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Cyclophanes. II. Preparation and Conformational Properties of 5,14-Bis(4-bromophenyl)diimidazolo[3^2]metacyclophane and a Higher Homolog

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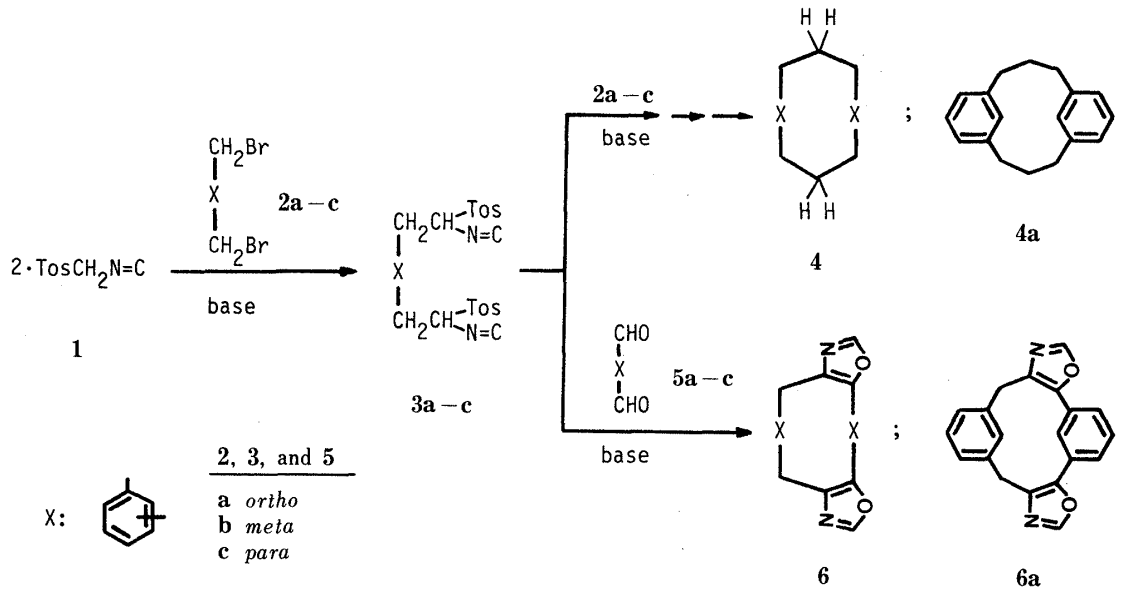
5,14-Bis(4-bromophenyl)diimidazolo[3^2]metacyclophane (**12**) and 5,14,29,38-tetrakis(4-bromophenyl)tetraimidazolo[3^4]metacyclophane (**13**) as a higher homolog were synthesized by the one-pot coupling reaction of 1,3-bis(2-isocyano-2-tosylethyl)benzene (**3b**) with 1,3-bis(4-bromophenyliminomethyl)benzene (**11**). At $-5\,^{\circ}C$, the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **12** strongly suggests the existence of two fixed conformers, *i.e.*, *syn* and *anti* forms, on the NMR time scale. Moreover, on the basis of the variable-temperature (VT)-NMR spectra of **12** at various temperatures between 25 °C and 100 °C, the coalescence temperature (T_c) of the methylene proton signals is 80 °C and the energy barrier ($\Delta G^{\ddagger}$) of the conformational change is determined to be 69.3 kJ/mol, which is higher than those of the parent [3^2]metacyclophane (**4a**) and dioxazolo[3^2]metacyclophane (**6a**). The conformational rigidity of **12** is attributed to the further substitutions of the bulky 4-bromophenyl groups on the imidazole moieties in addition to the annelations of two imidazole rings to the two methylene bridges of the [3^2]metacyclophane ring.

