{\ddagger}$ (Figure 4).

Comparison of Kinetics in Benzene and Methanol. It was reported that the rate of isomerization from *cis*- to *trans*-azobenzene is enhanced by polar media.[10] Shinkai et al. reported that the rate of this isomerization in *o*-dichlorobenzene is greater by a factor of 20 than that in benzene.[2b] They also reported, however, that the rate was somewhat smaller in methanol than in benzene.[2b] This result is not compatible with our observation that all cyclic and linear molecules studied in this experiment are transformed faster in methanol than in benzene, although the rate enhancement was 2 times at most (Table 4). Note that $\Delta H^{\ddagger}$ contributes favorably to rate acceleration in methanol, except for **8a**, whose isomerization is enhanced mainly by the $\Delta S^{\ddagger}$ term. In **8c** and **9a**−**c**, $\Delta S^{\ddagger}$ also contributes favorably in addition to $\Delta H^{\ddagger}$.

Compensation Relationship. We plotted $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ to confirm whether the isomerization proceeded under the same mechanism (Figure 5). Moderately good linearity was obtained both in benzene (r = 0.994) and in methanol (r = 0.950). Since **10** in benzene and **8a** in methanol deviate largely from linearity, they were not included in the calculation. Linear relations are expressed by eqs 1 and 2

$$H^{\ddagger} = 225\Delta S^{\ddagger} + 23.7 \text{ (in benzene)} \quad (1)$$

$$H^{\ddagger} = 269\Delta S^{\ddagger} + 23.7 \text{ (in methanol)} \quad (2)$$

where isokinetic temperatures are 225 and 269 K. These temperatures are those above which an increase in $\Delta S^{\ddagger}$ results in a decrease in $\Delta G^{\ddagger}$ and below which an increase in $\Delta S^{\ddagger}$ leads to an increase in $\Delta G^{\ddagger}$. With the present reaction temperature, the former case holds for both solvent systems (Figure 4). Since **10** has a type different from other azobenzene compounds, it probably deviates from the compensation relationship in benzene. The result that **8a** shows unusual kinetic behavior (Figure 4) and deviates from the compensation relationship in methanol (Figure 5) suggest the possibility that methanol may solvate to **8a** in a manner different from other compounds.

Conclusions

We successfully regulated the cyclization reaction photochemically. The 1:1 cyclic compound **8a**−**c** (51−55% of yields) and 2:2 **9a**−**c** (20−49%) were selectively synthesized under UV light irradiation (330 nm < λ < 380 nm) and in the dark. NMR and UV−vis spectra, kinetic data of cis to trans isomerization, and cyclization yields are all consistently explained by the relative structural flexibility of **8a**−**c** and **9a**−**c**. For metal binding, we preliminarily observed that the Cu^{2+} complex of the 1:1 cyclic ligand (**8b**) undergoes photocontrolled catch and release of anionic ligands. A further study is under way and will be published elsewhere.

Experimental Section

General Procedure and Materials. All chemicals and solvents were used without further purification unless otherwise noted. All cyclization reactions of **8a**−**c** and **9a**−**c** were conducted under N_2. 4-Bromobutylamine hydrobromide, $Br(CH_2)_4NH_2 \cdot HBr$ was prepared via a 2-step reaction as reported

(10) Zalukaev, L. P.; Voronkov, M. G.; Moiseeva, L. V.; Afanasev, S. V. *Dokl. Akad. Nauk SSSR*. **1976**, *230*, 136.

by Brown and Gulick.[11] ^{1}H and ^{13}C NMR spectra were acquired at 270 and 67.8 MHz, respectively. NOE difference spectrum (1-D) and NOESY (2-D) were acquired at 500 MHz. Mass spectra were recorded by MALDI TOF and FAB methods. Elemental analysis was obtained from the Analytical Center in the National Institute of Materials and Chemical Research, Japan. A 500 W super-high-pressure Hg lamp was used through a UV-D36B filter (Toshiba) for UV irradiation (330 nm < λ < 380 nm) and through a Y-46 filter (Toshiba) for visible irradiation (λ > 460 nm). Aluminum oxide 60 F_{254} neutral (Merck) and silica gel 60 F_{256} (Merck) were used for TLC.

