First synthesis of bridged and double calixsugars

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Abstract—Bridged and double calixarene–trehalose molecular architectures have been assembled through ester and amide linkages between the sugar and the macrocycle units; the double calixsugar showed selective receptor properties toward imidazole. © 2001 Elsevier Science Ltd. All rights reserved.

The ease of preparation in large scale quantities and variable size of the cavity, the tunable conformation, the selective and multiple derivatization are main features which have led calixarenes to the level of crown ethers and cyclodextrins as selective receptors for charged polar species, mainly cations.[1] On the other hand, the use of calixarenes as a platform for the implantation of biologically active molecules which can bind complementary neutral species is a much less investigated topic in supramolecular chemistry studies.[2] Within this context, we reported in recent years, back

to 1994, the synthesis of oxygen- and carbon-linked sugar calix[4]arenes (O-calixsugars[3–5] and C-calixsugars[6]) featuring up to four carbohydrate moieties on the lower or upper rim and also disclosed some of their receptor properties toward ions and neutral molecules. Other examples of glycosylated calix[4]arenes[7] and calix[4]resorcarenes[8] have been described in more recent years. In order to exploit the amphiphatic properties of calixsugars as hosts for ions and neutral molecules, we have designed more rigid structures in which a cavity is formed by bridging two
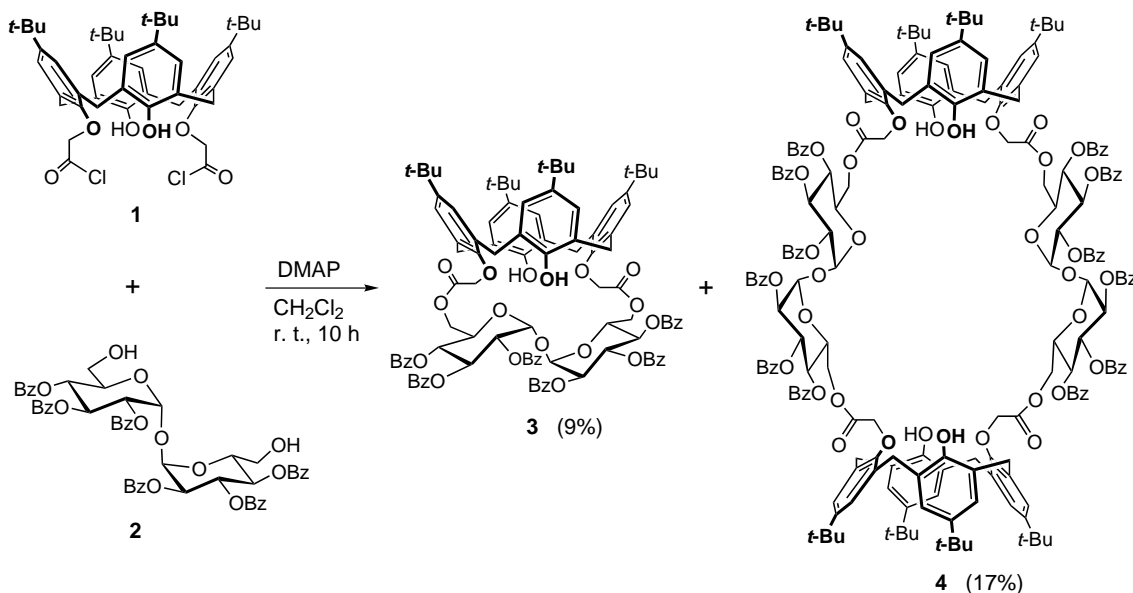
Scheme 1.

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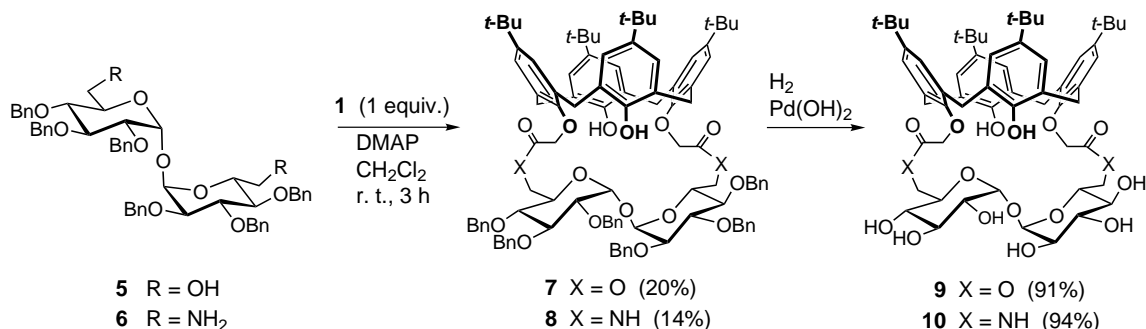
Scheme 2.

