Tetrahedron Letters, Vol. 34, No. 35, pp. 5605-5608, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis and Structure of a Novel Macrobicyclic Cyclophane with a Molecular Cavity

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Abstract: A novel bicyclic cyclophane **1** based on an aryl benzyl ether framework was synthesized. X-ray crystallographic analysis established the molecular bowl structure of **1**. Its structure in solution was investigated by NMR.

Macrobicyclic cyclophanes constitute a major class of complexing agents with high selectivity,[1] which is much due to their concave structures. A number of examples which have a functional group in the concave position have also been reported, but most of them are conformationally flexible.[2] If various functional groups are embedded in a rigid bowl-shaped cavity of moderate size, they are expected to show unique reactivities. Such a molecular bowl depicted schematically in Fig. 1, to which we refer as a "reaction bowl", would serve not only as a functionalized host but as a new kind of protection group for kinetic stabilization of highly reactive species. Here, we wish to report the synthesis of a novel bicyclic oxacyclophane **1**, which has been demonstrated to have a molecular bowl structure by crystallographic structure analysis.

Recently Hart and his co-workers reported a series of *m*-terphenyl-based cyclophanes.[3] They are shown

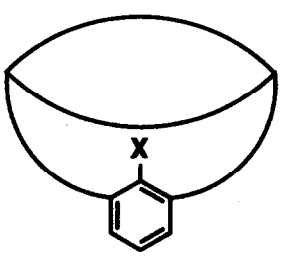
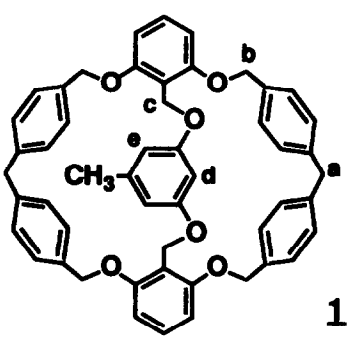


Fig. 1. Schematic drawing of a "reaction bowl".



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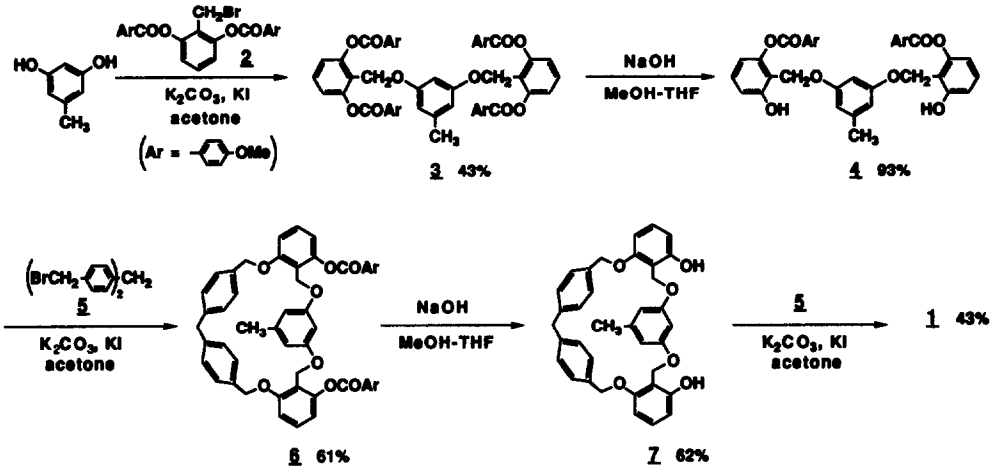
to have considerable rigidity, but their sizes are limited by the *m*-terphenyl framework. In designing **1**, orcinol dibenzyl ether and two diphenylmethane units were selected for central and side bridges, respectively, by con-



sidering the size and rigidity of the molecule.

The synthesis of **1** was effected by initial construction of the central bridge followed by stepwise cyclization. Dibenzyl ether **3** was obtained by treatment of orcinol with benzylbromide **2** which was derived from 2-methylresorcinol in a good yield.[4] Hydrolysis of **3** under dilute alkaline conditions led to the exclusive monodeprotection of each resorcinol unit to give **4**. The reaction of **4** with bromide **5** in the presence of potassium carbonate and potassium iodide under moderate dilution conditions gave oxacyclophane **6**, which was deprotected to afford **7**. The novel oxacyclophane **1** was obtained by coupling of **5** with **7**.

The structure of **1** was established by spectral data and elemental analysis.[5] The proton spectrum shows the equivalence of pertinent protons in the three kinds of CH_2 groups and diphenylmethane aromatic rings at room temperature. At low temperatures, however, the methylene protons H_a and H_b (δ 3.87 and 4.90, respectively) turned to AB systems, the coalescence temperature being 263 K for H_a and 262 K for H_b. On the other hand, H_c signal (δ 4.71) remained a sharp singlet even at 220 K. These results indicate that the side bridges have some conformational constraints, while C-CH_2-O-C bonds of the central bridge make a crank-like rotation with a low barrier.