Keywords——[3^2]metacyclophane; cyclophane; conformational analysis; VT-NMR; COSY; cyclization; isocyanide; tosylmethyl isocyanide; imine; imidazole

Recently, we reported that bis(2-isocyano-2-tosylethyl)benzenes (**3a—c**), prepared by the alkylation of tosylmethyl isocyanide (TosMIC, **1**) with α,α'-dibromoxylenes (**2a—c**), were useful synthetic tools for the convenient preparations of [3^n]cyclophanes (**4**),[1] dioxazolo[3^2]cyclophanes (**6**),[2] and benzologs of eight-membered heterocycles such as 3-benzazocines (**7**).[3] Moreover, it has been reported that the preferred conformation of dioxazolo[3^2]metacyclophane (**6a**) in solution at room temperature is *syn* and the conformational rigidity of **6a** is greater than that of the parent [3^2]metacyclophane (**4a**).[2a] The successful applications of **3a—c** for cyclophane synthesis suggested the possibility of analogous synthesis of [3^2]cyclophane derivatives possessing two heterocycles by the cyclization of **3a—c** with appropriate bifunctional reactants such as phthalaldehydes (**5a—c**). In connection with this consideration, the synthesis of 1,4,5-trisubstituted imidazoles (**10**) by the reaction of mono-alkylated TosMIC derivatives (**8**) with imines (**9**) has been reported by Possel and van Leusen,[4] as shown in Chart 2. This report led us to carry out the cyclization of **3b** with diimines (**11**) to give the corresponding [3^2]cyclophane derivatives of type **12** possessing a 4-bromophenyl-substituted imidazole ring fused on each of the two methylene bridges of the parent [3^2]metacyclophane ring.

In this paper, we would like to report the preparation of 5,14-bis(4-bromophenyl)-diimidazolo[3^2]metacyclophane (**12**)[5] and 5,14,29,38-tetrakis(4-bromophenyl)tetraimidazolo[3^4]metacyclophane (**13**),[5] and the spectroscopic properties and conformation of **12**. Thus, the reaction of 1,3-bis(2-isocyano-2-tosylethyl)benzene (**3b**) with 1,3-bis(4-bromophenyliminomethyl)benzene (**11**) in the presence of 2 eq of sodium hydride (NaH) in di-



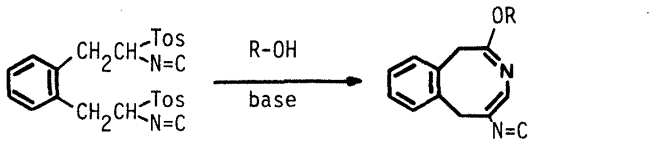
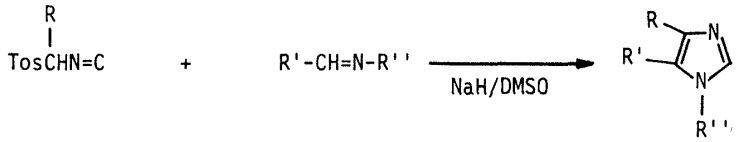
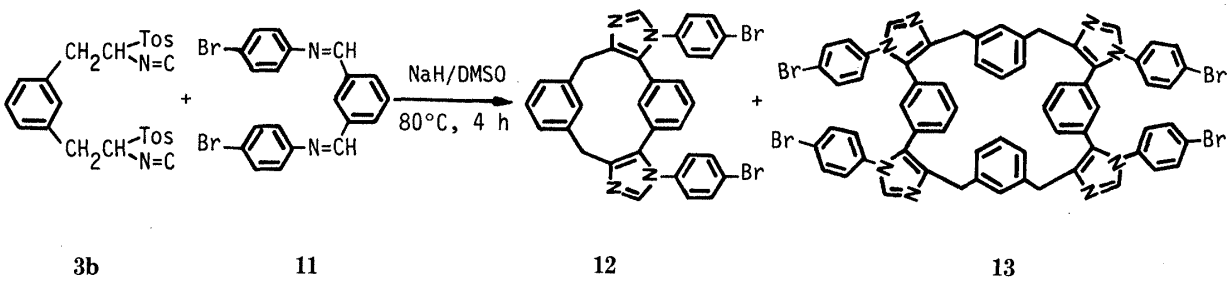


