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Cyclophanes. V. Synthesis and Conformational Analysis of Novel Heterocyclophanes Containing 2,5-Bis(5-oxazolyl)furan Units

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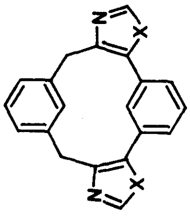
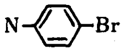
Two novel heterocyclophanes, dioxazolo$[3^2]$(2,5)furanometacyclophane (5) and the higher homolog (6) possessing 2,5-bis(5-oxazolyl)furan units, were synthesized by the one-pot coupling reaction of 1,3-bis(2-isocyano-2-tosylethyl)benzene (3) with furan-2,5-dicarbaldehyde (4). On the basis of the variable-temperature nuclear magnetic resonance (VT-NMR) spectra of 5, the conformations in solution both at room temperature and at $-18\,°C$ could be assigned as a *syn* form, and the energy barrier ($\Delta G^{\neq}$) for the conformational flipping at the coalescence temperature ($T_c = 12\,°C$) was determined to be 58.0 kJ/mol, which is lower than that of dioxazolo$[3^2]$metacyclophane (1a). Therefore, it was suggested that the oxygen atom of 5 with its lone pair is less bulky with respect to the conformational change than the aromatic carbon–hydrogen bond of 1a.

Keywords cyclophane; metacyclophane; furanophane; conformational analysis; VT-NMR; oxazole; isocyanide; furan-2,5-dicarbaldehyde

Since the synthesis of $[2^2]$(2,5)furanophane by means of the Hofmann elimination was reported in 1960,1) the preparation and conformational properties of furan-containing heterocyclophanes have been investigated in detail because of the high reactivity of the π-excessive furan ring and the interesting conformational characteristics.2) However, these reports mainly dealt with $[2^2]$ type heterophanes and few studies were done on the synthesis of furan-containing $[3^2]$cyclophanes.3) In a series of studies on the $[3^2]$cyclophanes, we previously reported the synthesis of diazolo$[3^2]$metacyclophanes, *i.e.*, dioxazolo$[3^2]$metacyclophane (**1a**)4) and diimidazolo$[3^2]$metacyclophanes (**1b** and **1c**),5) as shown in Fig. 1. Moreover, it was found that the annelation of two azole rings to the two methylene bridges of the parent $[3^2]$metacyclophane (**2**) caused the energy barrier of the conformational flipping of **1a, c** to be higher than that of **2**.4,5)



1

Compd. No.	X
1a	O
1b	NH
1c	

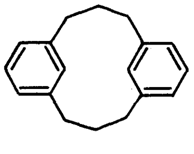


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Fig. 1. Diazolo$[3^2]$metacyclophanes (**1a—c**) and $[3^2]$Metacyclophane (**2**)

In this paper, we wish to report the synthesis and conformational analysis of two novel heterocyclophanes, *i.e.*, dioxazolo$[3^2]$(2,5)furanometacyclophane (**5**) and tetraoxazolo$[3^4]$(2,5)furanometacyclophane (**6**) possessing 2,5-bis(5-oxazolyl)furan units. The preparation of **5** and **6** is outlined in Chart 1.6) Thus, the one-pot coupling reaction of 1,3-bis(2-isocyano-2-tosylethyl)benzene (**3**) with furan-2,5-dicarbaldehyde (**4**) in refluxing ethanol for 2 h in the presence of 2 eq of sodium ethoxide afforded a mixture of the products (**5** and **6**), which was chromatographed on silica gel. Elution with AcOEt–$CHCl_3$ (1 : 9) and AcOEt–$CHCl_3$ (1 : 1) gave **5** (15%) and **6** (16%), respectively. The reference compound (**8**) was prepared in 48% yield by the reaction of 2 eq of 1-tosylethyl isocyanide (**7**)7) with **4** under the same conditions, as shown in Chart 1.

