Communications to the Editor

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SYNTHESIS AND CONFORMATIONAL PROPERTIES OF DIIMIDAZOLO[3²]METACYCLOPHANE AND HOMOLOGS[1)]

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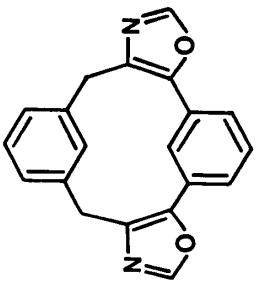
Diimidazolo[3²]metacyclophane (5a), a novel [3²]metacyclophane-diene (4) derivative, was synthesized by the ring transformation of the oxazole rings of dioxazolo[3²]metacyclophane (1a) to imidazole rings. On the basis of proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy, the preferred conformation of 5a in solution at room temperature could be assigned as a syn form.

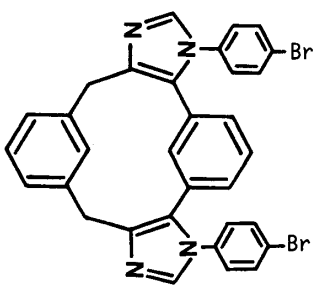
KEYWORDS —— cyclophane; metacyclophane; metaparacyclophane; ring transformation; oxazole; imidazole; conformational analysis

Previously, we have reported the synthesis and the conformational properties of diazolo[3²]metacyclophanes such as dioxazolo[3²]metacyclophane (1a)[2)] and 5,14-bis(4-bromophenyl)diimidazolo[3²]metacyclophane (2).[3)] The structural feature of these cyclophanes (1a and 2) as novel [3²]metacyclophane-diene (4)[4)] derivatives is to have two azole rings fused on the two methylene bridges of parent [3²]metacyclophane (3). The conformation of 1a in solution at room temperature is syn like 3.[4)] As expected, the energy barrier of the conformational change of 1a is higher than that of 3 because of the annelation of two oxazole rings. Similarly, the mobility of the cyclophane benzene rings of 2 annelated with two imidazole rings was more strongly restricted than that of 3. However, the effect of the imidazole ring on the conformation and the conformational rigidity could not be directly estimated because of further substitution of bulky 4-bromophenyl group to the imidazole rings at 1 position.

Here we describe the synthesis of diimidazolo[3²]-metacyclophane (5a) and homologous cyclophanes (5b and 5c)[6)] annelated with two non-substituted imidazole rings to the two methylene bridges of 3 by the ring transformation[7)] of the oxazole



1a



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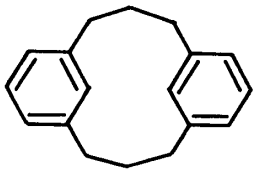

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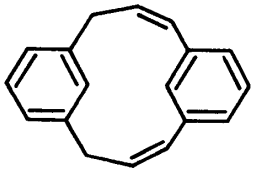

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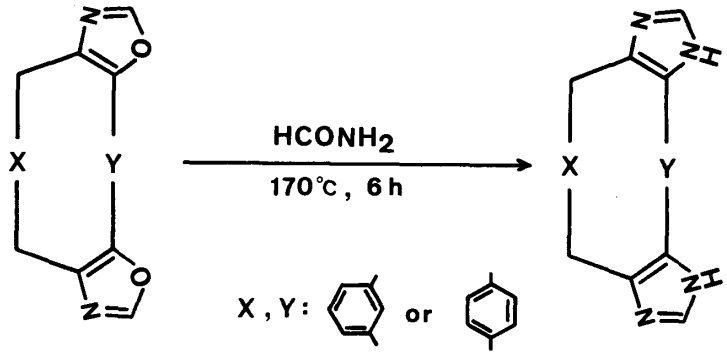
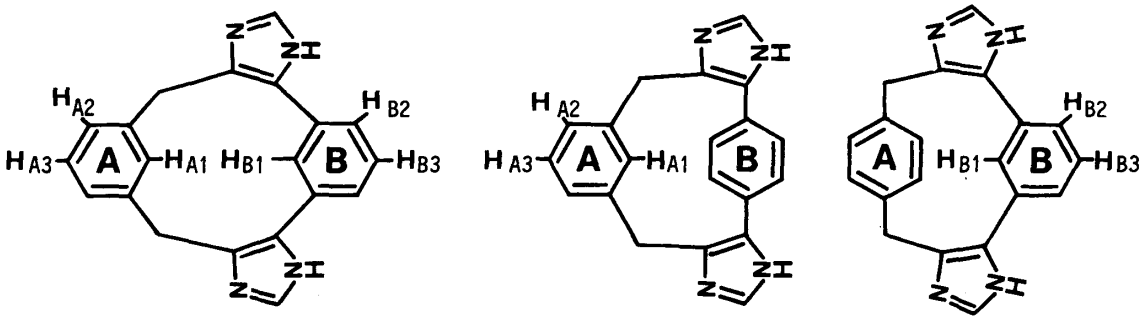