Chart 1



R; alkyl, aryl R′,R″; aryl

Chart 2



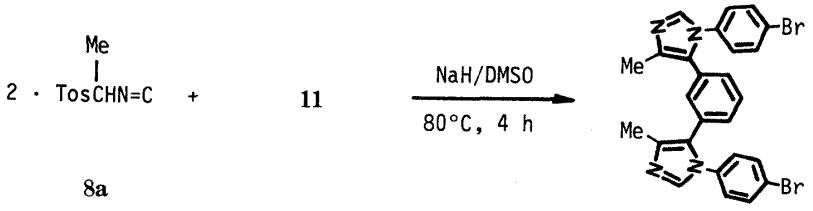
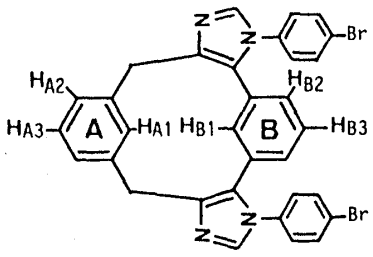
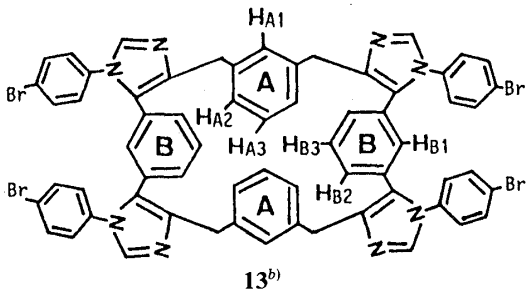


Chart 3

methyl sulfoxide (DMSO) for 4 h at 80 °C afforded **12** as an 1 : 1 adduct in 16% yield, together with **13** as a 2 : 2 adduct in 6% yield (Chart 3). On the other hand, 1,3-bis[1-(4-bromophenyl)-4-methyl-5-imidazolyl]benzene (**14**) as an acyclic reference compound was obtained in 31% yield by the reaction of 1-tosylethyl isocyanide (**8a**)[6] with **11** under the same conditions, as shown in Chart 3. The diimine (**11**) mentioned above was obtained by the condensation of isophthalaldehyde (**5b**) with 2 eq of 4-bromoaniline in the presence of a catalytic amount of benzenesulfonic acid in 83% yield. The structures of these cyclophanes (**12** and **13**) were confirmed by the spectroscopic properties and analytical data. The infrared (IR) spectra show the imidazole ring C=N stretching absorptions at 1488 cm^{-1},[7] and the mass spectrum (MS) of **12** and the field desorption (FD)-MS of **13** show the appropriate molecular ion peaks (M^+) along with the characteristic ion peaks, $M^+ + 2$ (622) and $M^+ + 4$ (1244), as base peaks of the dibromo and tetrabromo compounds, respectively. Figure 1 shows the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **12** in DMSO-d_6 at various temperatures between 25 °C and 100 °C. The spectrum at 25 °C suggests that the mobility of the cyclophane benzene rings is strongly restricted (the absorptions of both aromatic and methylene protons are very broad). When the temperature was raised stepwise to 100 °C, as expected, the signals of those protons began to sharpen above 50 °C and split sufficiently to permit assignment at 100 °C, as shown in Fig. 1. On the basis of the two-dimensional proton–proton chemical shift correlation (COSY) spectrum of **12** at 100 °C and a comparison of the chemical shifts of the proton signals with those of **14** and **6a**,[2a] the benzene and methylene protons signals of **12** were completely assigned, as summarized in Table I. In contrast, all proton signals of **13** appear as sharp signals at 25 °C, so that the cyclophane **13** is more flexible than **12**, and those proton signals were similarly assigned on the basis of the COSY spectrum of **13** in $CDCl_3$ at 25 °C, as summarized in Table I.

