From calixarenes to macrocyclic polyethers

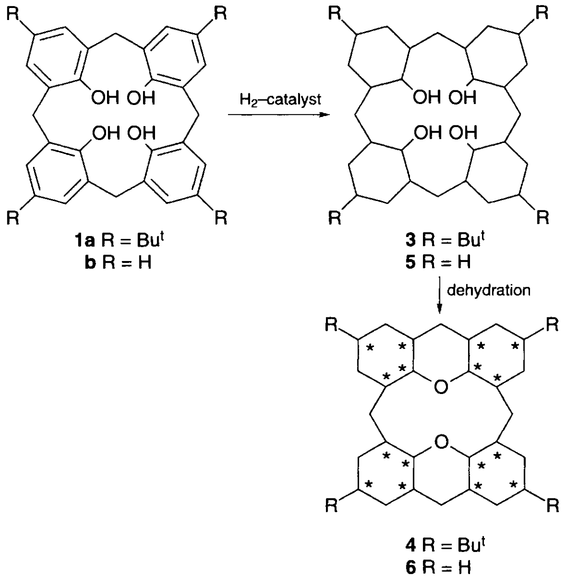
Flavio Grynszpan and Silvio E. Biali*

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

Catalytic hydrogenation of calix[4]arene [1450 psi H_2 (1 psi = *ca.* 6.89 kPa), Raney Ni–Pr^{i}OH, 240 °C] affords the *trans-syn-trans* macrocyclic diether 6b in 15% yield.

Two of the most popular synthetic macrocyclic hosts are the calix[*n*]arenes **1**[1] and the crown ethers, *e.g.* **2**.[2] The phenolic OH groups may serve as binding groups in the calix[*n*]arenes, while in the crown ethers this function is performed by the ether functionalities. Rearrangement of the monospirodienone derivatives of large-ring calixarenes results in the formation of xanthenocalixarenes, *i.e.* macrocyclic systems incorporating both ether and phenolic groups.[3] In this communication we report a previously unrecognized chemical transformation which converts a calix[*n*]arene into a saturated polyether macrocycle.

Exhaustive hydrogenation of the parent *para-tert*-butylcalix[4]arene **1a** may result in the formation of the saturated tetraalcohol **3**, which by intramolecular dehydration may afford the macrocyclic diether **4** eqn. (1). One drawback of this approach is that sixteen stereocenters are present in the tetraalcohol and in the final product, and in principle a very complex stereoisomeric mixture may be obtained. However, provided that under the hydrogenation conditions isomerization takes place, it could be expected that the thermodynamically more stable product will be formed preferentially. The use of calix[4]arene **1b**[4] somewhat improves the situation since the number of stereocentres in the final product **6** is reduced to twelve. In addition, since the phenol rings in **1b** are more sterically accessible than in **1a**, a more facile hydrogenation is expected.



1a R = Bu^t
b R = H

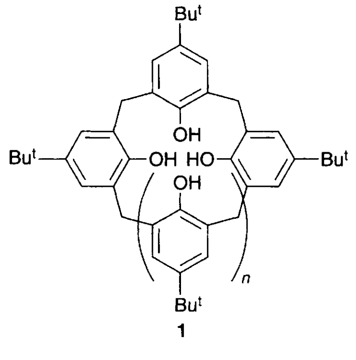
3 R = Bu^t
5 R = H

4 R = Bu^t
6 R = H

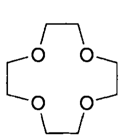
(1)

The macrocyclic diether **6** can be considered as possessing two perhydroxanthene subunits bridged by two methylene groups. Calculations and experimental data indicate that the *trans-syn-trans* isomer of perhydroanthracene, in which all rings adopt a chair conformation, is the lowest energy stereoisomeric form.[5,6] Provided that similar stereochemical effects operate on the two tricyclic subunits present in **6**, it should be expected that a similar *trans-syn-trans* arrangement will be preferred. The methylene groups should be located at equatorial positions of the condensed cyclohexane rings. Two different stereoisomeric forms exist in which both subunits in the macrocycle adopt a *trans-syn-trans* arrangement. These two forms can be viewed as possessing either alternating (*RSRS*, **6a**, C_{2v} symmetry) or nonalternating (*RRSS*, **6b**, C_s symmetry) arrangement of the configurations of the ether carbons along the internal periphery of the macrocycle. Molecular mechanics calculations (MM2 force field as implemented in MACROMODEL)[7] indicate that the alternating structure **6a** lies 6.2 kcal mol^{-1} (1 cal = 4.184 J) above the nonalternating structure **6b**.[†]

