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# Scandium triflate-catalyzed cyclocondensation of 1,3-dialkoxybenzenes with 1,3,5-trioxane. Formation of resorcin[4]arenes and confused resorcin[4]arenes

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**Abstract**—The cyclocondensation of 1,3-dialkoxybenzenes with 1,3,5-trioxane was catalyzed by $Sc(OTf)_3$ to produce resorcin[4]arene octaalkyl ethers as the major products. In addition, 'confused' resorcin[4]arene octaalkyl ethers bearing one alkoxy group at the intra-annular position were obtained as the minor products. The variable temperature $^1H$ NMR spectroscopy showed that the alkoxy group at the intra-annular position cannot pass through the macrocyclic annulus, indicating a rigid molecular framework. The structure of the ethoxy derivative of the confused resorcin[4]arene was determined by X-ray crystallography.

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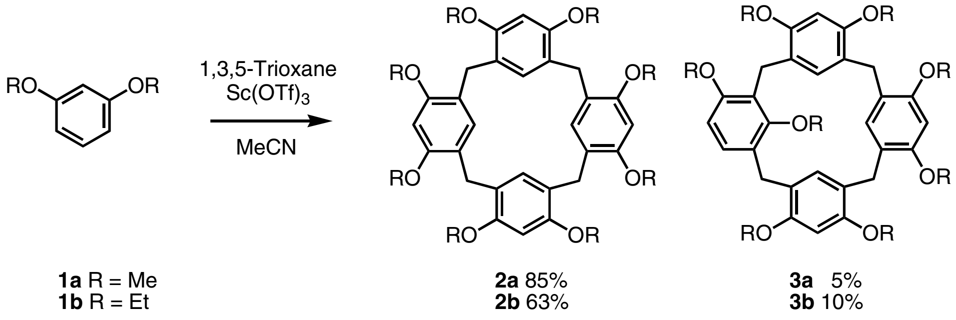
Resorcinarenes are $[1_4]$metacyclophanes, in which four resorcinol units are linked by methylene bridges at their 4- and 6-positions, and are widely used as molecular building blocks in the field of supramolecular chemistry.[1,2] A variety of resorcin[4] arenes have been readily prepared by the cyclocondensation of resorcinols with aldehydes in the presence of a Brønsted acid or a Lewis acid.[3–7] Their octaether derivatives have been prepared by the acid-catalyzed condensation of 1,3-dialkoxybenzenes with aldehydes.[8–10] Furthermore, the acid-catalyzed cyclooligomerization of 2,4-dialkoxycinnamates[11] or 2,4-dialkoxybenzyl alcohols[12–15] produces the cyclic products.

In these preparations, when Brønsted acids, such as hydrochloric acid or trifluoroacetic acid, were used as



**Scheme 1.** $Sc(OTf)_3$-catalyzed condensation of 1,3-dialkoxybenzene with 1,3,5-trioxane.

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*Keywords*: Resorcinarene; Metacyclophane; Crystal structure.

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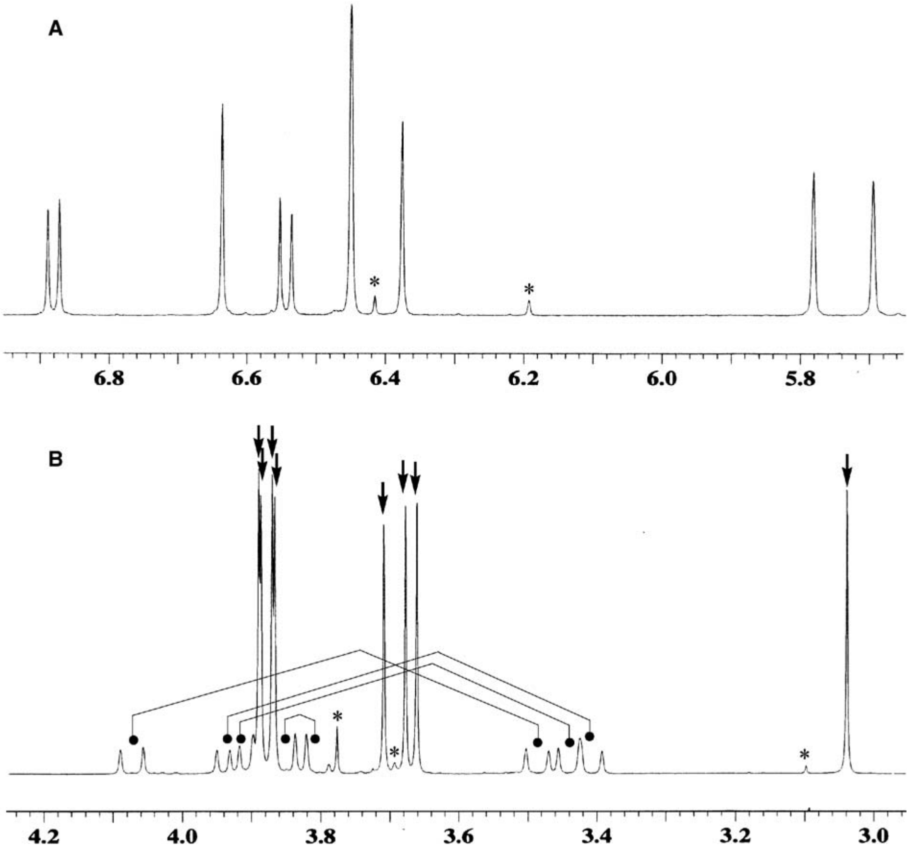