1 and 5	a	b	c
X:	meta	meta	para
Y:	meta	para	meta

Table I. ^{1}H-NMR Spectral Data of Diimidazolo[3^2]cyclophanes (5a-c) (400MHz, DMSO-d_6)

Compd. No.	$-CH_2-$	A ring-H	B ring-H	Imidazole C2-H
5a	4.03(4H, s)	6.74(2H, dd, J=6.6 and 1.6Hz, H_{A2}) 6.82(1H, t, J=6.6Hz, H_{A3}) 7.48(1H, br s, H_{A1})	6.49(1H, br s, H_{B1}) 7.00(2H, dd, J=7.7 and 1.7Hz, H_{B2}) 7.13(1H, t, J=7.7Hz, H_{B3})	7.84(2H, s)
5b	3.70(4H, s)	6.27(1H, br s, H_{A1}) 6.53(2H, dd, J=7.6 and 1.6Hz, H_{A2}) 6.76(1H, t, J=7.6Hz, H_{A3})	6.80(4H, s)	7.55(2H, s)
5c	3.69(4H, s)	6.79(4H, s)	5.40(1H, br s, H_{B1}) 6.92(2H, dd, J=7.6 and 1.7Hz, H_{B2}) 7.17(1H, t, J=7.6Hz, H_{B3})	7.54(2H, s)

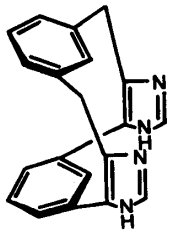


5a 5b 5c

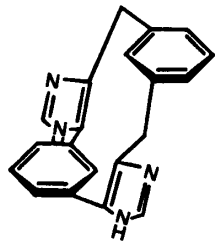
rings of dioxazolo[3²]metacyclophane (1a) to imidazole rings and the conformational properties of 5 on the basis of ^{1}H-NMR spectra. Typically, cyclophane 5a was prepared by the treatment of 1a (10 mmol) in formamide (20ml) for 6 h at 170°C. After the mixture was cooled to 5°C, the obtained precipitate was filtered and recrystallized from methanol to afford a pure product [mp 272-275°C (dec.)] in 88% yield.[8] The analogous cyclophanes (5b and 5c) were synthesized by the same ring transformation procedure in 63% and 65% yields,[8] respectively. Their infrared (IR) spectra indicate the characteristic broad absorption[9] of imidazole associated NH bond at 3500-2200cm^{-1} and the mass spectra (MS) show the appropriate molecular ions (M^+). The ^{1}H-NMR signals of 5a were assigned on the basis of the two-dimensional proton-proton chemical shift correlation (COSY) spectrum in dimethylsulfoxide (DMSO)-d_6. The ^{1}H-NMR spectra of homologs 5b and 5c were readily assigned from the coupling pattern and the intensity of signals and by comparison with those of acyclic reference compounds (6),[10] as summarized in Table I.

Cyclophane 5a undergoes rapid conformational change in solution at room temperature because the methylene signal appears as a sharp singlet. The observation of high-field shift of inner aryl protons is generally useful for determination of the preferred conformation of metacyclophane derivatives, but in the light of the CPK molecular models, it appeared that the corresponding protons (H_{A1} and H_{B1}) of 5a were strongly affected by both the anisotropic effect of imidazole rings and the electrostatic effect of the nitrogen atoms. As shown in Table I, the inner aryl proton of the B ring (H_{B1}) was observed as a broad singlet at δ 6.49 which was an allowable value for an inner aryl proton of an anti conformer. On the other hand, another A ring proton (H_{A1}) appeared as a broad singlet at δ 7.48, which was too low for the conformation of 5a to be assigned as an anti conformer even if the H_{A1} was affected by those effects. The H_{A2} and H_{A3}, which were little affected by those effects, were observed at slightly higher field than those of the corresponding protons of m-xylene (δ 6.88-7.05).[11] Judging from these findings, the preferred conformation of 5a in solution at room temperature can be assigned as a syn form. Both the H_{A1} (δ 7.48) and the H_{B1} (δ 6.49) of 5a were observed at higher field than the corresponding protons (δ 7.77 and δ 6.98, respectively) of 1a.[2a] This trend suggested that the inner aryl protons was deshielded more strongly by the electronegative oxygen atoms of 1a than by the nitrogen atoms of 5a.

