Cyclophanes. VII. Synthesis and Structures of Dioxazolo[3²]metacyclo(2,5)thiophenophane and a Higher Homolog[1)]

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The title compound (6) was synthesized by the one-pot coupling reaction of 1,3-bis(2-isocyano-2-tosylethyl)benzene (4) with thiophene-2,5-dicarbaldehyde (5), along with the higher homolog (7). On the basis of proton nuclear magnetic resonance (^{1}H-NMR) spectra at various temperatures, it was considered that (i) the conformational change of 6 at room temperature was strongly restricted because of the observation of very broad signals in both aromatic and aliphatic regions, (ii) the coalescence temperature (T_c) of the methylene proton signals is 69 °C and the energy barrier ($\Delta G^{\neq}$) of the conformational change is calculated to be 69.4 kJ/mol, which is higher than those of the dioxazolo[3²]-metacyclophane (1a) and dioxazolo[3²](2,5)furanometacyclophane (3), and (iii) at −31 °C, 6 exists in two fixed conformers, *i.e.*, *syn* and *anti* forms because of the observation of a set of the oxazole C2-H signals. These results suggest that the rigidity of the thiophene-containing heterophane 6 is due to the bulkiness of the large sulfur atom as well as the presence of a longer carbon–sulfur bond.

Keywords cyclophane; thiophenophane; metacyclophane; conformational analysis; VT-NMR; COSY; isocyanide; thiophene-2,5-dicarbaldehyde; oxazole

Recently, we have reported the synthesis and the conformational properties of [3²]metacyclophane derivatives (**1a**—**c**) annelated with two azole rings (imidazole or oxazole rings) to the two methylene bridges of the parent [3²]-metacyclophane[2)] and the formation of the 1:2 silver triflate complex of trioxazolo[2³]metacyclophane (**2**),[3)] as shown in Fig. 1. In the previous paper,[4)] we synthesized dioxazolo[3²](2,5)furanometacyclophane (**3**) and demonstrated that the conformational rigidity of **3** was reduced compared with that of **1a** because of the smaller bulkiness of the oxygen atom with lone pair as compared with an aromatic carbon–hydrogen bond. Some work has also been reported on the synthesis and the properties of [3²]cyclophanes containing a thiophene ring such as [3²](2,5)thiophenophane and [3²]metacyclo(2,5)thiophenophane-1,12-dione.[5)]

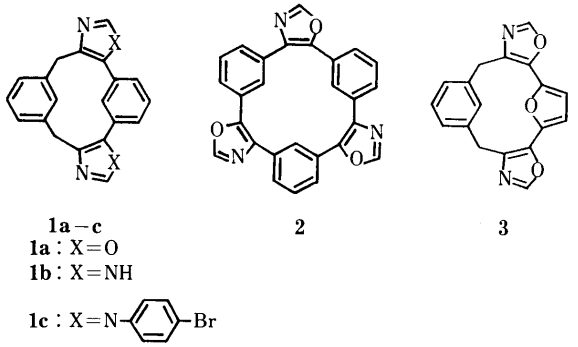


Fig. 1. Diazolo[3²]metacyclophanes (**1a**—**c**), Trioxazolo[2³]metacyclophane (**2**), and Dioxazolo[3²](2,5)furanometacyclophane (**3**)

In this paper, we wish to describe the synthesis and the structures of new thiophene-containing cyclophanes, dioxazolo[3²]metacyclo(2,5)thiophenophane (**6**) and its higher homolog (**7**). The preparation of **6** and **7** is outlined in Chart 1. Thus, the one-pot coupling reaction of 1,3-bis(2-isocyano-2-tosylethyl)benzene (**4**) with thiophene-2,5-dicarbaldehyde (**5**)[6)] in the presence of 2 eq of sodium ethoxide in refluxing ethanol for 2 h afforded **6** as an 1:1 adduct in 27% yield, together with **7** as a 2:2 adduct in 4% yield. The reference compound (**9**) was prepared by the reaction of 1-tosylethyl isocyanide (**8**)[7)] with **5** under the same conditions. The structures of the cyclophanes (**6** and **7**) were confirmed by the spectroscopic properties and analytical data. The infrared (IR) spectra of **6** and **7** show the characteristic absorption of oxazole $\nu_{C2\text{-}H}$ at 3132 cm^{-1} and 3112 cm^{-1}, respectively and the mass spectra (MS) show the expected molecular ions (*m/z*) at 320 (M^+) and