**Figure 1.** 500 MHz $^1$H NMR spectrum of **3a** in $CDCl_3$ at 30 °C. The signals marked with asterisks correspond to impurities: (A) the aromatic protons, and (B) the methoxy and methylene protons. The arrows indicate the methoxy signals and the solid circles represent the chemical shifts of the methylene protons.

a catalyst, the cyclic tetramers were obtained as the major products. This is due to the fact that the C–C bond formation is reversible and the cyclic tetramers are the thermodynamically favored products. On the other hand, the Lewis acid catalyzed reaction should produce kinetically controlled products, since these acids have no or a very low activity for the C–C bond scission. However, since the benzyl cation intermediates that are generated during the reaction can cleave the C–C bond and reconstruct the cyclic and linear oligomers, the yield of the cyclic tetramers is usually higher than those of other cyclic products.

Our continued interest in the synthesis of resorcinarene derivatives with unsubstituted methylene bridges[16] prompted us to investigate the $Sc(OTf)_3$-catalyzed reaction of 1,3-dialkoxybenzenes with 1,3,5-trioxane. The triflateis found to be stable in the presence of water and to work as a Lewis acid catalyst in several carbon–carbon bond forming reactions.[17,18] Therefore, it is anticipated that $Sc(OTf)_3$ is a very suitable catalyst for the condensation reaction with the formation of water. We would like to now describe the formation of two types of cyclic tetramers; the major product is the resorcin[4]arene bearing eight alkoxy groups at the extraannular positions and the minor product is a ‘confused’ resorcin[4]arene bearing one alkoxy group at the intra-annular positions.

The reaction of 1,3-dimethoxybenzene **1a** (2 mmol) with 1,3,5-trioxane (1.3 mmol) in $CH_3CN$ in the presence of $Sc(OTf)_3$ (0.04 mmol) at 80 °C for 3 h produced two cyclic tetramers **2a** and **3a**.[†] Most of **2a** (85%) was precipitated during the reaction and collected by filtration. The filtrate was subjected to GPC separation to afford the crude **3a** (5%), which was purified by repeated

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[†] *$1^{2,4}$,$3^{4,6}$,$5^{4,6}$,$7^{4,6}$-Octamethoxy-1,3,5,7(1,3)-tetrabenzenacyclooctaphane* **3a**: White powder from $CHCl_3$/acetone. Mp 300 °C (dec.); 500 MHz $^1$H NMR ($CDCl_3$, 30 °C): $\delta$ 6.88 (1H, d, $J = 8.3$ Hz, ArH), 6.64 (1H, s, ArH), 6.54 (1H, d, $J = 8.3$ Hz, ArH), 6.45 (2H, s, 2 × ArH), 6.38 (1H, s, ArH), 5.78 (1H, s, ArH), 5.70 (1H, s, ArH), 4.07 and 3.49 (2H, AB, $J = 16.5$ Hz, $CH_2$), 3.93 and 3.41 (2H, AB, $J = 16.0$ Hz, $CH_2$), 3.91 and 3.44 (2H, AB, $J = 16.1$ Hz, $CH_2$), 3.889 (3H, s, $OCH_3$), 3.887 (3H, s, $OCH_3$), 3.871 (3H, s, $OCH_3$), 3.867 (3H, s, $OCH_3$), 3.85 and 3.80 (2H, AB, $J = 16.5$ Hz, $CH_2$), 3.71 (3H, s, $OCH_3$), 3.68 (3H, s, $OCH_3$), 3.66 (3H, s, $OCH_3$), 3.04 (3H, s, $OCH_3$). *$1^{2,4}$,$3^{4,6}$,$5^{4,6}$,$7^{4,6}$-Octaethoxy-1,3,5,7(1,3)-tetrabenzenacyclooctaphane* **3b**: Colorless crystals from $CHCl_3$/hexane. Mp 155–156 °C; 500 MHz $^1$H NMR ($CDCl_3$, 30 °C): $\delta$ 6.80 (1H, d, $J = 8.3$ Hz, ArH), 6.65 (1H, s, ArH), 6.47 (1H, d, $J = 8.3$ Hz, ArH), 6.44 (1H, s, ArH), 6.42 (1H, s, ArH), 6.32 (1H, s, ArH), 5.86 (1H, s, ArH), 5.80 (1H, s, ArH), 4.12–3.70 (19H, m, $OCH_2$ and bridge $CH_2$), 3.54–3.45 (m, 3H, bridge $CH_2$), 3.18–3.08 (AB part of $ABX_3$, 2H, $OCH_2$), 1.44 (6H, t, 2 × $CH_3$), 1.43 (6H, t, 2 × $CH_3$), 1.19 (6H, t, 2 × $CH_3$), 1.16 (3H, t, $CH_3$), 0.87 (3H, t, $CH_3$).

