Synthesis of Bridged Thiourea Calix-sugar

Claudio Saitz-Barria[1], Antonio Torres-Pinedo, Francisco Santoyo-González*

Instituto de Biotecnología, Facultad de Ciencias, Universidad de Granada, 18071 Granada, Spain

Fax +34-958-243186; E-mail: fsantoyo@goliat.ugr.es

Abstract: The effective synthesis of a variety of bisthiourea-bridged calix[4]arenes substituted by carbohydrates units (D-glucose, D-mannose, D-galactose and lactose) at the narrow rim by reaction of bis(aminoethoxy)calix[4]arene **1** with glycosyl isothiocyanates is described.

Key words: calix-sugar, calix[4]arenes, thiourea, glycocsyl isothiocyanates, supramolecular chemistry

Calixarenes are macrocyclic molecules, like crown ethers and cyclodextrins, made up by base-induced condensation of *p*-substituted phenols and formaldehyde. The chemistry of calixarenes has been extensively discussed in several books[2-4] and review articles.[5-9] There are several reasons for the current widespread interest in calixarenes. An important one is the remarkably simple way used for the synthesis of the parent compounds. In addition, wide and narrow rim functionalization of these macrocycles has resulted in a massive expansion in the range of derivatives available.[10-14] In particular, calix[4]arenes provide a versatile platform of well defined shape for the construction of more sophisticated structures. Thus, calix[4]arene moieties has been connected to multiples systems, such us: crown ethers,[15] cyclodrextrins,[16,17] porphyrins,[18-20] aminoacids,[21] etc. However only limited efforts have been made to construct biologically calixarenes containing carbohydrates moieties. To this end, Dondoni and Ungaro[22-24] have described the synthesis of calix[4]arenes substituted by carbohydrate units at the wide and narrow rim. Roy et al.[25,26] have prepared a water soluble α-thiosialoside-p-*tert*-butylcalix[4]arene derivative used for protein binding studies and dendritic water-soluble carbohydrate-containing *p-tert*-butyl calix[4]arenes and their lectin-binding properties. Parrot-Lopez et al.[27] reported a

Table 1 Yields and Physical Data of **2a-h**

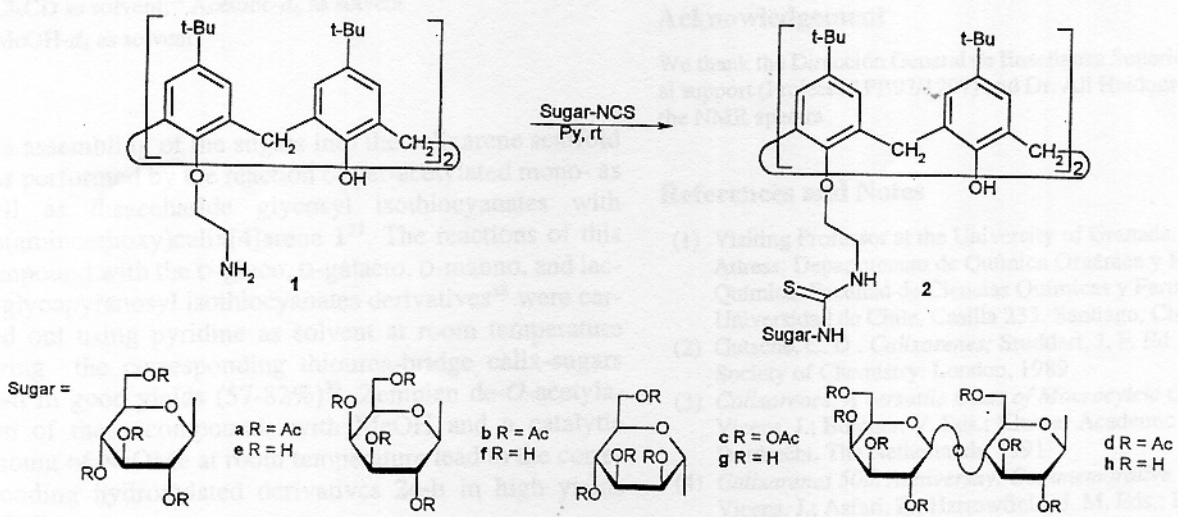
Compound	Yields (%)	ν_{max} (cm^{-1})	Mp (° C)	Optical Rotation	MS FAB + (*m/z*)		
					$[M + Na]^+$	Calc.	Found
2a	57	3461, 3434, 3355, 3312, 1754, 1227, 1037	130-132	+43[a]	$C_{78}H_{104}N_4O_{22}S_2Na$	1535.6481	1535.6479
2b	60	3483, 3444, 3413, 3364, 1752, 1226, 1051	155-156	+49[a]	$C_{78}H_{104}N_4O_{22}S_2Na$	1535.6481	1535.7
2c	82	3352, 1753, 1225, 1053	144-146	-19[b]	$C_{78}H_{104}N_4O_{22}S_2Na$	1535.6481	1535.6571
2d	57	3444, 3418, 1753, 1229, 1047	154-155	+26[a]	$C_{102}H_{136}N_4O_{38}S_2Na$	2111.8170	2111.89
2e	89	3347, 1075, 1029	>210 (dec)	+12[c]	$C_{62}H_{88}N_4O_{14}S_2Na$	1199.5636	1199.5619
2f	90	3342, 1086, 1042, 1025	142 (dec)	+ 25[c]	$C_{62}H_{88}N_4O_{14}S_2Na$	1199.5636	1199.5632
2g	85	3346, 1064	314-317 (dec)	+56[d]	$C_{62}H_{88}N_4O_{14}S_2Na$	1199.5636	1199.568
2h	86	3384, 1075, 1039	337-340 (dec)	+18[e]	$C_{74}H_{108}N_4O_{24}S_2Na$	1523.669	1523.671