Measurements of NMR Spectra of Trans and Cis Forms. NMR spectra of trans and cis forms were recorded as follows: Samples (10−12 mg) dissolved in 0.6 mL of solvent in a NMR tube were allowed to stand in the dark for 5−16 h at 60 °C. After reaching a thermal-stationary state, spectra in the trans form were measured at room temperature. Solutions in a UV cell with a cap were irradiated by UV light (330 nm < λ < 380 nm) for 10 min at 25 °C. After irradiation, cis spectra of NMR were measured immediately.

Measurements of Kinetic Rate Constants. The sample was sealed in a quartz UV cell with a cap. The concentration of the sample was decided by a maximum absorption intensity of 0.9−1.0. Rate constants of isomerization from cis to trans in the dark were determined by the increase of intensity at the wavelength of maximum absorption of trans from the cis photostationary state. This state was rapidly reached under UV irradiation (330 nm < λ < 380 nm) for 10 min. In the process of irradiation, the temperature of samples was kept the same as the workup temperature. The workup time was 1 h for each temperature.

4,4′-Dihydroxyazobenzene 1. Compound **1** was prepared based on the method of Willstätter and Benz.[5] A mixture of KOH (50 g, 760 mmol), *p*-nitrophenol (10 g, 72 mmol), and water (10 mL) was heated to 120 °C and left to stand for 1 h. When the temperature slowly rose to 195−200 °C, the reaction vigorously started to give a brown viscous liquid with a large number of bubbles developing. After the reaction was completed, products were dissolved in water. A dark-red solution was acidified to pH 3 with concentrated HCl and extracted with ether. Combined ether extracts were dried over Na_2SO_4 overnight. Ether was removed to dryness under reduced pressure. Residue was recrystallized from 50% (v/v) ethanol aqueous solution to give yellow crystals of compound **1**. 4.0 g, 43% yield. R_f = 0.32 (silica, hexane−EtOAc 1:1). TOF-MS: *m*/*z* 215 $(M + H)^+$. δ_H (DMSO-d_6): 10.10 (s, 2H), 7.71 (d, J = 8.91, 4H); 6.90 (d, J = 8.90, 4H). δ_C (DMSO-d_6): 160.1, 145.6, 124.3, 115.9.

***N*-Benzyloxycarbonyl-2-bromoethylamine 2a.** 2-Bromoethylamine hydrobromide, $Br(CH_2)_2NH_2$·HBr (2.05 g, 10 mmol), was dissolved in a solution of water (5 mL) and dioxane (5 mL). The solution was treated with alternating addition of a solution of carbobenzoxy chloride, ZCl (2.10 g, 12 mmol) in dioxane (5 mL), and of 3.5 M K_2CO_3 with vigorously stirring at room temperature. The pH was maintained at 6−7 by dropwise addition. After ZCl was added over 0.5 h, it was stirred under pH 7−8 for 1 h. Excess ZCl was hydrolyzed with 2 M aqueous NaOH (1 mL) with stirring for 2 h. The mixture was extracted with ether. The combined ether was washed with 1 M NaOH once and with water twice and dried over Na_2SO_4 overnight. A colorless oil of **2a** was isolated with a silica gel column. **2a** was slowly crystallized, 2.45 g, 95% yield. R_f = 0.43 (silica, hexane−EtOAc 10:1). TOF-MS: *m*/*z* 259 $(M + H)^+$. Anal. Calcd for $C_{10}H_{12}BrNO_2$: C, 46.53; H, 4.69; N, 5.43; Br, 30.96. Found: C, 46.57; H, 4.54; N, 5.40; Br, 30.72. δ_H ($CDCl_3$): 7.37−7.32 (m, 5H), 5.12 (s, 2H), 3.60 (q, J = 5.61, 2H), 3.46 (t, J = 5.61, 2H). δ_C ($CDCl_3$): 156.3, 135.8, 128.4, 128.1, 127.8, 66.4, 39.0, 31.4.