recrystallization. Analogously, the reaction of 1,3-diethoxybenzene **1b** also produced two cyclic tetramers **2b** and **3b**,[†] in 63% and 10% yields, respectively (Scheme 1).

In the $^1$H NMR spectrum, **2a** shows two singlets for the methoxy groups at 3.78 ppm and the bridge methylene groups at 3.70 ppm. On the other hand, compound **3a** displays eight singlets for the methoxy groups and four sets of AB quartets for the bridging methylene groups as shown in Figure 1. The assignments of the geminal pairs of the bridging methylene groups were made based on proton decoupling experiments. The most characteristic feature of this spectrum is the signal of one methoxy group that appeared at 3.04 ppm. The upfield shift of this signal, by 0.74 ppm compared to the methoxy signal of **2a**, suggests that this methoxy group is located inside the resorcinarene cavity. In addition, the two singlets at 5.78 and 5.70 ppm are assigned to the intra-annular aromatic protons, which are shifted upfield by the ring current effect of the adjacent aromatic nuclei. Furthermore, in the aromatic region, one AB quartet set (6.88 and 6.54 ppm, $J = 8.3$ Hz) is observed for the protons of the 1,2,3,4-tetrasubstituted benzene ring in accordance with the structure of the confused resorcin[4]arene **3**.

It is noteworthy that the chemical shifts of the eight methylene protons are different from each other, indicating that the molecule **3a** has a chiral conformation lacking any symmetry ($C_1$ point group). Moreover, variable temperature $^1$H NMR spectroscopy showed the nonequivalency of the eight methylene protons at 150 °C in DMSO-$d_6$. This observation indicates that the alkoxy group at the intra-annular position cannot pass through the macrocyclic annulus, therefore, the molecule **3a** has no time-averaged symmetry plane on the NMR time scale. Thus, we could not observe any interconversion between the pair of enantiomers of **3a** using NMR spectroscopy. This conformational property is in contrast to that of the calix[4]arene derivatives having four methoxy groups at the intra-annular positions. In fact, these calixarenes are conformationally mobile in solution, and their methoxy groups pass through the macrocyclic annulus at room temperature.[19–21] Therefore, the higher conformational rigidity of **3a** can be attributed to the steric hindrance arising from the seven exterior methoxy groups though the transition state geometry of the conformational change is not clear. Figure 2 shows the $^1$H NMR spectrum of the ethoxy derivatives **3b**. Its characteristic feature is very similar to that of **3a**, indicating that the conformational properties of **3b** are analogous to those of **3a**. The one upfield shifted ethoxy signal was assigned to the interior ethoxy group, which appeared as an ABX$_3$ multiplet, and this coupling pattern was maintained at 150 °C in DMSO-$d_6$ though there were some chemical shift changes. Hence, it is concluded that **3b** does not exhibit any