Since the methylene and para-substituted benzene proton signals of diimidazolo[3²]metaparacyclophane (5b) and diimidazolo[3²]parametacyclophane (5c) appear as sharp singlets, 5b and 5c undergo rapid conformational flipping in solution at room temperature. As shown in Table I, the H_{B1} (δ 5.40) of 5c appeared at higher field than the H_{A1} (δ 6.27) of 5b. This suggested that the difference of the relative positions, averaged on NMR time scale, between the H_{B1} of 5c and the H_{A1} of 5b to the corresponding opposite benzene ring was caused by the difference in the fused position with the imidazole rings.



syn



anti

5a

Thus, the convenient ring transformations of the two oxazole rings of dioxazolo[3^2]cyclophanes (1) readily gave diimidazolo[3^2]cyclophanes (5) annelated with two imidazole rings and the preferred conformation of 5a could be assigned as a syn form as well as that of 1a fused with two oxazole rings.

REFERENCES AND NOTES

1) This paper is Part 3 in the series "Cyclophanes". Part 2: Ref. 3.

2) a) H. Sasaki and T. Kitagawa, Chem. Pharm. Bull., 35, 4747(1987); b) H. Sasaki and T. Kitagawa, Chem. Pharm. Bull., 31, 756(1983).

3) H. Sasaki, K. Ogawa, Y. Iijima, T. Kitagawa, and T. Shingu, Chem. Pharm. Bull., in press.

4) The synthesis of 4 was presented by the following group. T. Shinmyozu, T. Inazu, and T. Yosino, Abstracts of Papers(II), The 4th Joint Symposium on Pure Organic Chemistry(Japan), Osaka, Oct. 1978, p. 85.

5) M. F. Semmelhack, J. J. Harison, D. C. Young, A. Gutierrez, S. Rafii, and J. Clardy, J. Am. Chem. Soc., 107, 7508(1985).

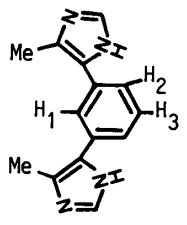
6) According to the nomenclature summarized in ref. 2a, these cyclophanes (5b and 5c) were termed diimidazolo[3^2]metaparacyclophane (5b) and diimidazolo[3^2]parametacyclophane (5c), respectively.

7) H. Bredereck and G. Theilig, Chem. Ber., 86, 88(1953).

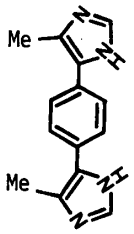
8) Data of 5a: hygroscopic colorless needles. mp 272-275°C(dec.). IR(KBr): 3400-2200(imidazole NH)cm^{-1}. MS m/z: 312(M^+). Anal. Calcd for $C_{20}H_{16}N_4 \cdot 1.4H_2O$: C, 71.45; H, 5.12; N, 16.67. Found: C, 71.67; H, 5.22; N, 16.32.
Data of 5b: hygroscopic colorless needles. mp >300°C. IR(KBr): 3500-2400 (imidazole NH)cm^{-1}. MS m/z: 312(M^+). Anal. Calcd for $C_{20}H_{16}N_4 \cdot H_2O$: C, 72.71; H, 5.49; N, 16.95. Found: C, 72.77; H, 5.65; N, 16.98.
Data of 5c: colorless needles. mp >300°C. IR(KBr): 3500-2200(imidazole NH)cm^{-1}. MS m/z: 312(M^+). Anal. Calcd for $C_{20}H_{16}N_4 \cdot CH_3OH$: C, 73.23; H, 5.73; N, 16.26. Found: C, 73.03; H, 5.73; N, 16.31.

9) A. R. Katrizky and A. J. Boulton, "Advances in Heterocyclic Chemistry," Vol. 12, Academic Press, New York, 1970, p. 144.

10) Compounds (6a and 6b) were prepared by the treatment of 1,3- or 1,4-bis(4-methyl-5-oxazolyl)benzenes (10 mmol)[2a] with formamide (20ml) for 6 h at 170°C.
Data of 6a: colorless prisms. mp 290-291°C(dec.). IR(KBr): 3400-2400(imidazole NH)cm^{-1}. ^{1}H-NMR(400MHz, DMSO-d_6) δ : 2.40(6H, s, -Me), 7.39(1H, dd, J=1.6Hz and 6.9Hz, H_3), 7.45(2H, t, J=6.9Hz, H_2), 7.56(2H, s, imidazole C2-H), and 7.86(1H, br s, H_1). Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.63; H, 5.91; N, 23.52.
Data of 6b: colorless prisms. mp >300°C. IR(KBr): 3300-2400(imidazole NH)cm^{-1}. ^{1}H-NMR(400MHz, DMSO-d_6) δ : 2.39(6H, s, -Me), 7.56(4H, s, phenyl-H), 7.62(2H, s, imidazole C2-H). Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.33; H, 5.94; N, 23.26.



6a



6b

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

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