***N*-Benzyloxycarbonyl-3-bromopropylamine 2b** was prepared in a manner analogous to **2a** from $Br(CH_2)_3NH_2$·HBr (2.19 g, 10 mmol) and ZCl (2.10 g, 12 mmol) to give a colorless oil of compound **2b**, 2.70 g, 99% yield. R_f = 0.47 (silica, hexane−EtOAc 10:1). TOF-MS: *m*/*z* 273 $(M + H)^+$. Anal. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.18; N, 5.15; Br, 29.36. Found: C, 48.60; H, 5.10; N, 5.13; Br, 29.43. δ_H ($CDCl_3$): 7.36−7.31 (m, 5H), 5.12 (s, 2H), 3.43 (t, J = 6.43, 2H), 3.37 (q, J = 6.43, 2H), 2.07 (t, J = 6.43, 2H). δ_C ($CDCl_3$): 156.3, 136.1, 128.4, 128.1, 127.6, 66.4, 39.0, 32.2, 30.5.

***N*-Benzyloxycarbonyl-3-bromobutylamine 2c** was prepared in a manner analogous to **2a** from $Br(CH_2)_4NH_2$·HBr (2.33 g, 10 mmol) and ZCl (2.10 g, 12 mmol) to give a colorless oil of compound **2c**, 2.73 g, 95% yield. R_f = 0.50 (silica, hexane−EtOAc 10:1). TOF-MS: *m*/*z* 287 $(M + H)^+$. Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.37; H, 5.63; N, 4.89; Br, 27.92% Found: C, 50.40; H, 5.62; N, 5.77; Br, 27.83. δ_H ($CDCl_3$): 7.36−7.31 (m, 5H), 5.12 (s, 2H), 3.42 (t, J = 6.60, 2H), 3.23 (q, J = 6.43, 2H), 1.87−1.69 (m, 2H). δ_C ($CDCl_3$): 156.4, 136.5, 128.5, 128.1, 127.0, 66.7, 40.1, 33.1, 29.8, 28.7.

4,4′-Di[γ-(*N*-benzyloxycarbonyl)aminoethanoxy]azobenzene 3a. To a solution of **1** (0.321 g, 1.5 mmol) in anhydrous DMF (5 mL) was added a white suspension of NaH (0.180 g, 4.5 mmol, 60% content) in anhydrous DMF (10 mL). The hydrogen produced was removed under reduced pressure until bubbles no longer developed from the yellow suspension. To this, *N*-benzyloxycarbonyl-2-bromoethylamine **2a** (0.936 g, 3.6 mmol) was added in anhydrous DMF (10 mL). After being stirred for 4 h at 60 °C, the mixture was cooled and poured into cold water (60 mL). Yellow crystals of **3a** were recrystallized from a mixture solvent of 2-propanol and ethanol, 0.579 g, 68% yield. TOF-MS: *m*/*z* 570 $(M + H)^+$. Anal. Calcd for $C_{32}H_{32}N_4O_6$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.50; H, 5.73; N, 9.85. δ_H (DMSO-d_6): 7.82 (d, J = 8.91, 4H), 7.36−7.31 (m, 10H), 7.10 (d, J = 8.91, 4H), 5.04 (s, 4H), 4.10 (t, J = 5.61, 4H), 3.42 (q, J = 5.61, 4H). δ_C (DMSO-d_6): 160.6, 156.3, 146.2, 137.1, 128.3, 127.7, 124.1, 115.0, 66.7, 65.3, 38.6.

