Synthesis, Conformation, and Reactivity of Ethylene-Bridged [2.2.1]Metacyclophanes

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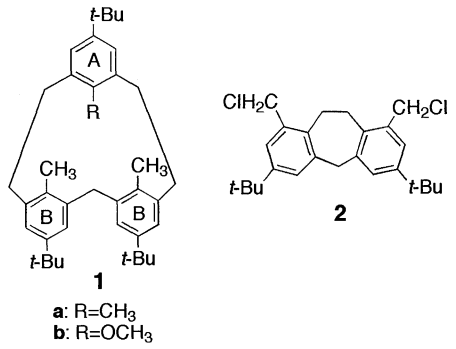
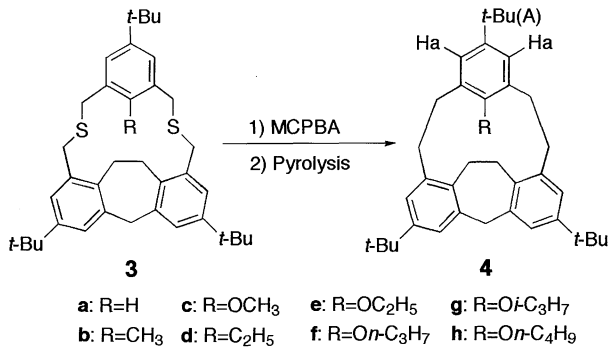
A series of ethylene-bridged [2.2.1]metacyclophanes has been synthesized. It was found out that they can adopt a new type of "inward-folded" conformation depending on the substituent of the one aromatic ring. This conformer exhibited different reactivities from another "inward-folded" one of the non-bridged [2.2.1]metacyclophanes.

Cyclophane chemistry dominates a major part of supramolecular chemistry, which is a new field attracting considerable attention recently.[1] During the course of our research on cyclophanes, we have been interested in metacyclophanes consisting of three aromatic rings because they can assume a rigid or a flexible conformation depending on the slight difference in the structure.

In this respect, the conformational features of [2.2.0]-,[2] [2.1.1]-,[3] and [2.2.2]metacyclophanes[4] have been already investigated. We have prepared various kinds of [2.2.1]metacyclophanes and confirmed their "inward-folded" conformation, which is characterized by one aromatic ring folding into the cavity produced by two other aromatic rings.[5,6] [2.2.1]Metacyclophanes (**1a,b**) tend to adopt two kinds of "inward-folded" conformations which have folded A ring and folded B ring, respectively. Bridging two aromatic rings of [2.2.1]metacyclophanes should produce a novel conformation.





Scheme 1.

Table 1. Chemical Shifts[a] of Bridged Metacyclophanes

Cyclophane	Terminal H of R		*tert*-Butyl H(A)		Aromatic Ha	
	3	**4**	**3**	**4**	**3**	**4**
a	6.50	7.03	1.34	1.30	7.26	7.06
b	2.19	0.80	1.32	1.40	7.22	7.04
c	2.93	3.81	1.41	0.66	7.26	5.95
d	0.88	1.17	1.32	0.59	7.23	5.89
e	0.60	1.49	1.39	0.65	7.29	5.95
f	0.70	1.18	1.33	0.66	7.32	5.96
g	0.68	—	1.35	—	7.22	—
h	0.82	1.07	1.30	0.82	7.31	5.96

[a]In $CDCl_3$, 27 °C (δ/ppm)

Thus, we would like to describe here the synthesis, the conformational property, and the reactivity of ethylene-bridged metacyclophanes (**4**).

It seems difficult to build up a bridging portion in the cyclic structure afterwards. We have already reported the facile synthesis of dibenzocycloheptene (**2**)[7], which has to be an appropriate candidate as a building component for synthesis of bridged metacyclophanes. Cyclization between **2** and mercaptomethyl compounds under a high-diluted condition afforded the corresponding dithiacyclophanes (**3a-h**) in 40-70% yields.

^1H NMR spectra of **3a-h** display characteristic feature as summarized in Table 1. A pair of doublets for the CH_2 bridge was observed in the spectra of dithiacyclophanes except for **3a**, indicating that **3b-h** exist in rigid conformations. The temperature-dependent ^1H NMR spectrum of **3a** in $CDCl_3$ gives rise to a coalescence temperature of -45 °C, corresponding to an inversion barrier of 10.1 kcal/mol. The terminal protons of R in **3d-h** show a remarkable upfield shift, which probably arises from a strong shielding effect of two aromatic rings of the dibenzocycloheptene unit, thus it is deduced that these cyclophanes adopt a "inward-folded" conformation with the substituent R located in the cavity. Such a considerable upfield shift for the protons of the substituents R in **3a-c** is not observed, because these are not big enough to be subject to the strong shielding effect. Taking into account the *tert*-butyl protons showing a normal shift, it is predictable that **3a-c** also assume a similar conformation to **3d-h**.