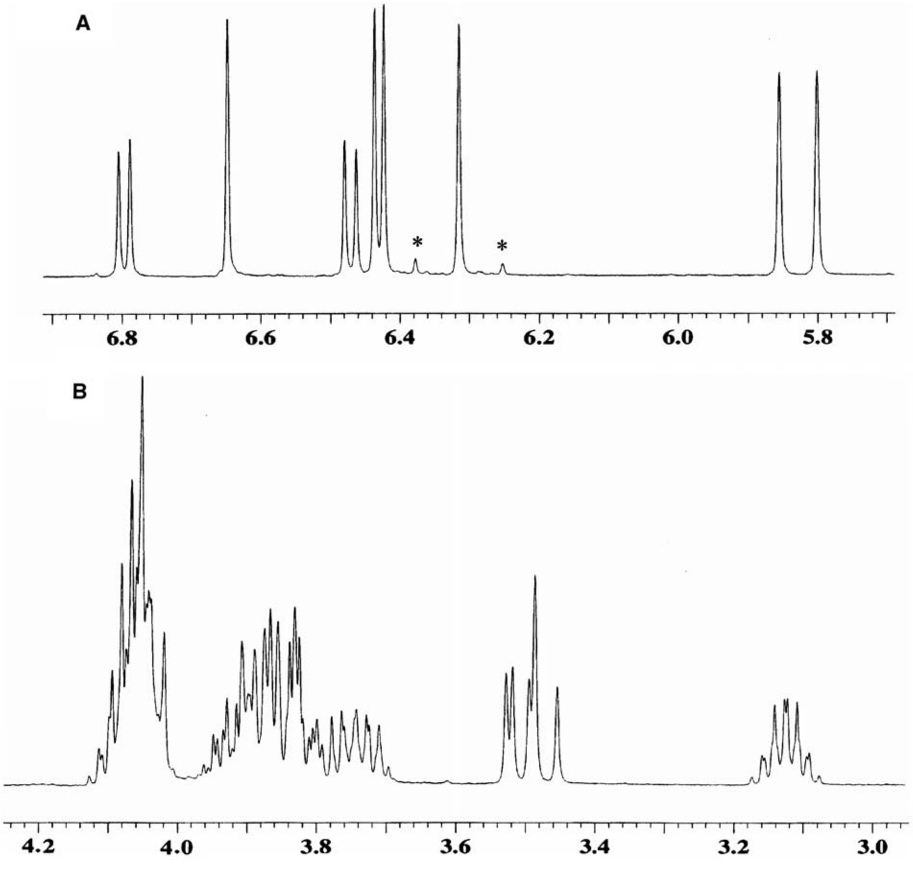

**Figure 2.** 500 MHz $^1$H NMR spectrum of **3b** in CDCl$_3$ at 30 °C. The signals marked with asterisks correspond to impurities: (A) the aromatic protons, and (B) the methoxy and methylene protons.

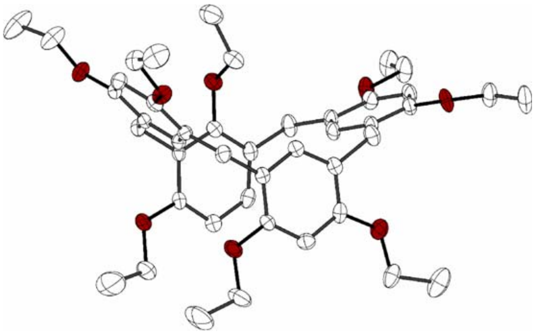

**Figure 3.** Single-crystal X-ray structure of **3b**. Hydrogen atoms and one chloroform molecule is omitted for clarity. The thermal ellipsoids are at the 30% probability level.

conformational inversion of the macrocycle on the NMR time scale.

Crystals of the confused resorcin[4]arene **3b** suitable for an X-ray diffraction analysis were obtained by the vapor diffusion of hexane into a chloroform solution in which these crystallize as a solvate of chloroform.[‡] In the solid state, **3b** adopts a highly disordered 1,3-alternate conformation, in which the four methylene bridge carbon atoms define a plane with a maximum deviation of 0.14 Å (Fig. 3). The aromatic ring bearing the interior ethoxy group and the opposing aromatic ring are nearly perpendicular to the mean plane; their corresponding dihedral angles are 84.2° and 87.2°, respectively. On the other hand, the dihedral angles between the other two aromatic rings and the mean plane are 20.2° and 43.5°. Seven ethoxy groups at the exterior positions are approximately coplanar to the attaching aromatic rings, whereas the interior ethoxy group twists with a rotation angle of 86.9° and points to the inside of the resorcinarene framework. These solid state conformational results are parallel with the solution conformational data obtained by $^1$H NMR.

In summary, we have reported a simple method for the synthesis of resorcin[4]arene octaalkyl ethers as the major products. The confused resorcin[4]arenes, as the minor products, are conformationally rigid molecules, and are a potentially useful molecular platform for construction of supramolecular systems with chiral recognition ability. Further studies on improving the yield and functionalization of the confused resorcin[4]arenes are now in progress.