Interestingly, at −5 °C the ^{1}H-NMR spectrum of **12** in $CDCl_3$ strongly suggests the existence of two fixed conformers on the NMR time scale because of the observation of a set

TABLE I. ^{1}H-NMR Spectral Data for 5,14-Bis(4-bromophenyl)diimidazolo[3²]metacyclophane (**12**) and 5,14,29,38-Tetrakis(4-bromophenyl)tetraimidazolo[3⁴]metacyclophane (**13**) (400 MHz, DMSO-d_6)

Structure Compd. No.	$-CH_2-$	A ring-H	B ring-H	4-Bromophenyl-H	Imidazole C2-H
 **12**[a]	3.67 (4H, br s)	6.39 (H_{A1}) (1H, br s) 6.69 (H_{A2}) (2H, dd, J=7.7, 1.7 Hz) 6.96 (H_{A3}) (1H, m)	6.64 (H_{B1}) (1H, br s) 6.86 (H_{B2}) (2H, dd, J=8.2, 1.5 Hz) 6.94 (H_{B3}) (1H, m)	7.05 and 7.40 (8H, each d, AB type, J=9 Hz)	7.74 (2H, s)
 **13**[b]	3.61 (8H, s)	6.57 (H_{A1}) (2H, br s) 6.83 (H_{A2}) (4H, dd, J=7.5, 1.5 Hz) 6.99 (H_{A3}) (—,[c] m)	6.99 (H_{B1}) (—,[c] m) 6.90 (H_{B2}) (4H, dd, J=7.7, 1.7 Hz) 7.17 (H_{B3}) (2H, t, J=7.7 Hz)	6.99 and 7.57 (16H, each d, AB type, J=9 Hz)	7.91 (4H, s)

a) At 100 °C. *b*) At 25 °C. *c*) Overlapped with the 4-bromophenyl signal.

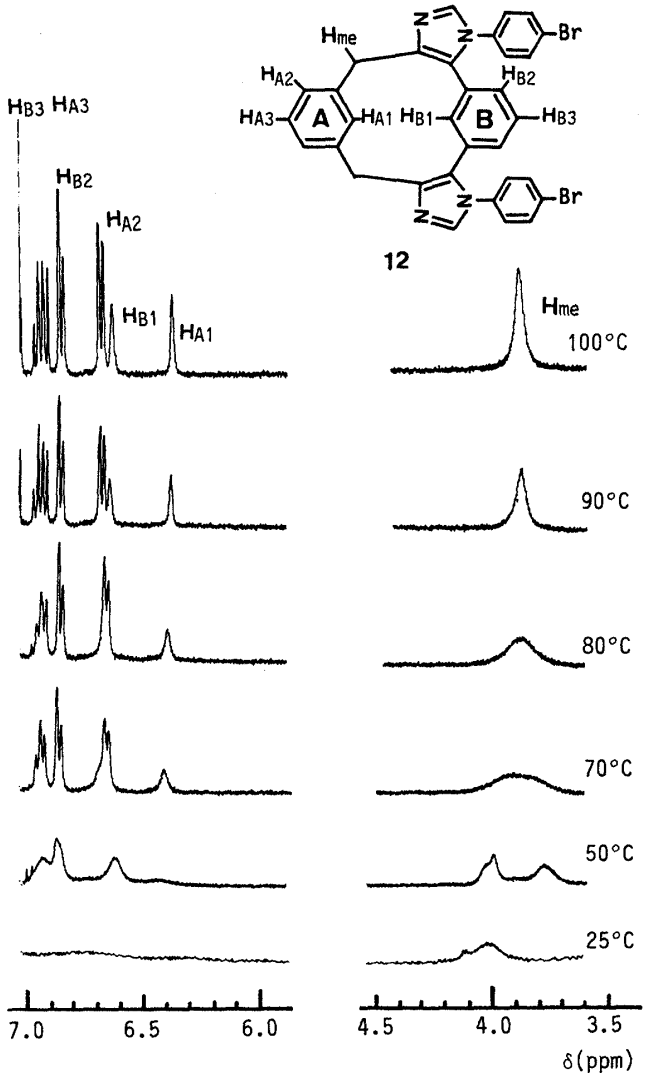


Fig. 1. VT-NMR Spectra and Assignment of Spectrum at 100 °C of 5,14-Bis(4-bromophenyl)diimidazolo[3²]metacyclophane (**12**) in DMSO-d_6

