

Synthesis of a Crown Ether with D_2 Symmetry

MARIANNE FRANTSI, GÖRAN LINDSTEN,
and OLOF WENNERSTRÖM

Department of Organic Chemistry, Chalmers
University of Technology and University of
Göteborg, S-412 96 Göteborg, Sweden

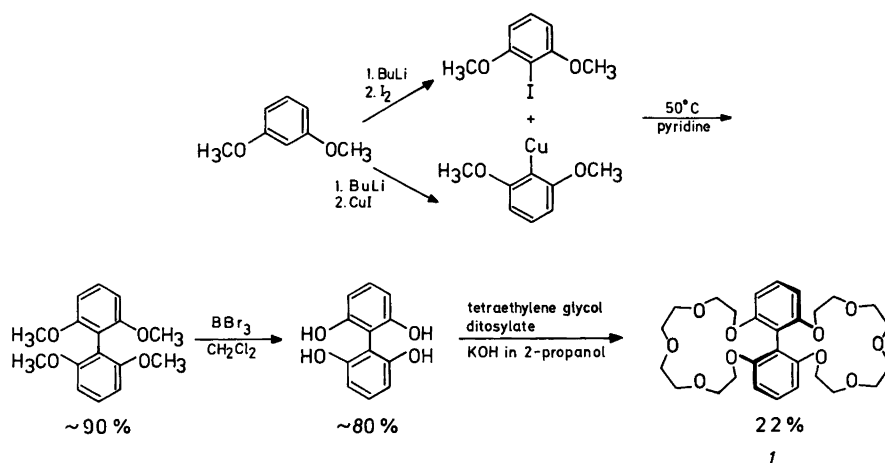
The rapid development of crown ether chemistry and the increasing interest in chiral crown ethers have encouraged us to report a facile synthesis of a new chiral crown ether from 2,2',6,6'-tetrahydroxybiphenyl. Crown ethers with D_2 symmetry are chiral, several examples of chiral crown ethers being known.¹ Recently, Rebek Jr. and coworkers have reported allosteric effects in a crown ether from 2,2',6,6'-tetra(hydroxymethyl)biphenyl.²

2,2',6,6'-Tetramethoxybiphenyl can conveniently be prepared from 2,6-dimethoxyiodobenzene and 2,6-dimethoxyphenylcopper.³ The cleavage of the methyl ether bonds has previously been performed with hydrobromic acid.⁴ We found that neither hydrobromic nor hydroiodic acid gave satisfactory yields, as ring closure reactions gave dibenzofurane derivatives at rates comparable with that of methyl ether bond cleavage. Instead, boron tribromide is the reagent of choice for the reaction, giving a near-quantitative yield of 2,2',6,6'-tetrahydroxybiphenyl. The two oligoethylene glycol chains were attached by refluxing the tetrahydroxybiphenyl with sodium hydroxide and tetraethylene glycol ditosylate in 2-propanol for 48 h. The structure of the crown ether formed (*1*), (according to IUPAC nomen-

clature; 2,5,8,11,14,20,23,26,29,32-decaoxatetracyclo[31.3.1.1^{15,19}.0^{37,38}]octatriaconta-1(37),15,17,19(38),33,35-hexaene), was determined from its mass and ¹H NMR spectra (270 MHz). The latter showed a distinct ABCD pattern for half of the methylene protons, interpreted as being due to restricted rotation around the phenyl bond on the NMR time scale. Recently, a reinvestigation of the rotational barriers in some 2,2',6-tri- and 2,2',6,6'-tetramethoxybiphenyls has revealed that the barriers are considerably higher than previously assumed.⁵ Whether the enantiomers of the crown ether can be isolated or not remains to be proven. The ABCD pattern is also compatible with an isomer having the chains linked 2,6 and 2',6'. However, reaction between 2-acetylresorcinol and tetraethylene glycol ditosylate gave a negligible yield of crown ether.⁶ We therefore consider it very unlikely that a 2,6-type isomer should form in 22 % yield, a conclusion which is supported by inspection of CPK-models.

The crown ether (*1*) forms complexes with simple cations. The complex constants were determined by extraction of picrates from water to a chloroform solution.⁷ The prerequisite for this method is that the crown ether is insoluble in water so that extraction of crown ether from chloroform to water can be neglected. The method also neglects the influence of water on the formation of the complex.⁸ In the calculation of the constants, independent complexation by the two crown ether groups in the molecule was assumed, *i.e.* no allosteric effects. As expected from the ring size, a small preference for sodium ($K = 54 \times 10^3 \text{ M}^{-1}$) over potassium ($K = 23 \times 10^3 \text{ M}^{-1}$) and ammonium ($K = 21 \times 10^3 \text{ M}^{-1}$) was observed.

Experimental. Mass spectra were recorded on an AEI MS 902 and NMR spectra on a Bruker WH 270



Scheme 1. Synthesis of crown ether *1*.

instrument. Absorbances for complex constant measurements were determined on a Varian Cary 210 spectrophotometer.