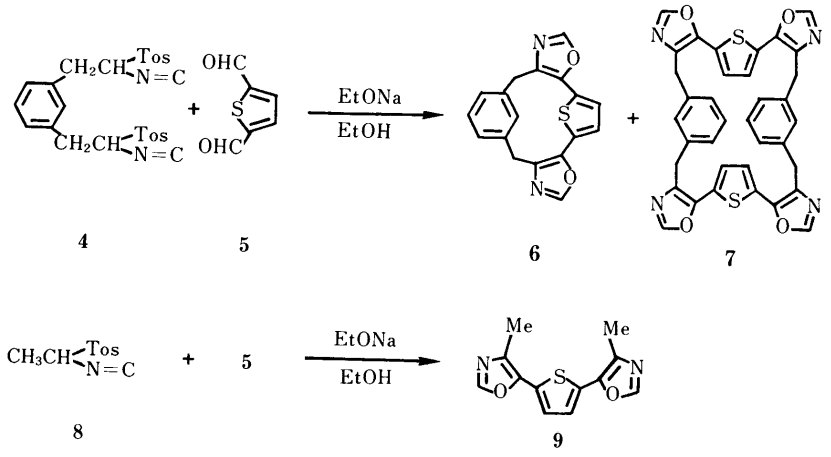
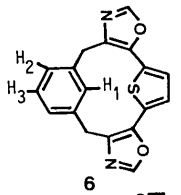
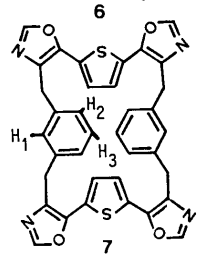
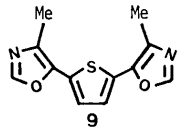


Chart 1

TABLE I. ^{1}H-NMR Data for Dioxazolo[3^2]metacyclo(2,5)thiophenophane (**6**), Tetraoxazolo[3^4]metacyclo(2,5)thiophenophane (**7**), and Reference Compound (**9**) (400 MHz, DMSO-d_6)

Structure Compd. No.	Temp. (°C)	CH_3–	–CH_2–	Thiophene-H	Benzene-H	Oxazole C2-H
 **6**	84	—	3.79 (4H, br s)	6.97 (2H, s)	6.50 (1H, br s, H_1), 6.81 (2H, dd, J=7.6, 1.7 Hz, H_2), 7.01 (1H, t, J=7.6 Hz, H_3)	8.26 (2H, s)
 **7**	24	—	4.00 (8H, s)	7.06 (4H, s)	6.86 (2H, br s, H_1), 7.27 (4H, m, H_2), 7.29 (2H, m, H_3)	8.39 (4H, s)
 **9**	24	2.35 (6H, s)	—	7.39 (2H, s)	—	8.36 (2H, s)