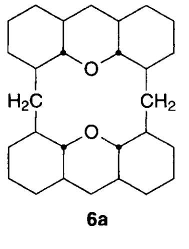
Reduction of **1b** was accomplished using harsh conditions (1450 psi H_2, Raney Ni–Pr^{i}OH, 240 °C) and the product was isolated by crystallization affording 15% of **6**, mp 272–275 °C[‡] Under the hydrogenation conditions, spontaneous intramolecular dehydration takes place. The assignment of signals in the ^{1}H and ^{13}C NMR was achieved by a combination of 2D NMR techniques (DQF COSY and inverse C–H correlation). The ^{1}H NMR of the diether (400 MHz, $CDCl_3$) displays two triplets at δ 2.46 and 2.71 which are assigned to methines attached to the oxygens. The large coupling constant observed (^3J 9.6–9.9 Hz) indicates an antiperiplanar arrangement with the two neighbouring methine protons, *i.e. trans* fusions of all rings. Notably, one pair of bridging methylene protons are strongly shielded (δ 0.80), while the second pair is strongly deshielded (δ 2.43). The low field signal is assigned to the two methylene protons pointing to centre of the cavity which should be deshielded due to their steric proximity to the ether oxygens.[8] The compound



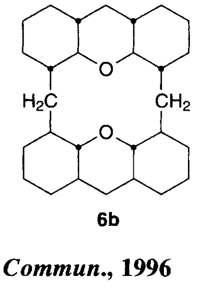
1



2



6a



6b

displays fifteen ^{13}C NMR signals with two signals at δ 81.64 and 86.48 which are assigned to symmetry unequivalent C–O carbons. These spectra are in agreement with a structure of C_s symmetry in which the mirror plane bisects the two tricyclic subunits. Since all fusions are *trans*, the symmetry is C_s, and only one pair of signals is observed for the bridging methylene protons it can be concluded, precluding accidental isochrony, that the stereochemistry of the tricyclic subunits is *trans-syn-trans*, *i.e.* **6b**. According to MM2 calculations, this is the more stable arrangement, suggesting that mutual isomerization of the isomeric diethers may take place under hydrogenation conditions.

A single crystal of the diether was grown from $CHCl_3$–CH_2Cl_2 and studied by X-ray crystallography. The numbering scheme of the molecular structure is displayed in Fig. 1.§ The crystal structure corroborates the stereochemistry (*trans-syn-trans*, **6b**) assigned from the NMR data. The crystal conformation is almost identical with that calculated by means of the MM2 force field. The internal periphery of the macrocycle has 12 atoms therefore **6b** can be regarded as a 12-crown-2 derivative. However, in the adopted conformation the oxygens almost completely fill the molecular cavity [the nonbonded O(1)–O(2) distance is 3.038(2) Å] as graphically shown by a space filling representation of the crystal structure (Fig. 1). The larger calix[*n*]arenes may serve as starting materials for the one-pot preparation of macrocyclic polyethers of large cavities in which the presence of the fused rings restricts their conformational flexibility.

We thank Dr Shmuel Cohen for the X-ray structural determination of **6b**. This research was supported by a Grant from the G.I.F., the German–Israeli Foundation for Scientific Research and Development.