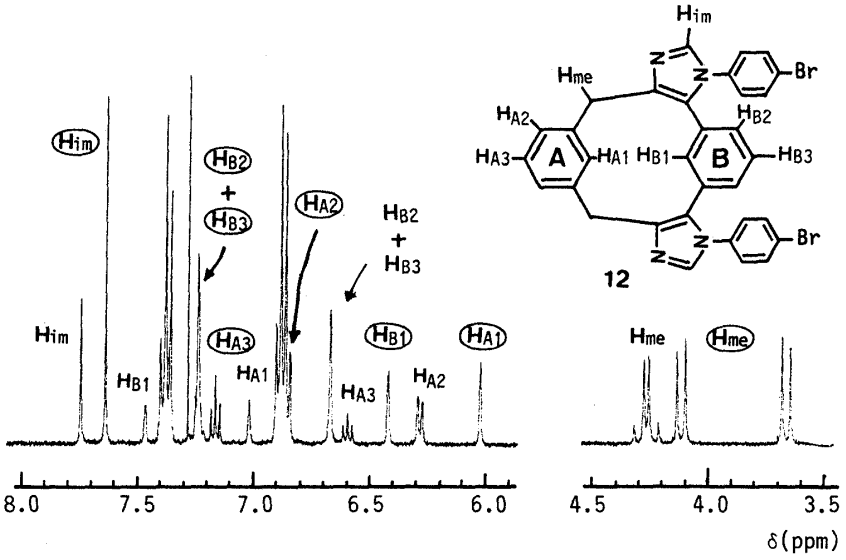


Fig. 2. ^{1}H-NMR Spectrum of 5,14-Bis(4-bromophenyl)diimidazolo[3²]metacyclophane (**12**) in $CDCl_3$ at −5 °C

The signals of the *anti* conformer are indicated by the symbols enclosed with a circle.

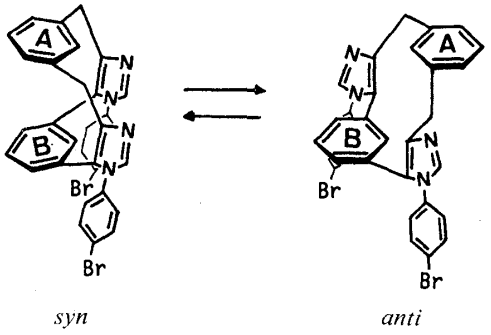


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Fig. 3. *syn* and *anti* Conformations of 5,14-Bis(4-bromophenyl)diimidazolo[3^2]metacyclophane (**12**)