The infrared (IR) spectra of **5** and **6** show the characteristic absorption of oxazole ν_{C2-H} at 3150 cm^{-1},8) and the mass spectra (MS) show the expected molecular ions at 304 (M^+)

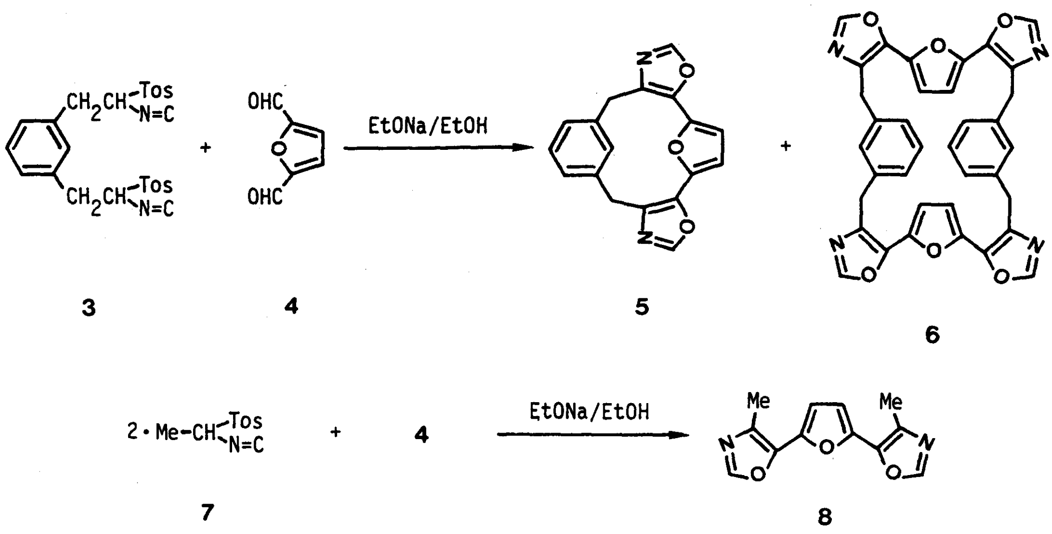
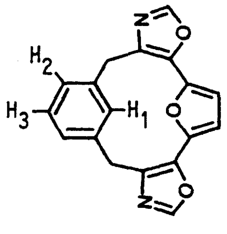
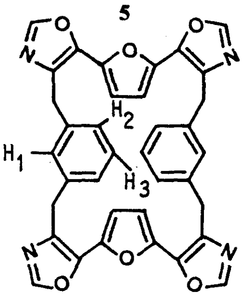
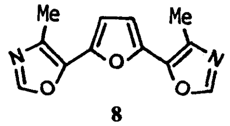


Chart 1

Table I. ^{1}H-NMR Data for Dioxazolo[3^2](2,5)furanometacyclophane (**5**), Tetraoxazolo[3^4](2,5)furanometacyclophane (**6**), and Reference Compound (**8**) (400 MHz, $CDCl_3$)

Structure Compd. No.	Temp. (°C)	CH_3–	–CH_2–	Furan-H	Benzene-H	Oxazole C2-H
 **5**	24	—	4.16 (4H, br s)	6.39 (2H, s)	7.00 (2H, m, H_2) 7.05 (1H, m, H_3) 7.73 (1H, br s, H_1)	7.80 (2H, s)
	−18	—	4.12 (2H, d, J=16.6 Hz) 4.24 (2H, d, J=16.6 Hz)	6.42 (2H, s)	7.03 (2H, m, H_2) 7.08 (1H, m, H_3) 7.77 (1H, br s, H_1)	7.86 (2H, s)
 **6**	24	—	3.99 (8H, s)	6.65 (4H, s)	6.84 (2H, br s, H_1) 6.92 (4H, dd, J=7.6, 1.6 Hz, H_2) 7.09 (2H, t, J=7.6 Hz, H_3)	7.76 (4H, s)
 **8**	24	2.48 (6H, s)	—	6.65 (2H, s)	—	7.80 (2H, s)