1,3-distal lower rim sites of a calix[4]arene molecule with an oligosaccharide or by assembling bis-calix[4]arene systems through lower rim–lower rim carbohydrate linkages. While covalently bridged and double or multiple calixarenes have been reported with various linkages,[9] there are no examples of compounds with carbohydrate tethers.

Aiming at assembling the calixsugar structure through ester and amide bonds, the C_2-symmetric and readily available α,α-trehalose diols $\mathbf{2}$[10] (Scheme 1) and $\mathbf{5}$[11] and the diamine[12] $\mathbf{6}$ (Scheme 2) were selected as disaccharide units for the construction of the designed novel three-dimensional macrocycles. The first coupling was carried out by condensation of the benzoylated trehalose derivative $\mathbf{2}$ (10 mM) with the known[13] 1,3-distal bis-carboxylic acid chloride $\mathbf{1}$ (1 equiv.) in CH_2Cl_2 in the presence of 4-dimethylaminopyridine (DMAP) at room temperature[14] (Scheme 1). This reaction afforded a complex mixture of products from which the bridged calixsugar[15] $\mathbf{3}$ (9%) and the double calixsugar[15] $\mathbf{4}$ (17%) were isolated by flash chromatography. A similar ratio of compounds $\mathbf{3}$ and $\mathbf{4}$, although in lower overall yield, was obtained using a 1 mM solution of the diol $\mathbf{2}$ and acid chloride $\mathbf{1}$. It was demonstrated that compound $\mathbf{4}$ was not transformed into $\mathbf{3}$ under the reaction conditions or during the chromatographic purification.

The condensation of the benzylated trehalose diol $\mathbf{5}$ (10 mM) with $\mathbf{1}$ under the same conditions outlined above also afforded a complex reaction mixture from which the diester bridged calixsugar $\mathbf{7}$ was isolated by flash chromatography in 20% yield[16] (Scheme 2). The diamine $\mathbf{6}$ reacted with $\mathbf{1}$ in a similar way to give the diamide bridged calixsugar $\mathbf{8}$ in 14% yield.[17] In both cases the corresponding double calixsugar derivatives were not isolated. At higher concentrations only unidentified polymeric materials appeared to be formed. The orthogonally protected compounds $\mathbf{7}$ and $\mathbf{8}$ were readily transformed into the free hydroxy derivatives $\mathbf{9}$ and $\mathbf{10}$ by debenzylation via hydrogenolysis.[18] The cone conformation of the calixarene scaffold in compounds $\mathbf{3}$, $\mathbf{4}$, and $\mathbf{7}$–$\mathbf{10}$ was substantiated by the chemical shifts of the protons and the multiplicity pattern of their signals, along with the chemical shifts of the carbon atoms of the methylene bridges.[19]

The receptor ability of the calixsugars $\mathbf{3}$, $\mathbf{4}$, and $\mathbf{7}$–$\mathbf{10}$ toward neutral and charged molecules was investigated by ^{1}H NMR analysis of suitable mixtures in organic solvents.[20] Evidence for complexation relied on the observed shift of signals of host and/or guest.[5,21] Only compound $\mathbf{4}$ in $CDCl_3$ solution showed substantial interaction with imidazole, while it appeared to be inert toward substituted derivatives (1-methylimidazole, benzimidazole) or the isomer pyrazole and various nitrogen containing heterocycles such as pyrrole, pyridine, thiazole, 2-aminopyrimidine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). An estimate of the recognition ability of $\mathbf{4}$ toward imidazole was obtained by ^{1}H NMR titration. These NMR experiments were performed at 295 K by adding a 100 mM solution of the guest to a 10 mM solution of the host (host–guest ratio from 2:1 to 1:9). For the K_{as} value determination eight different host and guest concentrations were considered using as a probe three proton signals (H-2, H-6a, and one ArH). The resulting association constant value of 11.1 ± 2.5 M^{-1} was calculated by nonlinear regression. Hence studies on the use of $\mathbf{4}$ or similar double calixsugars as molecular receptors of imidazole-bearing biologically active compounds[22] now become of interest.