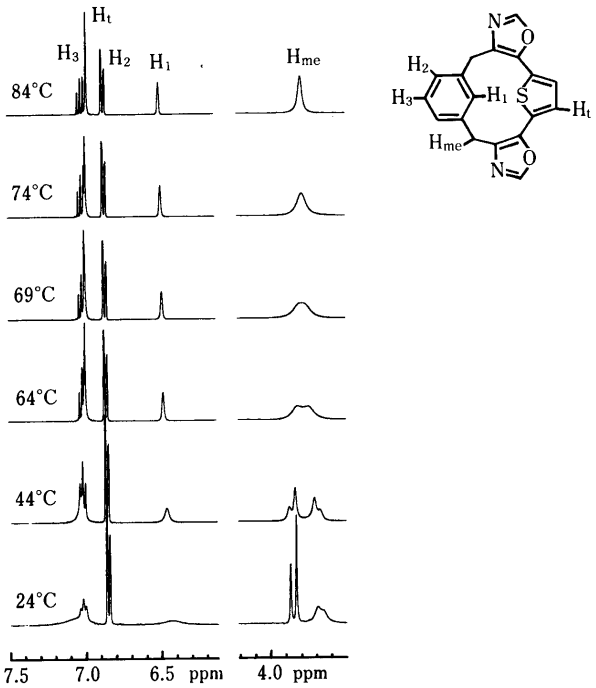


Fig. 2. VT-NMR Spectra and Assignment of Spectrum at 84 °C of Dioxazolo[3^2]metacyclo(2,5)thiophenophane (**6**) in DMSO-d_6

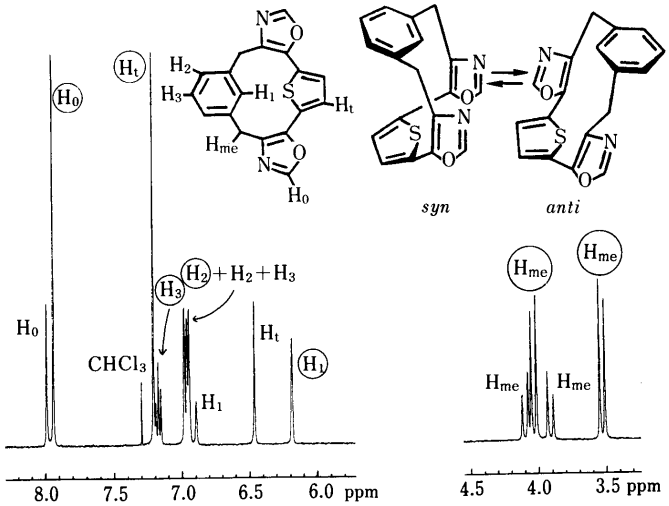


Fig. 3. ^{1}H-NMR Spectrum of Dioxazolo[3^2]metacyclo(2,5)thiophenophane (**6**) in $CDCl_3$ at −31 °C and Conformational Flipping between *syn* and *anti* Forms

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

640 (M^+), respectively.

Figure 2 shows the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **6** in dimethyl sulfoxide (DMSO)-d_6 at various temperatures between 24 °C and 84 °C. The spectrum at 24 °C suggests that the conformational change of **6** is strongly restricted because of the observation of the broad absorption of both aromatic and aliphatic protons. When the temperature was raised stepwise to 84 °C, the aromatic proton signals began to sharpen above 34 °C and split sufficiently to permit assignment at 84 °C. Moreover, the methylene signals of **6** appeared as a singlet at 84 °C. The aromatic proton signals of **6** at 84 °C were assigned from the coupling pattern and the intensity of signals, as summarized in Table I. In contrast, all proton signals of **7** were sharp at 24 °C, so that the cyclophane **7** is more flexible than **6**. The assignments of the signals of **7** are summarized in Table I, along with the ^{1}H-NMR spectral data for the reference compound **9**.

Interestingly, at −31 °C in $CDCl_3$, the ^{1}H-NMR spectrum of **6** showed the existence of two fixed conformers because of the observation of a set of oxazole C2-H signals in the ratio of about 5 : 2, as shown in Fig. 3. Figure 4 shows the two-dimensional proton–proton chemical shifts correlation (COSY) spectrum in $CDCl_3$ at −31 °C. Since the cross peak between major methylene signals and the broad

singlet at δ 6.18 was observed, the benzene proton signals, H_1, H_2, and H_3, of the major conformer, together with those of the minor conformer, were assigned as shown in Fig. 3. The two conformers could be characterized on the basis of the following considerations. (i) In the case of the major conformer, the H_1 (δ 6.18) signal shows an upfield shift compared with the corresponding signal of *m*-xylene (δ 6.89)[8] and the H_t (δ 7.21) signal is in the usual range for thiophene C3-H (δ 6.99).[9] (ii) In the case of the minor conformer, the H_1 (δ 6.89) signal is in the usual range for arene hydrogen (δ 6.89—7.05 in *m*-xylene)[8] and the signal of H_t (δ 6.46) shows an upfield shift compared with the corresponding protons of **9** and thiophene.[9] Thus, it is concluded that the major and minor conformers are the *anti* and *syn* forms (Fig. 3), respectively.