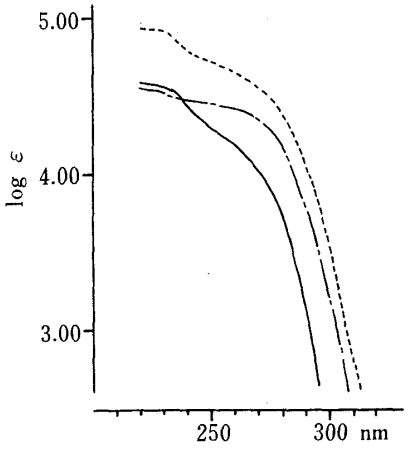


Fig. 4. UV Spectra of **12** (——), **13** (– – – –), and **14** (— · —) in EtOH

of sharp singlets for imidazole C2-H (δ 7.62 and 7.72), as shown in Fig. 2. The intensity ratio of these signals is *ca.* 5:3. On the basis of the COSY spectrum of **12** in $CDCl_3$ at 1 °C, the assignments of the proton signals for each conformer were accomplished as shown in Fig. 2. The conformers could be characterized on the basis of the following considerations. (i) In the case of the major conformer, the H_{A1} (δ 6.02) and H_{B1} (δ 6.37) signals show upfield shifts compared with the corresponding signals of **4a** (δ 6.84)[8] and *m*-xylene (δ 6.89)[9] and the signals of H_{A2} (δ 6.86) and H_{A3} (δ 7.16), which are little affected by the anisotropic effects of the 4-bromophenyl groups and imidazole rings in the light of the CPK molecular model, are in the usual range for arene hydrogens (δ 6.88—7.05 in *m*-xylene).[9] (ii) In the case of the minor conformer, the H_{A1} (δ 7.01) and H_{B1} (δ 7.45) signals are in the usual range for arene hydrogens, but the signals of H_{A2} (δ 6.28) and H_{A3} (δ 6.59), which are little affected by the effects mentioned above, show upfield shifts compared with the corresponding protons of **4a** and *m*-xylene. Thus, it is concluded that the major and the minor conformers are the *anti* and *syn* forms (Fig. 3), respectively.

Since the coalescence temperature (T_c) of the methylene protons signal of **12** is 80 °C (Fig. 1), the energy barrier ($\Delta G^{\neq}$) of the conformational change[10] shown in Fig. 3 is calculated to be 69.3 kJ/mol (16.6 kcal/mol),[11] which is higher than those of the parent [3^2]metacyclophane (**4a**) (48.1 kJ/mol)[8] and dioxazolo[3^2]metacyclophane (**6a**) (64.5 kJ/mol).[2a] Thus, **12** is more rigid than **4a** and **6a** probably because of the further substitutions of the bulky 4-bromophenyl groups on the imidazole moieties in addition to the annelations of two imidazole rings to the two methylene bridges of **4a**.

The ultraviolet (UV) spectra of **12**, **13**, and **14** in ethanol are shown in Fig. 4. Compound **14** shows a broad absorption around 260 nm ($\log \varepsilon = ca.$ 4.5) probably because of the presence of an extended conjugated system over the three aromatic rings, *i.e.*, imidazole, benzene, and imidazole.[12] Significant reduction in extinction and slight hypsochromic shift for **12** in the

region above 230 nm as compared with **14** in the corresponding region were observed. On the other hand, the absorption intensity of **13** is higher than that of **14** in the whole region. These facts suggest that the three aromatic rings of large [3⁴]metacyclophanes (**13**) can take a more planar conformation as compared with those of small [3²]metacyclophanes (**12**).

In conclusion, the one-pot coupling reaction of **3b** with **11** readily afforded rigid small [3²]metacyclophanes (**12**), together with flexible large [3⁴]metacyclophanes (**13**). On the basis of variable-temperature (VT)-NMR spectra, the conformational mobility of **12** was found to be restricted more strongly than that of the parent [3²]metacyclophane (**4a**) and dioxazolo[3²]metacyclophane (**6a**), probably because of the introduction of the bulky 4-bromophenyl groups into the two imidazole moieties. Furthermore, it became apparent that at -5 °C **12** exists in two fixed conformers on the NMR time scale, and these are assigned as *anti* and *syn* forms. The UV spectra of **12** and **13** were significantly affected by the planarity of the three linked aromatic rings, *i.e.*, imidazole, benzene, and imidazole.

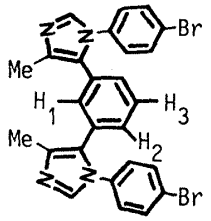
Experimental

All melting points were taken on a Yanagimoto micro melting point determination apparatus and are uncorrected. IR spectra were recorded on a Hitachi model 260-30 infrared spectrophotometer. ^{1}H-NMR and VT-NMR spectra were measured on a Bruker AM-400 (400 MHz) instrument and a Hitachi R-22 spectrometer (90 MHz) using tetramethylsilane as an internal reference. MS and FD-MS were measured on a Hitachi RMU-6MG mass spectrometer and a JEOL JMS-D300 mass spectrometer, respectively. UV spectra were measured on a Hitachi 323 spectrometer.