The structure of **1** was finally determined by X-ray crystallographic analysis as shown in Fig. 2.[6] The figure clearly shows that **1** is a bowl-shaped molecule as expected, its diameter being *ca.*14 Å. The central bridging unit has a conformation where the oxygen lone pairs are oriented outside the cavity, and the bridgehead aromatic rings are considerably flattened. As for the conformation in solution, $^1H\{^1H\}$ nuclear Overhauser effect (NOE) experiment provided valuable clues. Saturation of the methylene protons H_c gave rise to NOEs at H_d (42%) and H_e (8%), suggesting that the conformation shown in Fig. 2 is more populated than another possi-

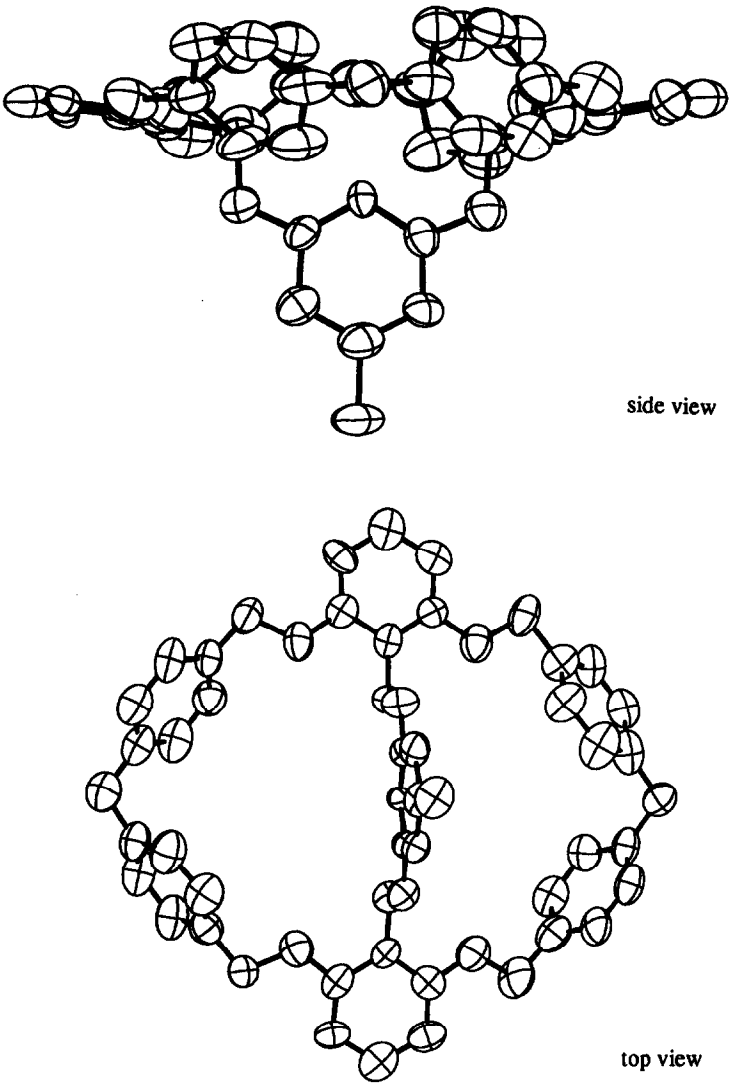


Fig. 2. *ORTEP* drawing of **1**.

ble conformation with the lone pairs in the cavity. Inspection of the CPK models reveals that, in the latter conformation, **1** still has a bowl structure with the bridgehead aromatic rings being less flattened to form a "wall". The CPK models also indicate that the central aromatic ring is prevented from rotating by the CH_3 group on it in both conformations.

Introduction of functional groups into the reactive center (X in Fig. 1) is currently in progress.

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4. Compound **2** was prepared by esterification of 2-methylresorcinol with 4-methoxybenzoyl chloride in pyridine followed by bromination with *N*-bromosuccinimide in the presence of benzoyl peroxide (84% from 2-methylresorcinol).
5. **1**; colorless crystals, mp 268-271 °C(dec); ^{1}H-NMR(500 MHz, $CDCl_3$) δ 2.34(s, 3H, CH_3), 3.87(s, 4H, H_a), 4.71(s, 4H, H_c), 4.90(s, 8H, H_b), 6.02(t, J = 1.9 Hz, 1H, H_d), 6.38(d, J = 1.9 Hz, 2H, H_e), 6.67 (d, J = 8.3 Hz, 4H, protons on the bridgehead rings), 7.03-7.06(m, 8H, protons on the diphenylmethane aromatic rings), 7.24-7.26(m, 8H, protons on the diphenylmethane aromatic rings), 7.32(t, J = 8.3 Hz, 2H, protons on the bridgehead rings); ^{13}C-NMR(125 MHz, $CDCl_3$) δ 21.5(q), 41.8(t), 58.6(t), 70.7(t), 94.3(d), 104.8(d), 109.2(d), 113.5(s), 128.6(d), 129.1(d), 130.3(d), 134.3(s), 138.7(s), 141.9(s), 159.0(s), 160.5(s); HRMS *m/z* 752.3140, calcd for $C_{51}H_{44}O_6$ 752.3138; Anal. found C, 81.28; H, 5.90%; calcd for $C_{51}H_{44}O_6$ C, 81.36; H, 5.89%.
6. Crystallographic data for $1 \cdot CH_2Cl_2$; FW = 837.84, *monoclinic*, a = 18.141(2) Å, b = 21.524(1) Å, c = 22.802(1) Å, β = 90.36(1) °, V = 8903(2) Å^3, Z = 8, space group $P2_1/a$, D_C = 1.2496 gcm^{-3}, R = 0.0947(w = 1.0). Data were collected through a capillary glass tube with Cu Kα radiation (λ = 1.5418 Å) on an Enraf-Nonius CAD-4 diffractometer, μ = 17.02 cm^{-1}. Of the 12836 independent reflections collected (4 ° < 2θ < 120 °), 4848 reflections ($|F_O| \geq 3\sigma|F_O|$) were observed. Empirical absorption correction was applied and the structure was solved by direct methods (*MULTAN 78*) using a program system *UNICS III*. All hydrogen atoms were located by calculation. Refinement was performed by block-approximation least square method. Cyclophane **1** was solvated by one molecule of dichloromethane and there were two independent structures in the unit cell, one of which is illustrated in Fig. 2. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

(Received in Japan 4 March 1993; accepted 30 April 1993)