4,4′-Di[γ-(*N*-benzyloxycarbonyl)aminopropanoxy]azobenzene 3b was prepared in a manner analogous to **3a** from **1** (0.321 g, 1.5 mmol) and **2b** (0.987 g, 3.6 mmol) to give yellow crystals of **3b**, 0.664 g, 74% yield. TOF-MS: *m*/*z* 598 $(M + H)^+$. Anal. Calcd for $C_{34}H_{36}N_4O_6$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.39; H, 6.11; N, 9.43. δ_H (DMSO-d_6): 7.86 (d, J = 8.91, 4H), 7.36−7.31 (m, 10H), 6.97 (d, J = 8.91, 4H), 5.11 (s, 4H), 4.10 (t, J = 5.94, 4H), 3.44 (q, J = 6.43, 4H), 2.05 (t, J = 6.10, 4H). δ_C (DMSO-d_6): 160.9, 156.3, 146.2, 137.3, 128.4, 127.8, 124.2, 115.0, 65.7, 65.3, 37.3, 29.1.

4,4′-Di[γ-(*N*-benzyloxycarbonyl)aminobutanoxy]azobenzene 3c was prepared in a manner analogous to **3a** from **1** (0.321 g, 1.5 mmol) and **2c** (1.038 g, 3.6 mmol) to give yellow crystals of **3c**, 0.667 g, 71% yield. TOF-MS: *m*/*z* 626 $(M + H)^+$. Anal. Calcd for $C_{36}H_{40}N_4O_6$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.22; H, 6.50; N, 8.84. δ_H ($CDCl_3$): 7.86 (d, J = 8.91, 4H), 7.36−7.31 (m, 10H), 6.97 (d, J = 8.91), 5.11 (s, 4H), 4.05 (t, J = 6.60, 4H), 3.30 (q, J = 6.43, 4H), 1.84−1.73 (m, 4H). δ_C ($CDCl_3$): 160.8, 156.4, 147.0, 136.5, 128.5, 128.1, 124.3, 114.5, 67.7, 66.7, 40.7, 26.8, 26.4.

4,4′-Di(γ-aminoethanoxy)azobenzene Dihydrobromide 4a. A saturated solution (1.0 g, 4.45 mmol) of 33% dry hydrogen bromide in glacial acetic acid was added to **3a** (0.284 g, 0.5 mmol) in a reaction flask with a calcium chloride dry tube. Immediately after the addition of the reagent, carbon dioxide began to develop. The mixture was allowed to stand at room temperature with occasional shaking for 1 h and washed with ether. A scarlet solid dried with desiccator **4a** was obtained in 88% yield, 0.203 g. TOF-MS: *m*/*z* 301 $(M + H)^+$. Anal. Calcd for $C_{16}H_{20}N_4O_2$·2HBr: C, 41.58; H, 4.36; N, 12.12. Found: C, 41.30; H, 4.46; N, 12.02. δ_H (DMSO-d_6): 8.15 (br, 6H), 7.85 (d, J = 8.91, 4H), 7.12 (d, J = 8.91, 4H), 4.30 (t, J = 5.61, 4H), 3.27 (q, J = 5.61, 4H). δ_C (DMSO-d_6): 160.1, 146.5, 124.2, 115.3, 64.6, 38.31.

4,4′-Di(γ-aminopropanoxy)azobenzene dihydrobromide 4b was prepared in a manner analogous to **4a** from **3b** (0.298 g, 0.5 mmol) and 33% HBr/AcOH (1.0 g, 4.45 mmol) to give a black solid of **4b**, 0.236 g, 96% yield. TOF-MS and FAB-MS: *m*/*z* 329 $(M + H)^+$. Anal. Calcd for $C_{18}H_{24}N_4O_2$·2HBr: C,

(11) Brown, R. F.; Gulick, N. M. *J. Am. Chem. Soc.* **1955**, *77*, 1079−1081.

