

Preparation, Conformation and Reaction of Medium-sized [1.n.n]Metacyclophanes

Akihiko Tsuge,* Nobuko Takagi, Takehiro Kakara, Tetsuji Moriguchi, and Kazunori Sakata
 Department of Applied Chemistry, Kyushu Institute of Technology, Tobata-ku, Kitakyushu 804-8550

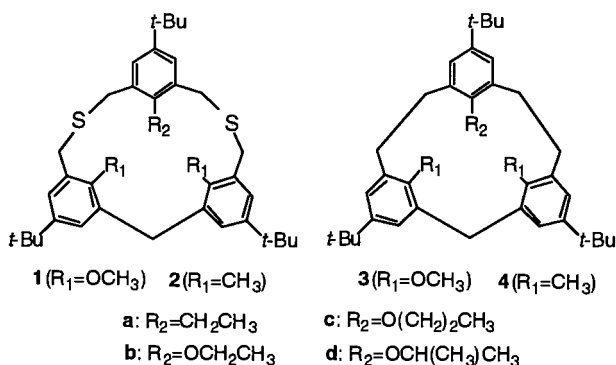
(Received May 15, 2000; CL-000468)

A series of metacyclophanes consisting of three aromatic rings have been prepared. The detailed study of their conformational properties by means of the NMR spectroscopy and the X-ray analysis confirmed the “n,m-alternate(folded-inwards)” and “n,m-alternate(cone-like)” conformations. Two conformers of **3a** exhibited a different reactivity in demethylation by BBr_3 .

Cyclophane compounds dominate a considerable field as components in supramolecular aggregates.¹ One of the most characteristic features of such cyclophane components is their dynamic structure, which is significantly dependent on their molecular structures. To date great attention has been paid to conformational properties of cyclophanes in order to create novel functionalized host molecules.² In course of the research on cyclophane chemistry it has been found out³⁻⁵ that medium-sized cyclophanes exhibit unique conformational properties, since they could have moderate rigidity. Some conformational properties and reactivities of [1.n.n]metacyclophanes carrying the methyl or methoxy substituent at the inner position have already been reported,^{3,4} however, the effect of the large substituent of the cyclophane on its characteristics still remains unclear.

Thus, we describe here the conformation and the reaction of the medium-sized [1.n.n]metacyclophanes which have a larger inner substituent than the ethyl group.

Cyclophanes **1-4** were prepared according to the reported methods.³



1a and **1b** were confirmed to exist in rigid structure up to at 50 °C by their temperature-dependent NMR spectra, suggesting that the other cyclophanes should assume the rigid conformation at room temperature.

Selected chemical shifts in cyclophanes **1** and **3** are summarized in Table 1. Although the chemical shift of two methoxy groups in **1a** was seen in the normal position, its ethyl group showed a remarkable upfield shift. Such a shift can be interpreted in terms of the “folded inwards” conformation in which the ethyl benzene unit folds into the cavity formed by the

Table 1. Selected chemical shifts^a of cyclophanes (**1,3**)

Compd	1		3	
	$R_1(\text{OCH}_3)$	R_2	$R_1(\text{OCH}_3)$	R_2
a	3.57(6H,s)	0.36(3H,t,J=7.50) 0.69(2H,q,J=7.50)	3.39(6H,s)	0.37(3H,t,J=7.53) 0.54(2H,q,J=7.53)
a'			1.64(3H,s) 3.49(3H,s)	0.70(3H,t,J=7.60) 1.52(2H,q,J=7.60)
b	3.59(6H,s)	0.79(3H,t,J=7.50) 3.22(2H,q,J=7.50)	3.67(6H,s)	-0.03(3H,t,J=7.00) 2.68(2H,q,J=7.00)

^aδ / ppm, in CDCl_3 at 27 °C.

other two aromatic rings, thus, **1a** can be assigned to the “3,3-alternate(folded-inwards)” conformation where “n,m-alternate” means that the aromatic ring connected by two bridges whose numbers of the atoms are n and m, respectively, inverts against the other aromatic rings. Such a “folded inwards” conformation can be assured by the X-ray analysis of **1a**⁶ as shown in Figure 1 in which the aromatic ring carrying the ethyl group obviously plunges into the cavity. **1b** is likewise designated as the “3,3-alternate(folded-inwards)” conformation.