and 608 (M^+). The proton nuclear magnetic resonance (^{1}H-NMR) spectra of **5** and **6** were assigned from the coupling pattern and the intensity of signals and by comparison with those of **8**, as summarized in Table I. At 24 °C the H_1 signal (δ 7.73) of **5** (broad singlet) shows a downfield shift compared with the corresponding signal of *m*-xylene (δ 6.88—7.05).[9] It was suggested that the H_1 is located close to the oxygen atom of the opposite furan ring, averaged on the NMR time scale. On the other hand, the furan ring protons of **5** show a slight upfield shift compared with the corresponding protons of the reference compound (**8**). This shift was attributed to the shielding effect of the opposite benzene ring. These findings suggested that the preferred conformation of **5** in solution at room temperature could be assigned as a *syn* form like **1a**, **b** and **2**.[4,5] Furthermore, the variable-temperature (VT)-NMR behavior of **5** was studied. Figure 2 shows the VT-NMR spectra of **5** in $CDCl_3$ at various temperatures between −18 °C and 24 °C. At −18 °C the conformational flipping of **5** is frozen, because the methylene signals are observed as a sharp AB quartet. The H_1 (δ 7.77) and the furan ring proton (δ 6.42) signals at −18 °C are similar to the corresponding signals at room temperature, as summarized in Table I. These facts suggest that the conformation of **5** in solution at −18 °C could be assigned as a *syn* form, like the preferred conformation at room temperature. Since the coalescence temperature (T_c) of the methylene signal is 12 °C, the value of the energy barrier ($\Delta G^{\neq}$) for conformational flipping (Fig. 2) is calculated to be 58.0 kJ/mol (13.9 kcal/mol),[10] which is lower than that of dioxazolo[3^2]metacyclophane (**1a**) [T_c = 38 °C, $\Delta G^{\neq}$ = 64.5 kJ/mol (15.4 kcal/mol)].[4] This fact suggested that the oxygen atom with its lone pair in the furan ring is less bulky with respect to the conformational change than the aromatic carbon–hydrogen bond.[11] On the other hand, the benzene and the furan proton signals of the higher homolog (**6**) exhibit similar δ-values to the corresponding proton signals of *m*-xylene and **8**, respectively.

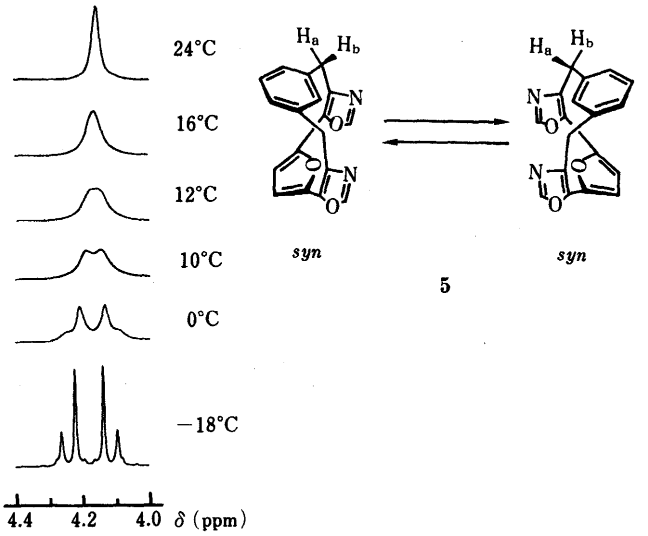


Fig. 2. VT-NMR Spectra of Aliphatic Regions of **5** at Various Temperatures and Conformational Flipping

The ultraviolet (UV) spectra of the cyclophanes (**5** and **6**) and the reference compound (**8**) in ethanol are shown in Fig. 3. Compound **8** shows a broad absorption around 320 nm (log ε = 4.40) because of the presence of an extended conjugated system over three aromatic rings of the 2,5-bis(5-oxazolyl)furan unit. The absorption band of **5** (λ_{max} =