44.10; H, 4.93; N, 11.43. Found: C, 44.43; H, 5.20; N, 11.06. UV (MeOH) for trans form: λ_{max} 356 nm (ϵ 26 600 dm^3 mol^{-1} cm^{-1}); for cis form: λ_{max}319 nm (ϵ 10 900), 445 nm (ϵ 3600 dm^3 mol^{-1} cm^{-1}). δ_H (CD_3OD) for trans form: 7.72 (d, J = 8.91, 4H), 6.94; (d, J = 8.91, 4H), 4.01 (t, J = 6.30, 4H), 2.74 (t, J = 6.90, 4H), 1.85 (q, J = 6.80, 4H); for cis form: 6.77 (d, J = 8.91, 4H), 6.75; (d, J = 8.91, 4H), 3.89 (t, J = 6.30, 4H), 2.70 (t, J = 6.90, 4H), 2.00 (q, J = 6.80, 4H). δ_C (CD_3OD) for trans form: 160.5, 146.2, 124.1, 115.1, 65.1, 36.2, 26.7; for cis form: 157.3, 146.8, 122.1, 114.6, 64.9, 36.2, 26.7.

4,4′-Di(γ-aminobutanoxy)azobenzene dihydrobromide 4c was prepared in a manner analogous to **4a** from **3c** (0.312 g, 0.5 mmol) and 33% HBr/AcOH (1.0 g, 4.45 mmol) to give a black solid of **4c**, 0.218 g, 84% yield. TOF-MS: m/z 357.5 (M + H)$^+$. Anal. Calcd for $C_{20}H_{28}N_4O_2$·2HBr: C, 46.35; H, 5.45; N, 10.81. Found: C, 46.34; H, 5.28; N, 11.02. δ_H (DMSO-d_6): 7.85 (br, 6H), 7.83 (d, J = 8.91, 4H), 7.10 (d, J = 8.91, 4H), 4.08 (t, J = 6.60, 4H), 2.87 (q, J = 6.43, 4H), 1.90−1.74 (m, 4H). δ_C (DMSO-d_6): 160.7, 146.1, 124.1, 115.0, 67.3, 40.7, 25.6, 23.8.

1,7-Dicarboxymethyl-4,10-di(benzyloxycarbonyl)-1,4,7,-10-tetraazacyclododecane 6. Compound **5** was prepared by the method of Kovacs and Sherry.[6] A solution of KOH (0.753 g, 11.4 mmol, 85% content) in MeOH (6 mL) was cooled to 0 °C and carefully added to a solution of bromoacetic acid (1.584 g, 11.4 mmol) in MeOH (10 mL) at 0 °C on an ice bath. The temperature did not rise above 5 °C during addition. The resulting solution was added to a suspension of **5** (2.201 g, 5 mmol) and anhydrous K_2CO_3 (1.575 g, 11.4 mmol) in MeOH (50 mL). The mixture was stirred first at 45 °C for 7 h, and then at 65 °C overnight. The solvent was removed to near dryness under reduced pressure. The resulting white solid was dissolved in water (50 mL) and acidified to pH 1 with 6 M HCl. The supernatant liquid was decanted, and the residue was washed with chilled water and dried under reduced pressure to give **6**, 2.464 g, 89% yield. FAB-MS: m/z 557.6 (M + H)$^+$ and TOF-MS: m/z 558 (M + H)$^+$. Anal. Calcd for $C_{28}H_{36}N_4O_8$·H_2O: C, 58.53; H, 6.67; N, 9.75. Found: C, 58.57; H, 6.70; N, 9.68. δ_H ($CDCl_3$): 7.33 (br, 10H), 5.21 (br m, 4H), 3.82 (br m, 8H), 3.23 (br, 12H). δ_C ($CDCl_3$): 170.6, 155.7, 135.5, 128.2, 127.9, 67.2, 58.8, 57.0, 46.7.