Since the coalescence temperature (T_c) of the methylene protons signal of **6** is 69 °C (Fig. 2), the energy barrier ($\Delta G^{\neq}$) of the conformational change shown in Fig. 3 is calculated to be 69.4 kJ/mol (16.6 kcal/mol),[10] which is higher than those of dioxazolo[3²]metacyclophane (**1a**) (64.5 kJ/mol)[2a] and dioxazolo[3²](2,5)furanometacyclophane (**3**) (58.0 kJ/mol).[4] Thus, **6** is more rigid than **1a** and **3** because of the bulkiness of the large sulfur atom as well as the presence of the longer carbon–sulfur bond as compared with the aromatic carbon–hydrogen bond in **1a** and the oxygen atom of **3**.[5]

The ultraviolet (UV) spectra of the cyclophanes (**6** and **7**) and reference compound (**9**) in ethanol are shown in Fig. 5. Compound **9** shows a broad, high-intensity absorption around 334 nm ($\log\varepsilon = 4.43$) probably because of the presence of an extended conjugated system over three aromatic rings of the 2,5-bis(5-oxazolyl)thiophene moiety. The absorption band of **6** (λ shoulder = 270 nm) exhibits large hyperchromic shifts (64 nm) and a significant reduction of intensity in the region between 280 nm and 340 nm as compared with those of **9**. In contrast, the absorption intensity of **7** is slightly reduced compared with that of **9** in the whole region. These observations suggest that the three aromatic rings, *i.e.*, the 2,5-bis(5-oxazolyl)thiophene moiety, of the large cyclophane **7** can take a more planar conformation as compared with those of the small cyclophane **6**. In the light of corey pauling koltum (CPK) molecular models, it was considered that the cyclophane **7** has a hydrophobic cavity (diameter *ca.* 0.6 nm) surrounded by 2,5-bis(5-oxazolyl)-thiophene and benzene walls. Further studies on the properties of the novel heterocyclophane **7** are in progress.