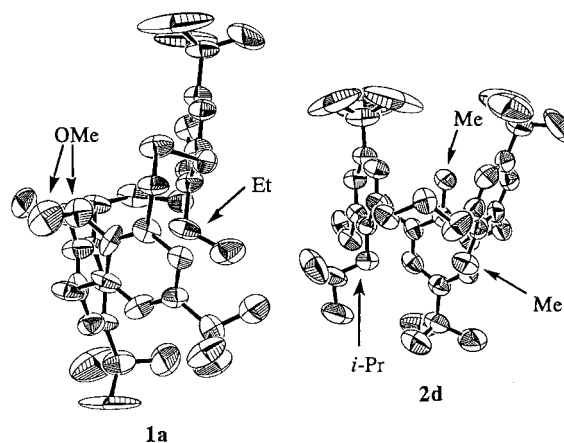


Figure 1. Perspective view of **1a** and **2d**.

Interestingly two kinds of conformations were confirmed for **3a**. One of them can be assigned as the “2,2-alternate (folded-inwards)” conformation (**3a**) characterized by the upfield shifts of the ethyl protons. The other one presents two kinds of resonances for methoxy protons, thus it can be concluded as a “1,2-alternate (folded-inwards)” conformation (**3a'**) in which one aromatic ring with the methoxy group folds into the cavity. The ratio of these two conformers is approximately 1:2. By careful column chromatography (silica gel, Wako C-300, toluene as eluent), two conformers **3a** and **3a'** were separated in 27 and 45% yield, respec-

tively. On the other hand when R_2 is the ethoxy group "2,2-alternate(folded inwards)" is the only conformer to be identified for **3b**. The conformations observed here are summarized in Table 2.

Table 2. Conformations of cyclophanes

Conformation	Cyclophane
3,3-Alternate(folded-inwards)	1a, 1b, 2a
2,2-Alternate(folded-inwards)	3a, 3b, 4a
1,2-Alternate(folded-inwards)	3a', 4a', 4b, 4c
1,3-Alternate(cone-like)	2b, 2c, 2d

As mentioned above the size of the inner substituent is crucial to the conformational properties in these cyclophanes. For the cyclophanes which have two methoxy groups instead of methoxy groups their NMR behaviors were examined in detail as shown in Table 3. A large upfield shift of ethyl protons in **2a** seems to be consistent with the "3,3-alternate(folded-inwards)" conformation.

Table 3. Selected chemical shifts^a of cyclophanes(2,4)

Compd	2		4	
	R_1 (CH ₃)	R_2	R_1 (CH ₃)	R_2
a	2.39(6H,s)	-0.08(3H,t,J=7.63) 0.49(2H,q,J=7.63)	1.64(6H,s)	0.46(3H,t,J=7.33) 1.73(2H,q,J=7.33)
a'			0.49(3H,s) 1.64(3H,s)	0.73(3H,t,J=7.63) 2.05(2H,q,J=7.60)
b	1.58(6H,s)	1.09(3H,t,J=7.02) 3.33(2H,q,J=7.02)	0.49(3H,s) 1.66(3H,s)	1.13(3H,t,J=7.02) 3.40(2H,q,J=7.02)
c	1.28(6H,s)	0.93(3H,t,J=7.32) 1.61-1.65(2H,m) 3.36(2H,t,J=6.71)	0.46(3H,s) 1.64(3H,s)	0.91(3H,t,J=7.33) 1.50-1.58(2H,m) 3.29(2H,t,J=6.10)
d	1.48(6H,s)	1.08(6H,d,J=6.10) 3.76-3.82(1H,m)		

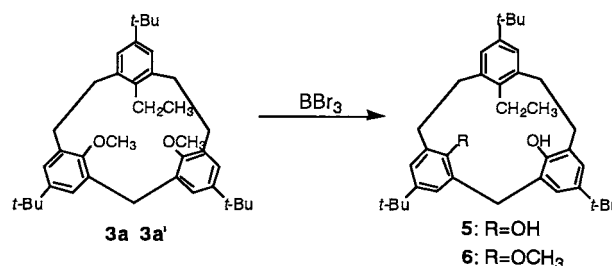
^aδ / ppm, in CDCl₃ at 27 °C.