Acknowledgements

References

1. (a) Gutsche, C. D. In *Calixarenes, Monograph in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1989; Vol. 1; (b) Gutsche, C. D. In *Calixarenes Revisited, Monograph in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1998; Vol. 6.
2. For reviews, see: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Diamond, D.; McKervey, M. A.

Chem. Soc. Rev. **1996**, 15. (c) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713. (d) Lhoták, P.; Shinkai, S. *J. Phys. Org. Chem.* **1997**, *10*, 273.

3. Marra, A.; Scherrmann, M.-C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2479.

4. Marra, A.; Dondoni, A.; Sansone, F. *J. Org. Chem.* **1996**, *61*, 5155.

5. Dondoni, A.; Marra, A.; Scherrmann, M.-C.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Eur. J.* **1997**, *3*, 1774.

6. Dondoni, A.; Kleban, M.; Marra, A. *Tetrahedron Lett.* **1997**, *38*, 7801.

7. (a) Meunier, S. J.; Roy, R. *Tetrahedron Lett.* **1996**, *37*, 5469; (b) Curtis, A. D. M. *Tetrahedron Lett.* **1997**, *38*, 4295; (c) Félix, C.; Parrot-Lopez, H.; Kalchenko, V.; Coleman, A. W. *Tetrahedron Lett.* **1998**, *39*, 9171; (d) Roy, R.; Kim, J. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 369; (e) Saitz-Barria, C.; Torres-Pinedo, A.; Santoyo-González, F. *Synlett* **1999**, 1891; (f) Budka, J.; Tkadlecová, M.; Lhoták, P.; Stibor, I. *Tetrahedron* **2000**, *56*, 1883; (g) Calvo-Flores, F. G.; Isac-Garcia, J.; Hernández-Mateo, F.; Pérez-Balderas, F.; Calvo-Asín, J. A.; Sanchéz-Vaquero, E.; Santoyo-González, F. *Org. Lett.* **2000**, *2*, 2499.

8. (a) Fujimoto, T.; Shimizu, C.; Hayashida, O.; Aoyama, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6676; (b) Hayashida, O.; Shimizu, C.; Fujimoto, T.; Aoyama, Y. *Chem. Lett.* **1998**, 13; (c) Hayashida, O.; Nishiyama, K.; Matsuda, Y.; Aoyama, Y. *Tetrahedron Lett.* **1999**, *40*, 3407.

9. For reviews, see: Asfari, Z.; Weiss, J.; Vicens, J. *Synlett* **1993**, 719. Böhmer, V. *Liebigs Ann./Recueil* **1997**, 2019. See also: Hwang, G. T.; Kim, B. H. *Tetrahedron Lett.* **2000**, *41*, 5917.

10. Coterón, J. M.; Vicent, C.; Bosso, C.; Penadés, S. *J. Am. Chem. Soc.* **1993**, *115*, 10066.

11. Liav, A.; Goren, M. B. *Chem. Phys. Lipids* **1980**, *27*, 345.

12. Liav, A.; Goren, M. B. *Carbohydr. Res.* **1980**, *87*, 153.

13. Collins, E. M.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3137.

14. A mixture of calixarene dichloride **1** (160 mg, 0.20 mmol), diol **2** (193 mg, 0.20 mmol), DMAP (97 mg, 0.80 mmol), and anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 10 h and then concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane–AcOEt to afford a 1:2 mixture of **3** and **4** contaminated by uncharacterized byproducts (130 mg). Purification of this mixture by column chromatography on silica gel (100:1 CH_2Cl_2–Et_2O) gave first **3** (31 mg, 9%) as a white solid; mp 169–171°C, $[\alpha]_D^{20} = +120$ ($c = 0.8$, $CHCl_3$). ^1H NMR: δ 8.26–8.22, 7.85–7.81, 7.64–7.27, and 7.13–7.10 (4m, 38H, ArH), 6.31 (s, 2H, 2OH), 6.06 (dd, 2H, $J_{2,3} = 9.7$, $J_{3,4} = 9.5$ Hz; 2H-3), 5.96 (d, 2H, $J_{1,2} = 3.8$ Hz; 2H-1), 5.47 (dd, 2H, $J_{4,5} = 10.0$ Hz; 2H-4), 4.88 and 4.54 (2d, 4H, $J = 15.0$ Hz; 2OCH$_2$CO$_2$), 4.64 and 3.46 (2d, 4H, $J = 13.6$ Hz; 2ArCH$_2$Ar), 4.62 and 3.37 (2d, 4H, $J = 13.1$ Hz; 2ArCH$_2$Ar), 4.58 (dd, 2H, $J_{5,6a} = 5.5$, $J_{6a,6b} = 12.0$ Hz; 2H-6a), 4.14 (dd, 2H, $J_{5,6b} = 2.2$ Hz; 2H-6b), 4.02 (ddd, 2H, 2H-5), 1.32 and 0.93 (2s, 36H, 4t-Bu). MALDI-TOF MS ($C_{102}H_{102}O_{23}$): 1718.6 (M+Na), 1734.8 (M+K). Eluted second was **4** (58 mg, 17%) as a white solid; mp 205–207°C, $[\alpha]_D^{20} = +119$ ($c = 0.9$, $CHCl_3$). ^1H NMR: δ 8.21–8.18, 7.97–7.94, 7.90–7.87 and