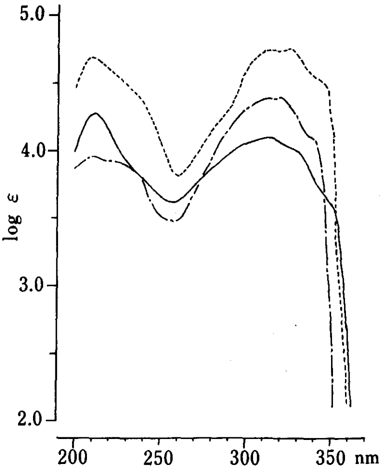


Fig. 3. UV Spectra of 5 (——), 6(------), and 8 (—–—) in EtOH

313 nm) exhibits a hypsochromic shift (7 nm) and a significant reduction of intensity in the region between 275 and 345 nm as compared with that of **8** ($\lambda_{max}=320$ nm). On the other hand, the absorption intensity of **6** is higher than that of **8** over the whole region. These facts suggest that the higher homolog **6**, as well as **8**, retains the coplanarity of the 2,5-bis(5-oxazolyl)furan unit as compared with **5**. On the basis of ^{1}H-NMR and UV spectroscopies, it is suggested that the structure of the higher homolog **6** involves simple linking of the two parts, that is, the *m*-xylene and 2,5-bis(5-oxazolyl)furan moieties. Based on a consideration of Corey Pauling Koltum (CPK) models, the cyclophane **6** was considered to have a rigid hydrophobic cavity (diameter *ca.* 0.6 nm) and two 2,5-bis(5-oxazolyl)furan units as a metal binding site at the periphery of the cyclophane ring. Further studies on the properties of this novel heterocyclophane (**6**) are in progress.

In conclusion, the one-pot coupling reaction of **3** with **4** readily afforded two novel furan-containing heterocyclophanes, dioxazolo[3^2](2,5)furanometacyclophane (**5**) and the higher homolog (**6**). On the basis of the VT-NMR spectra of **5**, the conformations in solution both at room temperature and at −18 °C could be assigned as a *syn* form. Moreover, the $\Delta G^{\neq}$ value for conformational flipping of **5** is lower than that of **1a**, which is due to a difference of the bulkiness of the oxygen atom with its lone pair in the furan ring of **5** and the aromatic carbon–hydrogen bond of **1a**.

Experimental

All melting points were taken on a Yanagimoto micro melting point determination apparatus and are uncorrected. IR spectra were recorded on a Hitachi 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 RMU-6MG mass spectrometer. UV spectra were measured on a Hitachi 150-20 spectrophotometer.

Dioxazolo[3^2](2,5)furanometacyclophane (5) and Tetraoxazolo[3^4](2,5)furanometacyclophane (6) A solution of furan-2,5-dicarbaldehyde (**4**) (1.24 g, 10 mmol) in EtOH (100 ml) was added dropwise to a stirred suspension of 1,3-bis(2-isocyano-2-tosylethyl)isocyanide (**3**) (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 solvent was removed under reduced pressure, and then a mixture of AcOEt (200 ml) and water (50 ml) was poured onto the residue. The organic layer was separated, washed with three 50 ml portions of brine, and then dried over anhydrous $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel with (i) a mixture of AcOEt–$CHCl_3$ (1 : 9) and (ii) a mixture of AcOEt–$CHCl_3$ (1 : 1). (i) Concentration of the AcOEt–$CHCl_3$ (1 : 9) eluate gave a crude product, which was recrystallized from $CHCl_3$ to yield 0.46 g (15%) of **5**, colorless prisms. mp 140—141 °C. IR (KBr): 3150 (oxazole $\nu_{C2\text{-}H}$) cm^{-1}. MS *m/z*: 304 (M$^+$). *Anal.* Calcd for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.97; N, 9.21. Found: C, 71.24; H, 3.80; N, 9.18. (ii) Concentration of the AcOEt–$CHCl_3$ (1 : 1) eluate gave a crude product, which was recrystallized from $CHCl_3$ to yield 0.49 g (16%) of **6**, colorless prisms. mp 298—300 °C. IR (KBr): 3150 (oxazole $\nu_{C2\text{-}H}$) cm^{-1}. MS *m/z*: 608 (M$^+$). *Anal.* Calcd for $C_{36}H_{24}N_4O_6$: C, 71.05; H, 3.97; N, 9.21. Found: C, 70.89; H, 4.01; N, 9.13.