1,7-Di(1′-*N*-acetyl-1,3-thiazolidine-2-thione)-4,10-di(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane 7. To a solution of **6** (0.557 g, 1 mmol) and 1,3-thiazolidine-2-thione, TTH (0.262 g, 2.2 mmol) in CH_2Cl_2 (8 mL) cooled to 0 °C on an ice-bath, was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiomide hydrochloride, WSC (0.478 g, 2.5 mmol) and 4-(*N*,*N*′-dimethyl)aminopyridine, DMAP (0.020 g). The mixture was stirred at 0 °C for 5 h and then at room temperature overnight. The yellow solution was diluted with CH_2Cl_2 (20 mL), washed twice with water, and dried over anhydrous $MgSO_4$. The solvent was removed under reduce pressure. A residue was dissolved in $CHCl_3$ (5 mL) and a pale yellow compound **7** was precipitated with addition of a large volume of ethyl ether (150 mL), 0.426 g, 56% yield. TOF-MS: m/z 760 (M + H)$^+$. δ_H ($CDCl_3$): 7.34−7.30 (m, 10H), 5.11 (s, 4H), 4.48, 4.35 (br, 4H), 3.42 (br, 8H), 3.28 (br, 4H), 2.91 (br, 8H). δ_C ($CDCl_3$): 201.3, 173.1, 156.5, 136.9, 128.4, 127.9, 127.8, 66.9, 60.0, 55.6, 29.0, 54.3, 47.4.

General Procedures for 1:1 (8a−c) and 2:2 (9a−c) Cyclic Products. To THF (350 mL), a solution of **7** (0.190 g, 0.25 mmol) in THF (75 mL), and of **4b** (0.123 g, 0.25 mmol) and Et_3N (0.069 mL, 0.5 mmol) in 75 mL of THF−H_2O (1:2) were simultaneously added with ace dropping funnels at 2.0 mL/min under vigorous stirring at room temperature. After addition, the solution was continuously stirred for 1 h. Solvents were removed under reduced pressure; the remaining residue was dissolved in CH_2Cl_2 (50 mL). The organic phase was washed twice each subsequently with 1 M K_2CO_3, H_2O, 1 M HCl, and H_2O and dried over Mg_2SO_4 overnight. Products were isolated by preparative TLC on aluminum oxide.

1:1 Cyclic Products 8a−c. When cyclization reactions were conducted under UV irradiation with a 500-W super-high-pressure Hg lamp through a color glass filter (330 nm < λ < 380 nm). **8a−c** yellow solids were obtained.

2:2 Cyclic Products 9a−c. When cyclization reactions were conducted in the dark, **9a−c** yellow solids were obtained. Note that to completely convert the cis form to trans form, before solutions of **4a−c** were added, solutions were allowed to stand in a darkroom for 24 h at 30 °C, or irradiated with light (λ > 460 nm) for 5 min and then allowed to stand in a darkroom at 30 °C for 8 h.

1:1 Cyclic Products 8a. 51% yield. R_f = 0.47 (EtOAc−MeCN 8:1). TOF-MS and FAB-MS: m/z 822 (M + H)$^+$. Anal. Calcd for $C_{44}H_{52}N_8O_8$·$2H_2O$: C, 61.67; H, 6.59; N, 13.08. Found: C, 61.73; H, 6.50; N, 12.85. UV (MeOH) for trans form: λ_{max} 364 nm (ϵ 22 700 dm^3 mol^{-1} cm^{-1}); for cis form: λ_{max}315 nm (ϵ 6800), 446 nm (ϵ 2300 dm^3 mol^{-1} cm^{-1}). δ_H ($CDCl_3$): 7.86 (d, J = 8.25, 4H), 7.38−7.31 (m, 10H), 7.07 (br, 4H), 5.10 (s, 4H), 4.38 (br, 4H), 3.36 (br, 4H), 3.16 (br, 4H), 2.76 (br, 8H), 2.41 (br, 8H). δ_C ($CDCl_3$): 170.3, 162.1, 156.0, 147.0, 136.3, 128.6, 128.2 128.0, 124.9, 122.5 (small), 118.0, 114.2 (small), 69.2, 67.3, 56.6, 51.4, 45.5 (br), 41.5.