7.58–7.31 (4m, 60H, ArH), 7.80 (s, 4H, 4OH), 7.05 and 7.02 (2d, 8H, $J = 2.0$ Hz; ArH), 6.91 and 6.88 (2d, 8H, $J = 2.0$ Hz; ArH), 6.36 (dd, 4H, $J_{2,3} = 10.0$, $J_{3,4} = 9.7$ Hz; 4H-3), 5.96 (d, 4H, $J_{1,2} = 3.5$ Hz; 4H-1), 5.92 (dd, 2H, $J_{4,5} = 10.0$ Hz; 4H-4), 5.55 (dd, 4H, 4H-2), 4.61 and 4.41 (2d, 8H, $J = 16.0$ Hz; 4OCH$_2$CO$_2$), 4.46 and 3.34 (2d, 8H, $J = 13.0$ Hz; 4ArCH$_2$Ar), 4.35 and 3.28 (2d, 8H, $J = 13.5$ Hz; 4ArCH$_2$Ar), 4.27 (ddd, 4H, $J_{5,6a} = 3.5$, $J_{5,6b} = 4.5$ Hz; 4H-5), 4.02 (dd, 4H, $J_{6a,6b} = 12.0$ Hz; 4H-6a), 3.91 (dd, 4H, 4H-6b), 1.19 and 1.13 (2s, 72H, 8t-Bu). MALDI-TOF MS ($C_{204}H_{204}O_{46}$): 3412.0 (M+Na), 3427.9 (M+K).

15. Since the elemental analyses of calixarenes are very often uncorrected[4,5] (found carbon values considerably lower than the calculated ones), the identity and purity of the following new compounds were established by MS and NMR analyses. See also: (a) Böhmer, V.; Jung, K.; Schön, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790. (b) Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527.

16. A mixture of calixarene dichloride **1** (160 mg, 0.20 mmol), diol **5** (177 mg, 0.20 mmol), DMAP (97 mg, 0.80 mmol), and anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 10 h and then concentrated. The residue was eluted from a column of silica gel with 5:1 CH_2Cl_2–cyclohexane and then cyclohexane–AcOEt (from 5:1 to 3:1) to give **7** (64 mg, 20%) as a white solid; mp 124–125°C, $[\alpha]_D^{20} = +78$ ($c = 0.8$, $CHCl_3$). ^1H NMR: δ 7.40–7.22 (m, 30H, ArH), 7.16 and 7.08 (2d, 4H, $J = 2.3$ Hz; ArH), 6.74 and 6.70 (2d, 4H, $J = 2.3$ Hz; ArH), 6.10 (s, 2H, 2OH), 5.29 (d, 2H, $J_{1,2} = 3.4$ Hz; 2H-1), 4.94 and 4.82 (2d, 4H, $J = 11.1$ Hz; 2PhCH$_2$O), 4.93 and 4.65 (2d, 4H, $J = 11.3$ Hz; 2PhCH$_2$O), 4.59 and 4.53 (2d, 4H, $J = 14.5$ Hz; 2OCH$_2$CO$_2$), 4.55 (s, 4H; 2PhCH$_2$O), 4.53 and 3.28 (2d, 4H, $J = 13.4$ Hz; 2ArCH$_2$Ar), 4.46 (dd, 2H, $J_{5,6a} = 6.1$, $J_{6a,6b} = 11.5$ Hz; 2H-6a), 4.42 and 3.41 (2d, 4H, $J = 13.5$ Hz; 2ArCH$_2$Ar), 4.36 (dd, 2d, $J_{5,6b} = 2.7$ Hz; 2H-6b), 4.18 (dd, 2H, $J_{2,3} = 9.5$, $J_{3,4} = 9.0$ Hz; 2H-3), 4.08 (ddd, 2H, $J_{4,5} = 9.8$ Hz; 2H-5), 3.50 (dd, 2H; 2H-4), 3.46 (dd, 2H; 2H-2), 1.32 and 0.93 (2s, 36H, 4t-Bu). MALDI-TOF MS ($C_{102}H_{114}O_{17}$): 1635.2 (M+Na), 1650.8 (M+K).