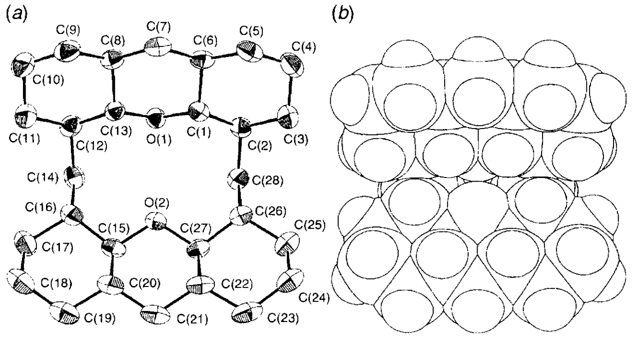


Fig. 1 (*a*) Numbering scheme of the crystal structure of **6b**; (*b*) Space filling representation of the crystal structure

Footnotes

† The macrocyclic ring imposes constrains in the torsional angles of the macrocycle. According to the calculations, eclipsed arrangements are forced between the H–C(ring)–C(bridging methylene)–C(ring) bonds. Whereas four eclipsed arrangements exist for **6a**, only two such arrangements exist in **6b**, resulting in its relative stabilization.

‡ A suspension of calix[4]arene (100 mg, 0.24 mmol) and Raney Nickel (0.6 g, 50% slurry in water) in isopropanol (100 ml) was heated in a pressure reactor to 240 °C in the presence of hydrogen, during three hours, with stirring. After cooling the catalyst was filtered off and the solvent evaporated yielding a mixture of reduced and fragmentation products, as judged by the ^{13}C NMR and MS analysis. Recrystallization of the mixture from light petroleum (bp 60–80 °C) afforded **6b** (15 mg, 15%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77–0.97 (partially overlapping d, 8 H), 1.03 (dt, 2 H, ^{2}J 13.1 Hz, ^{3}J 3.4 Hz), 1.22 (m, 12 H), 1.54 (m, 16 H), 2.43 (dt, 2 H, ^{2}J 13.6 Hz, ^{3}J 2.4 Hz), 2.46 (t, 2 H, ^{3}J 9.6 Hz), 2.71 (t, 2 H, ^{3}J 9.9 Hz). ^{13}C NMR ($CDCl_3$) δ 25.63, 23.03, 29.29, 31.61, 31.80, 33.20, 35.92, 37.12, 38.28, 38.87, 41.76, 42.11, 42.82, 81.64 (C–O), 86.48 (C–O).

§ *Crystal data* for **6b**: $C_{28}H_{44}O_2$, FW = 412.66 g mol^{-1}, space group $P2_1/c$,a = 5.387(2) Å, b = 21.611(4) Å, c = 19.820(4) Å, β = 93.45(3)°; V = 2303.4(9) Å^3, z = 4, D_c = 1.19 g cm^{-3}, μ(Cu-Kα) = 5.16 cm^{-1}, no. of unique reflections = 3512, no. of reflections with $I \geqslant 2\,\sigma_I$ = 2071, R = 0.048, R_w = 0.064.

References

1 For reviews on calixarenes see: C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, 1989; *Calixarenes: A Versatile Class of Macrocyclic Compounds*, ed. J. Vicens and V. Böhmer, Kluwer, Dordrecht, 1991; C. D. Gutsche, *Aldrichimica Acta*, 1995, **28**, 1; V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713.
2 For reviews see: *Crown Ethers and Analogs, Updates from the Chemistry of Functional Groups*, ed. S. Patai and Z. Rappoport, Wiley, Chichester, 1989.
3 O. Aleksiuk, S. Cohen and S. E. Biali, *J. Am. Chem. Soc.*, 1995, **117**, 9645. For a review on the spirodienone derivatives of the calixarenes see: O. Aleksiuk, F. Grynszpan, A. M. Litwak and S. E. Biali, *New. J. Chem.*, in the press.
4 C. D. Gutsche, J. A. Levine and P. K. Sujeeth, *J. Org. Chem.*, 1985, **50**, 5802.
5 N. L. Allinger and M. T. Wuesthoff, *J. Org. Chem.*, 1971, **36**, 2051.
6 For a review on fused ring systems see: E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 771.
7 For a description of the MACROMODEL program see: F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, E. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
8 van der Waals contacts result in downfield shifts. See: H. Günther, *NMR Spectroscopy*, Wiley, Chichester, 1980, p. 88.

Received, 18th September 1995; Com. 5/06119I