1:1 Cyclic Products 8b. 52% yield. R_f = 0.55 (EtOAc−MeCN 8:1). FAB-MS and TOF-MS: m/z 850.0 (M + H)$^+$. Anal. Calcd for $C_{46}H_{56}N_8O_8$·$2H_2O$: C, 62.43; H, 6.83; N, 12.66. Found: C, 62.44; H, 6.55; N, 12.41. δ_H ($CDCl_3$) for trans form: 7.85 (d, J = 8.25, 4H), 7.36−7.31 (m, 10H), 6.98 (br, 4H), 5.10 (s, 4H), 4.28 (br, 4H), 3.35 (br, 4H), 2.86 (br, 12H), 2.47 (br, 8H), 1.95 (br, 4H); for cis form: 7.38−7.20 (m, 10H), 6.81 (d, J = 8.91, 4H), 6.73 (d, J = 8.91, 4H), 4.94 (s, 4H), 3.97 (br, 4H), 3.37 (br, 12H), 3.13 (br, 4H), 2.77 (br, 8H), 1.94 (br, 4H). δ_C ($CDCl_3$) for trans form: 170.5, 161.2, 156.1, 147.0, 136.5, 128.6, 128.4, 128.3, 128.1, 124.8, 116.8, 67.7, 67.4, 56.8, 52.0, 45.8 (br), 35.7, 28.1; for cis form: 170.5, 157.7, 156.5, 147.1, 136.0, 128.6, 128.4 128.3, 128.1, 122.4, 114.4, 67.4, 66.0, 58.6, 54.6, 47.4 (br), 36.1, 28.6.

1:1 Cyclic Products 8c. 55% yield. R_f = 0.57 (EtOAc−MeCN 8:1). TOF-MS and FAB-MS: m/z 878.0 (M + H)$^+$. Anal. Calcd for $C_{48}H_{60}N_8O_8$·$2H_2O$: C, 63.14; H, 7.06; N, 12.27. Found: C, 63.41; H, 6.87; N, 12.51. δ_H ($CDCl_3$): 7.79 (d, J = 8.25, 4H), 7.36−7.31 (br, 10H), 6.95 (br, 4H), 5.08 (s, 4H), 4.29 (br, 4H), 3.35 (br, 4H), 2.90 (br, 12H), 2.56 (br, 8H), 1.69 (br, 8H). δ_C ($CDCl_3$): 171.5, 159.8, 156.7, 146.7, 136.6, 128.6, 128.3, 127.9, 124.3, 122.6 (small), 116.6, 114.3 (small), 67.5, 67.2, 56.8, 55.0, 47.2 (br), 38.6, 26.4, 25.5.

2:2 Cyclic Products 9a. 47% yield. R_f = 0.30 (EtOAc-MeCN 8:1). TOF-MS and FAB-MS: m/z 1643.0 (M + H)$^+$. Anal. Calcd for $C_{88}H_{104}N_{16}O_{16}$·$4H_2O$: C, 61.67; H, 6.59; N, 13.08. Found: C, 61.83; H, 6.45; N, 12.90. UV (MeOH) for trans,-trans form: λ_{max} 356 nm (ϵ 51 700 dm^3 mol^{-1} cm^{-1}); for cis,cis form: λ_{max}317 nm (ϵ 15 700), 447 nm (ϵ 5200 dm^3 mol^{-1} cm^{-1}). δ_H ($CDCl_3$): 7.71 (d, J = 8.89, 8H), 7.38−7.31 (m, 10H), 6.91 (d, J = 8.38, 8H), 5.06 (s, 8H), 4.02 (br, 8H), 3.42 (br, 24H), 3.17 (br, 8H), 2.77 (br, 16H). δ_C ($CDCl_3$): 170.3, 161.1, 156.0, 147.0, 136.3, 128.6, 128.3, 128.2, 124.4, 122.4 (small), 114.6, 114.5 (small), 67.5, 65.8, 56.7, 51.3, 45.4 (br), 38.6.