2,2',6,6'-Tetramethoxybiphenyl. To a stirred solution of 1,3-dimethoxybenzene (44 g, 0.32 mol) in dry ether (500 ml) *n*-butyllithium (200 ml, ca. 15 % in hexane, Merck) was added *via* syringe. The mixture was stirred overnight under nitrogen at room temperature. Copper(I) iodide (61 g, 0.32 mol), dried overnight in an oven at 110 °C, was added in portions, and the mixture was stirred at room temperature for another 2 h. 2,6-Dimethoxyiodobenzene (66 g, 0.25 mol) was then added in portions together with dry pyridine (600 ml). The mixture was heated to 50 °C, and most of the diethyl ether was distilled off. The dark solution was stirred at 50 °C for three days under nitrogen. The product mixture was poured onto ice and acidified with hydrochloric acid (4 M). The solid residue was collected by filtration, dried and recrystallised from dichloromethane–ethanol to give 2,2',6,6'-tetramethoxybiphenyl (70 g, 90 %, m.p. 174–175 °C).

2,2',6,6'-Tetrahydroxybiphenyl. 2,2',6,6'-Tetramethoxybiphenyl (18 g, 65 mmol) was dissolved in dichloromethane (250 ml) and cooled to –78 °C. Boron tribromide (25 ml) dissolved in dichloromethane (150 ml) was added, and the stirred solution was allowed to reach room temperature slowly during 5 h. Water was added carefully to the reaction mixture, followed by ether. The acidic water phase was extracted several times with ether, sodium chloride was added and the mixture was again extracted with ether. The combined ether solutions were dried and the solvent distilled off. The residue slowly crystallised from ethanol to give 2,2',6,6'-tetrahydroxybiphenyl (11.5 g, 78 %, m.p. 191–192 °C after careful drying to remove ethanol).

¹H NMR (270 MHz, acetone-*d*₆): δ 6.48 (4 H, d, *J* 8.2 Hz), 7.03 (2 H, t, *J* 8.0 Hz), 7.46 (4 H, broad s).

MS (50 eV): *m/e* 218 (M⁺, 100 %), 200 (39), 173 (15), 150 (15), 147 (16), 122 (18), 115 (16). Mol.wt., obs. 218.058, calc. for C₁₂H₁₀O₄ 218.058.

Crown ether (1). 2,2',6,6'-Tetrahydroxybiphenyl (0.50 g, 2.3 mmol) and sodium hydroxide (0.50 g, 12 mmol) were added to 2-propanol (65 ml) which was then heated to reflux. After 30 min tetraethylene glycol ditosylate (2.43 g, 48 mmol) suspended in a small amount of 2-propanol was added, and the mixture was refluxed for 48 h. The reaction mixture was cooled, and the precipitate (sodium tosylate, 1.7 g) was filtered off and washed with dichloromethane and acetone. The solvent was removed by distillation from the combined solutions and the residue slowly crystallised from ethanol to give the crown ether **1** (0.27 g, 22 %, m.p. 140–144 °C).

¹H NMR (270 MHz, CDCl₃): δ 3.53 (16 H, m), 3.67 (8 H, m), 3.96 (4 H, m), 4.11 (4 H, m), 6.63 (4 H, d, *J* 8.5 Hz), 7.18 (2 H, t, *J* 8.2 Hz).

MS (50 eV): *m/e* 535 (31), 534 (M⁺, 100 %), 227 (33), 226 (18), 201 (13), 200 (16), 199 (16), 197 (11), 89 (13), 87 (12). Mol.wt., obs. 534.244, calc. for C₂₈H₃₈O₁₀ 534.246.

Acknowledgements. We thank Dr. B. Thulin for helpful discussions. Financial support from the Swedish Board for Technical Development is greatly appreciated.

1. a. Kyba, E. B., Koga, K., Sousa, L. R., Siegel, M. G. and Cram, D. J. *J. Am. Chem. Soc.* 95 (1973) 2692; b. Girodeau, J.-M., Lehn, J.-M. and Sauvage, J.-P. *Angew. Chem.* 87 (1975) 813; c. Rebek, J., Jr., Wattley, R. V., Costello, T., Gadwood, R. and Marshall, L. *J. Am. Chem. Soc.* 102 (1980) 7398.
2. Rebek, J., Jr., Wattley, R. V., Costello, T., Gadwood, R. and Marshall, L. *Angew. Chem.* 93 (1981) 584.
3. Björklund, C., Nilsson, M. and Wennerström, O. *Acta Chem. Scand.* 24 (1970) 3599.
4. Van Arendonk, A. M., Cupery, M. E. and Adams, R. *J. Am. Chem. Soc.* 55 (1933) 4225.
5. Kawano, N., Okigawa, M., Hasaka, N., Kouno, I., Kawahara, Y. and Fujita, Y. *J. Org. Chem.* 46 (1981) 389.
6. Reinhoudt, D. N., de Jong, F. and van de Vondervoort, E. M. *Tetrahedron* 37 (1981) 1753.
7. Moore, S. S., Tarnowski, T. L., Newcomb, M. and Cram, D. J. *J. Am. Chem. Soc.* 99 (1977) 6398.
8. de Jong, F., Reinhoudt, D. N. and Smit, C. J. *Tetrahedron Lett.* (1976) 1371.

Received October 29, 1981.