17. A mixture of calixarene dichloride **1** (160 mg, 0.20 mmol), diamine **6** (176 mg, 0.20 mmol), DMAP (97 mg, 0.80 mmol), and anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 3 h and then concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane–AcOEt to give **8** (45 mg, 14%) as a white solid mp 148–150°C. $[\alpha]_D^{20} = +33$ ($c = 1.0$, $CHCl_3$). ^1H NMR: $\delta = 7.72$ (dd, 2H, $J_{NH,6a} = 5.5$, $J_{NH,6b} = 6.0$ Hz; 2NH), 7.41–7.22 (m, 30H, ArH), 7.19 and 7.14 (2d, 4H, $J = 2.4$ Hz; ArH), 6.63 and 6.61 (2d, 4H, $J = 2.5$ Hz; ArH), 5.43 (s, 2H, 2OH), 5.26 (d, 2H, $J_{1,2} = 3.5$ Hz; 2H-1), 4.96 and 4.82 (2d, 4H, $J = 11.0$ Hz; 2PhCH$_2$O), 4.90 and 4.70 (2d, 4H, $J = 10.8$ Hz; 2PhCH$_2$O), 4.62 and 4.59 (2d, 4H, $J = 11.2$ Hz; 2PhCH$_2$O), 4.57 and 4.37 (2d, 4H, $J = 15.6$ Hz; 2OCH$_2$CON), 4.32 and 3.40 (d, 4H, $J = 13.5$ Hz; 2ArCH$_2$Ar), 4.18 and 3.41 (2d, 4H, $J = 13.5$ Hz; 2ArCH$_2$Ar), 4.15 (dd, 2H, $J_{2,3} = 9.4$, $J_{3,4} = 9.0$ Hz; 2H-3), 3.94 (ddd, 2H, $J_{4,5} = 9.6$, $J_{5,6a} = 3.4$, $J_{5,6b} = 7.1$ Hz; 2H-5), 3.87 (ddd, 2H, $J_{6a,6b} = 13.5$ Hz; 2H-6a), 3.56 (dd, 2H; 2H-2), 3.55 (dd, 2H; 2H-6b), 3.39 (dd, 2H; 2H-4), 1.37 and 0.87 (2s, 36H, 4t-Bu). MALDI-TOF MS ($C_{102}H_{116}N_2O_{15}$): 1632.8 (M+Na), 1649.0 (M+K).

18. Compound **9**: mp 175°C (dec.); $[\alpha]_D^{20} = +32$ ($c = 0.8$, CH_3OH). Compound **10**: mp 240°C (dec.); $[\alpha]_D^{20} = +41$ ($c = 1.0$, CH_3OH).

19. Calix[4]arenes adopting a cone conformation show the signals for the equatorial and axial protons of the methylene bridges as well resolved doublets at $\delta \sim 3$ and 4 ppm, respectively. Moreover, the signals for the carbon atoms of the methylene bridges appear at $\delta \sim 31$. See Refs. 1 and 3–6.

20. The following compounds were examined: methyl mandelate, *N,N'*-diphenylethylenediamine, 2,2'-bipyridine, 2,9-dimethyl-1,10-phenantroline, (−)-*N*-methylephedrine, tetrabutylammonium dihydrogenphosphate, phenyl tetra-*O*-acetyl-α-D-galactopyranoside, D-mannosamine hydrochloride, guanosine, uracil, (+)-naproxen, *N*-phthaloyl-glycine, Boc-L-histidine methyl ester, Cbz-L-histidine, L-histidine, and L-phenylalanine ethyl ester hydrochloride.

21. (a) Morzherin, Y.; Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. M. *J. Org. Chem.* **1993**, *58*, 7602; (b) Araki, K.; Hayashida, H. *Chem. Lett.* **2000**, 20.

22. Carver, D. S.; Lindell, S. D.; Saville-Stones, E. A. *Tetrahedron* **1997**, *53*, 14481 and references cited therein.