2:2 Cyclic Products 9b. 49% yield. R_f = 0.32 (EtOAc−MeCN 8:1). TOF-MS and FAB-MS: m/z 1669.0 (M + H)$^+$. Anal. Calcd for $C_{92}H_{112}N_{16}O_{16}$·$4H_2O$: C, 62.43; H, 6.83; N, 12.66. Found: C, 62.50; H, 6.42; N, 12.30. δ_H ($CDCl_3$) for trans,trans-form: 7.73 (d, J = 8.90, 8H), 7.36−7.31 (m, 10H), 6.80 (d, J = 8.58, 8H), 5.09 (s, 8H), 3.89 (br, 8H), 3.53, 3.41 (br, 24H), 3.19 (br, 8H), 2.79 (br, 16H), 1.96 (br, 8H); for cis,cis form: 7.30−7.27 (m, 20H), 6.82 (d, J = 8.91, 8H), 6.69 (d, J = 8.91, 8H), 5.03 (s, 8H), 3.89 (br, 8H), 3.42, 3.33 (br d, 24H), 3.15 (br, 8H), 2.77 (br, 16H), 1.92 (br, 8H). δ_C ($CDCl_3$) for trans,trans form: 170.9, 160.5, 156.9, 147.0, 136.1, 128.7, 128.6, 128.3, 128.1, 124.4, 114.5, 67.7, 65.6, 56.4, 54.8, 47.7 (br), 35.7, 28.1; for cis,-cis form: 171.0, 157.6, 156.8, 146.8, 136.1, 128.7, 128.4, 128.1, 122.7, 114.5, 67.5, 65.8, 58.6, 55.5, 47.8 (br), 36.3, 29.1.

2:2 Cyclic Products 9c. 20% yield. R_f = 0.33 (EtOAc−MeCN 8:1). TOF-MS and FAB-MS: m/z 1755.0 (M + H)$^+$. Anal. Calcd for $C_{96}H_{120}N_{16}O_{16}$·$4H_2O$: C, 63.14; H, 7.06; N, 12.27. Found: C, 63.48; H, 6.91; N, 12.60. δ_H ($CDCl_3$): 7.73 (d, J = 8.91, 8H), 7.36−7.31 (m, 10H), 6.81 (d, J = 8.91, 8H), 5.06 (s, 8H), 3.88 (br, 8H), 3.50, 3.35 (br, 24H), 3.17 (br, 8H), 2.87 (br, 16H), 1.75 (m, 16H). δ_C ($CDCl_3$): 171, 160.3, 156.9, 146.8, 136.3, 128.6, 128.3, 127.9, 124.1, 122.8 (small), 114.4, 67.1, 65.6, 56.8, 55.0, 47.0 (br), 38.5, 26.4, 25.4.

4,4′-Di(γ-aminopropanoxy)azobenzene 10. To a solution of compound **4b** (0.245 g, 0.5 mmol) dissolved in H_2O-MeOH (25 mL, 10:1), toluene (50 mL) and Et_3N (0.7 mL, 5 mmol) were added. The mixture was vigorously shaken in a separatory funnel. The water phase was extracted with toluene. The combined toluene extracts were washed with water and dried over granular CaO for 2 days. Toluene was removed under the protection of nitrogen gas to give a yellow solid of **10**. 0.117 g, 71% yield. **10** was stored in desiccator-filled nitrogen gas. δ_H ($CDCl_3$): 7.86 (d, $J = 8.91$, 4H), 6.89 (d, $J = 8.91$, 4H), 4.01 (t, $J = 6.30$, 4H), 2.93 (t, $J = 6.90$, 4H), 1.98 (q, $J = 6.80$, 4H). δ_C ($CDCl_3$): 160.6, 146.4, 124.2, 114.4, 65.2, 36.0, 26.6.

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Supporting Information Available: ^1H NMR spectra of **9c** including all-cis (cis,cis) to all-trans (trans,trans), and cis,-trans isomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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