4a was found out to exist in two kinds of "2,2-" and "1,2-alternate (folded-inwards)" (**4a'**) conformations. The similar conformational behavior was observed for the compound having the methyl group as the substituent R_2 .⁴ On the contrary the cyclophanes (**4b-c**) which have a larger inner substituent R_2 than the ethyl group exclusively assume the "1,2-alternate (folded-inwards)" conformation, indicated by the upfield shift of the protons of one methyl group. On the basis of these results the somewhat bulky substituent seems difficult to plunge into the cavity formed by the aromatic rings resulting in a "1,2-alternate (folded-inwards)" conformation which undergoes folding of the aromatic ring with the methyl group.

However, in some cyclophanes such as **2b**, **2c**, and **2d** no considerable upfield shifts of the substituent protons were observed. Furthermore they show the one signal for the methyl groups unlike **4b** and **4c**. These facts suggest there is no aromatic ring folding into the cavity, implying that these cyclophanes exist in the "cone-like" conformation. To gain further insight into this conformation the X-ray analysis of **2d**⁷ was carried out as shown in Figure 1. It shows that one aromatic ring with the methyl group inverts, indicating the "1,3-alternate" conformation. Consequently **2d** assumes "1,3-alternate (cone-like)" conformation. Taking account into this fact the "1,3-alternate (cone-like)" conformation can be assigned to **2b**

and **2c**. It is suggested from these results that in cyclophanes **2a** a larger substituent (R_2) than ethoxy group apparently promotes the inversion of the aromatic ring substituted with the methyl group probably due to the steric hindrance of the substituent (R_2) and the flexible thiaether bridge.

In demethylation of the 2,2-alternate conformer the inner methoxy group could not react.³ Thus, we investigated a similar reaction for the 1,2-alternate conformer.



Scheme 1.

Conformers **3a** and **3a'** behaved differently in demethylation (Scheme 1), on treatment with a large excess of BBr₃ at room temperature for 24 h. Although **3a** gave the desired demethylated compound **5** in 64%, in the reaction of **3a'** the monohydroxy compound **6** was isolated in 58%. This result implies that the methoxy group in the cavity of **3a'** could be inert to attack by BBr₃.

It is noted that four kinds of conformations were assigned to the metacyclophanes which have three aromatic rings depending on their structures, especially the "folded-inwards" conformation is unique to this system. It was also found out that in demethylation by BBr₃ methoxy cyclophane **3a** gave the different product depending on its conformation.

Financial support from Tokuyama Science Foundation and the Mazda Foundation's Research Grant is gratefully acknowledged.

References and Notes

- For example, see: F. Vögtle, "Supramolecular Chemistry," Wiley, Chichester (1989); J.-M. Lehn, "Supramolecular Chemistry," VCH, Weinheim (1995); "Supramolecular Control of Structure and Reactivity," ed. by A. D. Hamilton, Wiley, Chichester (1996).
- For example, see: F. Diederich, "Cyclophanes," The Royal Society of Chemistry, Cambridge (1991); F. Vögtle, "Cyclophane Chemistry," Wiley, Chichester (1989).
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- F. Vögtle, *Liebigs Ann. Chem.*, **728**, 17 (1969); T. Sato, M. Wakabayashi, K. Hata, and M. Kainosho, *Tetrahedron*, **27**, 2737 (1971).
- Crystal Data for **1a**: C₃₉H₅₄O₂S₂, Mw = 618.97, triclinic, space group P1(No.2), a=16.074(9), b=19.213(6), c=14.565(4) Å, β=108.47(3)°, V=3763(3) Å³, Z=4, D_{calc}=1.092 g/cm³, μ(Cu Kα)=14.97 cm⁻¹, Rigaku AFC7R diffractometer, 306 reflections with I>3.00σ(I), R=0.082, R_w=0.064.
- Crystal Data for **2d**: C₄₀H₅₆O₂S₂, Mw = 617.00, triclinic, space group P1(No.2), a=14.756(2), b=19.037(2), c=14.318(1) Å, β=106.647(9)°, V=3832.2(7) Å³, Z=4, D_{calc}=1.069 g/cm³, μ(Cu Kα)=14.48 cm⁻¹, Rigaku AFC7R diffractometer, 6929 reflections with I>3.00σ(I), R=0.081, R_w=0.075.