2,5-Bis(4-methyl-5-oxazolyl)furan (8) According to the procedure described above for **5** and **6**, the reaction of 1-tosylethyl isocyanide (**7**) (4.2 g, 20 mmol) with **4** (1.24 g, 10 mmol) in the presence of EtONa (Na; 0.46 g, 20 mmol) gave a crude product, which was recrystallized from a mixture of CH_2Cl_2–benzene (1 : 1) to yield 1.1 g (48%) of **8**, pale yellow prisms. mp 137—138 °C. IR (KBr): 3150 (oxazole $\nu_{C2\text{-}H}$) cm^{-1}. MS *m/z*: 230 (M$^+$). *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.35; H, 4.20; N, 12.07.

References and Notes

1) H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.*, **82**, 1428 (1960).

2) P. M. Keehn and S. M. Rosenfeld (ed.), "Cyclophanes: Organic Chemistry, A Series of Monographs," Vol. 45-II, Academic Press, New York, 1983, p. 359.

3) Y. Miyahara, T. Inazu, and T. Yoshino, *Chem. Lett.*, **1980**, 397; The synthesis of [3^2] (2,5) furanometacyclophane was presented by the following group. T. Shinmyozu, T. Shima, Y. Hirai, T. Inazu, and T. Yoshino, Abstracts of Papers (II), The 6th Joint Symposium on Pure Organic Chemistry (Japan), Kyoto, Oct. 1982, p. 112. To the best of our knowledge, the details have not been published yet.

4) H. Sasaki and T. Kitagawa, *Chem. Pharm. Bull.*, **35**, 4747 (1987).

5) H. Sasaki and T. Kitagawa, *Chem. Pharm. Bull.*, **36**, 1593 (1988); H. Sasaki, K. Ogawa, Y. Iijima, T. Kitagawa, and T. Shingu, *ibid.*, **36**, 1990 (1988).

6) It has been reported that the reaction of 1-alkylated tosylmethyl isocyanides with aromatic aldehydes afforded 4,5-disubstituted oxazoles. See: O. Possel and A. M. van Leusen, *Heterocycles*, **7**, 77 (1977).

7) A. M. van Leusen, R. J. Bouma, and O. Possel, *Tetrahedron Lett.*, **1975**, 3487.

8) A. R. Katrizky and A. J. Boulton, "Advances in Heterocyclic Chemistry," Vol. 17, Academic Press, New York, 1974, p. 163.

9) W. Brügel, "Handbook of NMR Spectral Parameters," Vol. 1, Heyden and Son Ltd., London, 1979, p. 42.

10) Calculation was based on the following equations:

$$k_c=(\pi/\sqrt{2})[(\nu_A+\nu_B)^2+6J^2]^{1/2}$$
$$\Delta G^{\neq}=2.303\times 8.314T_c(10.319-\log k_c+\log T_c)$$

See: Ref. 2, Vol. 45-I, p. 265.

11) It has been demonstrated that in the case of the furan-containing cyclophanes such as [2^2] (1,5) furanoparacyclophane and [2^2] (2,5) furanophane, compared to [2^2] metaparacyclophane and [2^2] metacyclophane, respectively, the steric bulk of the lone pair on the oxygen atom is smaller than that of a carbon–hydrogen bond. See: S. Rosenfeld and P. M. Keehn, *Tetrahedron Lett.*, **1973**, 4021; I. Gault, B. J. Price, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, **1967**, 540.