1,3-Bis(4-bromophenyliminomethyl)benzene (11)——A solution of isophthalaldehyde (**5b**) (4.0 g, 30 mmol), 4-bromoaniline (10.3 g, 60 mmol), and benzenesulfonic acid (0.70 g, 4 mmol) in benzene (400 ml) was refluxed for 4 h, and then cooled to room temperature, and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from cyclohexane to yield colorless needles, mp 121—123 °C, 11 g (83%). This product was used in the following reactions without further purification. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 7.08, 7.48 (8H, each d, AB type, $J=8.5$ Hz, 4-bromophenyl-H), 7.90—8.40 (4H, m, *m*-substituted phenyl-H), 8.44 (2H, s, –CH=N–).

5,14-Bis(4-bromophenyl)diimidazolo[3²]metacyclophane (12) and 5,14,29,38-Tetrakis(4-bromophenyl)tetraimidazolo[3⁴]metacyclophane (13)——A solution of 1,3-bis(2-isocyano-2-tosylethyl)benzene (**3b**) (4.92 g, 10 mmol) and **11** (4.42 g, 10 mmol) in DMSO (100 ml) was added dropwise to a stirred suspension of NaH (0.96 g, 20 mmol) in DMSO (100 ml) for 1 h at room temperature. After being heated for 3 h at 80 °C, the resulting mixture was cooled to room temperature and poured into ice-water (*ca.* 1000 ml), and then the aqueous solution was extracted with three 100 ml portions of $CHCl_3$. The extracts were combined, washed with three 100 ml portions of water, and then dried over anhydrous $MgSO_4$. The organic solvent was evaporated off, and the residue was chromatographed on neutral alumina with (i) $CHCl_3$ and (ii) a mixture of $CHCl_3$–CH_3CN (4:1). (i) Concentration of the $CHCl_3$ eluate gave a crude product, which was recrystallized from MeOH to yield 1.0 g (16%) of **12**, colorless prisms. mp 266—268 °C. *Anal.* Calcd for $C_{32}H_{22}Br_2N_4 \cdot MeOH$: C, 60.57; H, 4.00; N, 8.56. Found: C, 60.50; H, 3.84; N, 8.54. IR (KBr): 1488 (C=N) cm^{-1}. MS (*m/z*): 622 ($M^+ +2$), 620 (M^+). (ii) Concentration of the $CHCl_3$–CH_3CN (4:1) eluate gave a crude product, which was recrystallized from $CHCl_3$ to yield 0.37 g (6%) of **13**, colorless prisms. mp 282—283 °C. *Anal.* Calcd for $C_{64}H_{44}Br_4N_8$: C, 61.76; H, 3.56; N, 9.00. Found: C, 61.57; H, 3.32; N, 8.82. IR (KBr): 1488 (C=N) cm^{-1}. FD-MS (*m/z*): 1244 ($M^+ +4$), 1242 ($M^+ +2$), 1240 (M^+).

1,3-Bis[1-(4-bromophenyl)-4-methyl-5-imidazolyl]benzene (14)——A solution of 1-tosylethyl isocyanide (**8a**)[6] (2.09 g, 10 mmol) and **11** (2.21 g, 5 mmol) in DMSO (60 ml) was added dropwise to a stirred suspension of NaH (0.48 g, 10 mmol) in DMSO (40 ml) for 1 h at room temperature. After being heated for 3 h at 80 °C, the resulting mixture was cooled to room temperature and poured into ice-water (*ca.* 500 ml), and then the aqueous solution was extracted with three 50 ml portions of AcOEt. The extracts were combined, washed with three 50 ml portions of water, and then dried over anhydrous $MgSO_4$. The organic solvent was evaporated off, and the residue was