## References and notes

1. Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663–2704.
2. Botta, B.; Cassani, M.; D'Acquarica, I.; Misiti, D.; Subissati, D.; Delle Monache, G. *Curr. Org. Chem.* **2005**, *9*, 337–355.
3. Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046–6050.
4. Abis, L.; Dalcanale, E.; Du-vosel, A.; Spera, S. *J. Org. Chem.* **1988**, *53*, 5475–5479.
5. Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305–1312.
6. Konishi, H.; Iwasaki, Y.; Okano, T.; Kiji, J. *Chem. Lett.* **1989**, 1815–1816.
7. Konishi, H.; Nakamura, T.; Ohata, T.; Kobayashi, K.; Morikawa, O. *Tetrahedron Lett.* **1996**, *37*, 7383–7386.
8. Iwanek, W.; Syzdól, B. *Synth. Commun.* **1999**, *29*, 1209–1216.
9. Vuano, B.; Pieroni, O. I. *Synthesis* **1999**, 72–73.
10. Li, D.; Kusunoki, T.; Yamagishi, T.; Nakamoto, Y. *Polym. Bull.* **2002**, *47*, 493–499.
11. Botta, B.; Giovanni, M. C.; Delle Monache, G.; De Rosa, M. C.; Gacs-Baitz, E.; Botta, M.; Corelli, F.; Tafi, A.; Santini, A.; Benedetti, E.; Carlo Pedone, C.; Misitit, D. *J. Org. Chem.* **1994**, *59*, 1532–1541.
12. Falana, O. M.; Al-Farhan, E.; Keehn, P. M.; Stevenson, R. *Tetrahedron Lett.* **1994**, *35*, 65–68.
13. Konishi, H.; Sakakibara, H.; Kobayashi, K.; Morikawa, O. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2583–2584.
14. Stursda, J.; Dvorakova, H.; Smidrkal, J.; Petrickova, H.; Moravcova, J. *Tetrahedron Lett.* **2004**, *45*, 2043–2046.
15. Morikawa, O.; Ishizaka, T.; Sakakibara, H.; Kobayashi, K.; Konishi, H. *Polym. Bull.* **2005**, *53*, 97–107.
16. Konishi, H. In *New Trends in Structural Organic Chemistry 2005*; Takemura, H., Ed.; Research Signpost: Kerala, 2005; pp 145–153.
17. Kobayashi, S.; Hachiya, I. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 370–380.
18. Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S. *J. Org. Chem.* **1997**, *62*, 6997–7005.
19. van Loon, J.-D.; Groeen, L. C.; Wijmenga, S. S.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2378–2384.
20. Juneja, R. K.; Robinson, K. D.; Johnson, C. P.; Atwood, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3818–3819.
21. Iwamoto, K.; Ikeda, A.; Araki, K.; Harada, T.; Shinkai, S. *Tetrahedron* **1993**, *49*, 9937.
22. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435–436.
23. Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. The DIRDIF-94 Program System, Technical Report of Crystallography Laboratory, University of Nijmegen, The Netherlands; 1994.

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[‡] *X-ray crystal structure analysis.* X-ray data were collected at 123 K using a Rigaku-RAPID imaging plate area detector with graphite monochromated Mo-K$\alpha$ ($\lambda = 0.7107$ Å) radiation in the $\omega$ scan mode. The structure was solved by direct methods (SIR92)[22] and expanded using Fourier techniques (DIRDIF-94).[23] The nonhydrogen atoms were anisotropically refined. Hydrogen atoms were included at the calculated positions, but not refined. All calculations were performed using a crystallographic software package, CrystalStructure version 3.7.0. Crystals of **3b** were obtained by the vapor diffusion of hexane into a chloroform solution: $C_{44}H_{56}O_8 \cdot CHCl_3$, $M = 832.30$, monoclinic, space group $P2_1/c$ (No. 14), $a = 12.212(4)$, $b = 25.436(13)$, $c = 15.107(6)$ Å, $\beta = 108.25\ (2)$, $V = 4456.6(32)$ Å$^3$, $Z = 4$, $\rho_c = 1.204$ g cm$^{-3}$, $2\theta_{\max} = 55.0°$. $F(000) = 1768$. A total of 35,169 reflections were measured with 10,069 being unique. The final cycle of the full-matrix least squares refinement was based on all the observed reflections, 563 variable parameters, with factors of $R = 0.1027$, $Rw = 0.2190$, and GOF = 1.150. Crystallographic data in cif format (Ref. CCDC 299770) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.