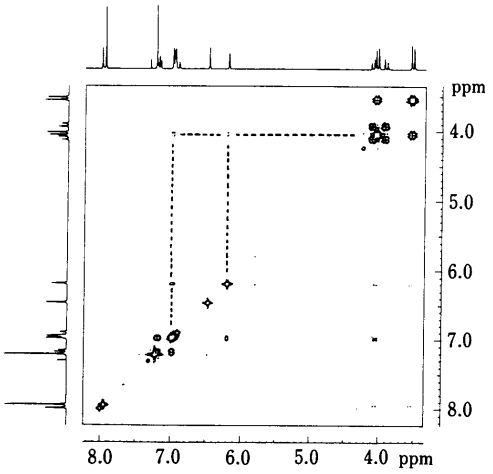


Fig. 4. COSY Spectrum of **6** in $CDCl_3$ at −31 °C

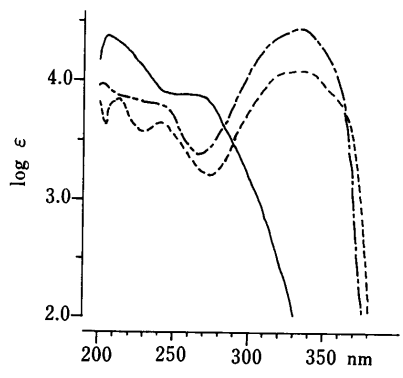


Fig. 5. UV Spectra of **6** (——), **7** (– – – –), and **9** (—·—·—) in EtOH

In conclusion, the one-pot coupling reaction of 1,3-bis(2-isocyano-2-tosylethyl)benzene (**4**) with thiophene-2,5-dicarbaldehyde (**5**) afforded the small rigid cyclophane **6** and the large flexible cyclophane **7**. On the basis of the variable-temperature (VT)-NMR spectra, the conformational mobility of **6** was found to be more restricted than those of dioxazolo[3²]metacyclophane (**1a**) and dioxazolo[3²](2,5)-furanometacyclophane (**3**) because of the bulkiness of the sulfur atom as well as the presence of the longer carbon–sulfur bond. Furthermore, it was suggested that at −31 °C **6** exists in two fixed conformers, which can be assigned as *syn* and *anti* forms.

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 270-30 infrared spectrophotometer. ^{1}H-NMR and VT-NMR spectra were measured on a Bruker AM-400 (400 MHz) instrument using tetramethylsilane as an internal reference. MS were measured on a Hitachi M-60 mass spectrometer. UV spectra were measured on a Hitachi 150-20 spectrophotometer.

Dioxazolo[3²]metacyclo(2,5)thiophenophane (6) and Tetraoxazolo[3⁴]-metacyclo(2,5)thiophenophane (7) A solution of thiophene-2,5-dicarbaldehyde (**5**) (1.40 g, 10 mmol) in EtOH (100 ml) was added dropwise to a stirred suspension of 1,3-bis(2-isocyano-2-tosylethyl)benzene (**4**) (4.92 g, 10 mmol) and EtONa (Na; 0.46 g, 20 mmol) in EtOH (400 ml). After the mixture had been refluxed for 2 h, the resulting mixture was cooled to 5 °C, and filtered with suction to collect a yellowish precipitate. Then, the precipitate was recrystallized from $CHCl_3$ to yield 0.13 g (4%) of **7**, pale yellow prisms. mp 293—294 °C. IR (KBr): 3112 (oxazole $\nu_{C2\text{-}H}$) cm^{-1}. MS *m/z*: 640 (M^+). *Anal.* Calcd for $C_{36}H_{24}N_4O_4S_2 \cdot 1/2H_2O$: C, 65.74; H, 3.83; N, 8.52. Found: C, 65.61; H, 3.58; N, 8.40. The filtrate was concentrated under reduced pressure, and then a mixture of AcOEt (200 ml) and water (100 ml) was poured onto the residue. The organic layer was separated, washed with three 50 ml portions of brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel with $CHCl_3$ to give a crude product, which was recrystallized from $CHCl_3$ to yield 0.86 g (27%) of **6**, colorless needles. mp 204—205 °C. IR (KBr): 3132 (oxazole $\nu_{C2\text{-}H}$) cm^{-1}. MS *m/z*: 320 (M^+). *Anal.* Calcd for $C_{18}H_{12}N_2O_2S$: C, 67.48; H, 3.78; N, 8.74. Found: C, 67.39; H, 3.73; N, 8.60.

2,5-Bis(4-methyl-5-oxazolyl)thiophene (9) According to the procedure described above for **6** and **7**, the reaction of 1-tosylethyl isocyanide (**8**) (4.18 g, 20 mmol) with **5** (1.40 g, 10 mmol) in the presence of EtONa (Na; 0.46 g, 20 mmol) gave a crude product, which was recrystallized from benzene to yield 1.88 g (76%) of **9**, pale orange prisms. mp 145—146 °C. IR (KBr): 3088 (oxazole $\nu_{C2\text{-}H}$) cm^{-1}. MS *m/z*: 246 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.52; H, 4.00; N, 11.44.

References and Notes

1) Part of this work was presented at The 38th Meeting of the Kinki Branch, Pharmaceutical Society of Japan, Osaka, November 1988, p.

25.
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9) A. R. Katritzky and C. W. Rees, ed. "Comprehensive Heterocyclic Chemistry," Vol. 4, Pergamon Press, Oxford, 1984, p. 7.
10) Calculations were based on the following equations:

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

$$\Delta G^*=2.303\times 8.314T_c\,(10.319-\log k_c+\log T_c)$$

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.