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chromatographed on neutral alumina with AcOEt to give a crude product, which was recrystallized from benzene to yield 0.85 g (31%) of **14**, colorless prisms. mp 228—229 °C. *Anal.* Calcd for $C_{26}H_{20}Br_2N_4$: C, 56.96; H, 3.68; N, 10.22. Found: C, 57.22; H, 3.52; N, 10.21. IR (KBr): 1490 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.00 (6H, s, $-CH_3$), 6.91 (1H, t, $J=1.7$ Hz, H_1), 6.98 (2H, dd, $J=1.7$, 7.7 Hz, H_2), 7.29 (1H, t, $J=7.7$ Hz, H_3), 7.09 and 7.63 (8H, each d, AB type, $J=9$ Hz, 4-bromophenyl-H), 7.89 (2H, s, imidazole C2-H). MS (*m/z*): 548 ($M^+ +2$), 546 (M^+).

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References and Notes

1) H. Sasaki and T. Kitagawa, *Chem. Pharm. Bull.*, **31**, 2868 (1983).
2) *a*) H. Sasaki and T. Kitagawa, *Chem. Pharm. Bull.*, **35**, 4747 (1987); *b*) *Idem, ibid.*, **31**, 756 (1983).
3) H. Sasaki and T. Kitagawa, *Chem. Pharm. Bull.*, **35**, 3475 (1987).
4) O. Possel and A. M. van Leusen, *Heterocycles*, **7**, 77 (1977).
5) According to the "Phane Nomenclature," the 1:1 adduct **12** is 12,21-bis(4-bromophenyl)[1]metacyclo-[1](4,5)imidazolo[0]metacyclo[0](5,4)imidazolophane and the 2:2 adduct **13** is 12,21,36,45-tetrakis(4-bromophenyl)[1]metacyclo[1](4,5)imidazolo[0]metacyclo[0](5,4)imidazolo[1]metacyclo[1](4,5)imidazolo[0]-metacyclo[0](5,4)imidazolophane. See: F. Vogtle and P. Neumann, *Tetrahedron*, **26**, 5847 (1970).
6) A. M. van Leusen, R. J. Bouma and O. Possel, *Tetrahedron Lett.*, **1975**, 3487.
7) A. R. Katrizky and A. J. Boulton (ed.), "Advances in Heterocyclic Chemistry," Vol. 12, Academic Press, New York, 1970, p. 144.
8) M. F. Semmelhack, J. J. Harrison, D. C. Young, A. Gutierrez, S. Rafii and J. Clardy, *J. Am. Chem. Soc.*, **107**, 7508 (1985).
9) W. Brügel, "Handbook of NMR Spectral Parameters," Vol. 1, Heyden and Son Ltd., London, 1979, p. 42.
10) It has been reported that the benzene ring substituted with a bulky halogen atom in 9-chloro- and 9-bromo-2,11-dithia[3^2]metacyclophanes can not invert. Therefore, it seems likely that the B ring inversion in **12** can not occur because two imidazole rings substituted with a bulky 4-bromophenyl group are attached to the B ring. See: F. Vogtle and L. Schunder, *Chem. Ber.*, **102**, 2677 (1969).
11) Calculations were based on the following equations:

$$k_c=(\pi/\sqrt{2})[(\nu_A+\nu_B)^2+6J^2]^{1/2}$$

$$\Delta G^{\ddagger}=2.303\times 8.314T_c(10.319-\log k_c+\log T_c)$$

See: P. M. Keehn and S. M. Rosenfeld (ed.), "Cyclophanes: Organic Chemistry, A Series of Monographs," Vol. 45-I, Academic Press, New York, 1983, p. 265.
12) It has been reported that 5-phenyl substitution of imidazole caused a marked bathochromic shift and an increase in the intensity of the bands of the parent molecule. See: H. Bredereck, R. Gompper and F. Reich, *Chem. Ber.*, **93**, 1389 (1960).