After oxidation of **3a-h** pyrolysis was carried out to obtain the cyclophanes **4a-h** (Scheme 1). The desired cyclophanes (**4a-f**, **4h**) were isolated in 20-35% yields. The cyclophane **4g** was not obtained, which might be due to a bulky isopropoxy group. It is noted that the cyclophanes **4f** and **4h** carrying *n*-propoxy and *n*-buthoxy group, respectively, were formed. These facts indicate that the pyrolysis is much influenced by a slight difference in the structure of R. In **4b** methyl protons appear at 0.80 ppm, which

can be explained by the methyl group existing in the cavity. Such an upfield shift of methyl protons compared to the shift of those in **3b** is certainly due to a stronger shielding effect owing to the smaller cavity size. It is considered that **4b** assumes a similar conformation to the dithiacyclophanes **3**.

On the contrary, the terminal protons of the substituent R in other cyclophanes (**4c-h**) show the NMR signals in the same region as those in the corresponding substituted benzene derivatives, indicating that the substituent R is accommodated outside of the cavity. This is supposed to reflect another "inward-folded" conformation in which one *tert*-butyl group exists in the cavity. This is in fairly good agreement with a considerable upfield shift for the protons of the *tert*-butyl group and the protons neighboring the *tert*-butyl group. This conformation is also established by the X-ray crystallography of **4e**[8]. As shown in Figure 1, one *tert*-butyl group is obviously located in the cavity formed by two aromatic rings.

Although the reason for **4c-h** to assume such a conformation is not clear at the present, it might be attributed to the recombination of radical intermediates in pyrolysis, that is, the aromatic ring having the substituent R bigger than methyl group could invert. The conformation of **4a** is supposedly similar to that of **4b**, because upfield shifts of the *tert*-butyl and the aromatic protons were not observed in the spectrum of **4a**.

Reactions of small and medium-sized cyclophanes are one of the most interesting subjects, because a through-space interaction among the aromatic rings is supposed to extensively affect the reactivity.

To begin with, nitration was employed in the cyclophanes **1b**, **4c**, and **4d**. Treatment of **4c** with 65% HNO_3 gave a mono-nitrated compound **5a** where one *tert*-butyl group of **4c** is replaced *via* the *ipso*-nitration[9] (Scheme 2); however, a similar nitration of **1b** or **4d** only gave a inseparable mixture containing some nitrated compounds. These results imply that other factors than the para activation with the methoxy group should play a decisive role in the nitration.

Yamato *et al*[10] studied *ipso*-nitration of *tert*-butylated diphenyl alkanes in detail, emphasizing stabilization of initial σ-complex intermediates by a through-space electronic interaction with the other benzene ring. A similar effect should be involved in the *ipso*-nitration presented here, because the *tert*-butyl group which is *ipso*-nitrated exists in the cavity formed by two aromatic rings of the dibenzocycloheptene unit leading to a stabilization of σ-complex intermediate. On the contrary, such stabilization cannot be expected in **1b** because of the *tert*-butyl group located outside of the cavity. Formylation of **4c** with dichloromethyl methyl ether in the presence of $TiCl_4$ also gave the *ipso*-formylated product **5b** in less than 20% yield.

Further investigation on reactivities of the new " inward-folded" conformers of ethylene-bridged [2.2.1]metacyclophanes is under progress in our laboratories.

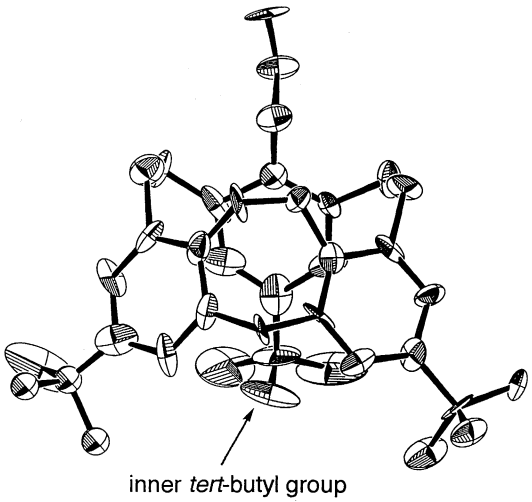
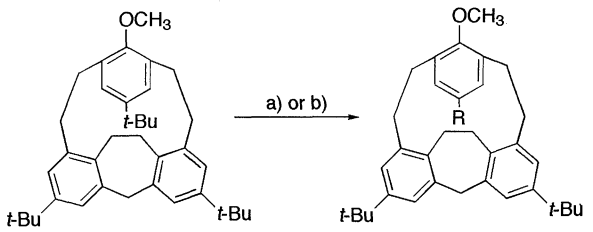


Figure 1. Perspective view of **4e**.



4c **5**

a: R=NO_2

b: R=CHO

Reagents and conditions: a) nitration; 65% HNO_3, AcOH, CH_2Cl_2, 40min, r.t. b) formylation; Cl_2CHOCH_3, $TiCl_4$, CS_2, 5h, r.t.

Scheme 2.

References and Notes

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8 Crystal Data for **4e**: $C_{38}H_{52}O$, M=536.84, monoclinic, space group $P2_1/a$(No.14), a=12.90(1), b=17.60(1), c=17.742(6) Å, β=97.97(5)°, V=3315(3) $Å^3$, Z=4, D_{calc}=1.076 g/cm^3, μ(MoKα)=0.62 cm^{-1}, Rigaku AFC7R diffractometer, 1011 reflections with I>4.00σ(I), R=0.098, R_w=0.088.

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