[a] $[\alpha]_D$ (*c* 1, chloroform); [b] $[\alpha]_{436}$ (*c* 1, chloroform); [c] $[\alpha]_{436}$ (*c* 1, acetone); [d] $[\alpha]_D$ (*c* 1, pyridine); [e] $[\alpha]_{365}$ (*c* 1, pyridine)

Table 2 Selected ^{1}H NMR Chemical Shifts (ppm) and coupling constants (Hz) of **2a-d** at Room Temperature

Compound	Sugar-N*H*	CH_2NH	OH	Ar-H	ArCH_2Ar	H-1
2a[a]	6.77 d (9.3)	8.71 br s	9.04 br s	7.10 d (2.1), 7.07 d (2.0), 7.05 d (2.1), 7.01 d (2.0)	4.37, 3.49 AB system (13.4), 4.16, 3.38 AB system (13.1)	5.82 t (9.2)
2a[b]	← 8.37-8.27 br s and 8.00 br s →			7.12 s, 7.10 s	4.19 d (12.3), 3.40 d[c] (13.0), 3.38 d[c] (12.8)	5.79 br s
2b[a]	6.76 d (9.0)	8.63 br s	9.01 br s	7.13 d (1.9), 7.09 br s, 7.04 d (2.1), 7.01 br s	4.35 , 3.51 AB system (13.0), 4.20, 3.40 AB system (13.1)	5.84 br t (9.0)
2b[b]	8.41 d (8.9)	←8.26 br s, 7.89 br s→		7.11 s, 7.09 s	3.38 d[c] (12.9)	5.80 br s
2c[a]	7.32 d (8.2)	8.20 br s	8.53 br s	7.12 br s, 7.05 br s, 6.99 br s, 6.92 br s	4.26, 3.44 AB system (13.6), 4.24, 3.38 AB system (13.2)	6.13 br s
2c[b]	8.99 d (8.1)	← 8.34 br s, 7.87 br s →		7.13 s, 7.11 s	4.23, 3.41 AB system (12.4), 4.22 , 3.38 AB system (12.2)	5.94 br s
2d[a]	6.65 d (9.2)	8.62 br s	8.33 br s	7.1 d (2.0), 7.08 br s, 7.03 d (2.0), 7.01 d (2.0)	4.46, 3.46 AB system (13.8), 4.15, 3.37 AB system (13.2)	5.77 t (9.3)
2d[b]	← 8.27 br s, 7.95 br s →			7.11 s, 7.09 s	3.39 d[c] (11.9)	5.74 br s

[a] Cl_3CD as solvent; [b] DMSO-d_6 as solvent; [c] The corresponding signal for the A proton of the AB system is not resolved by overlapping

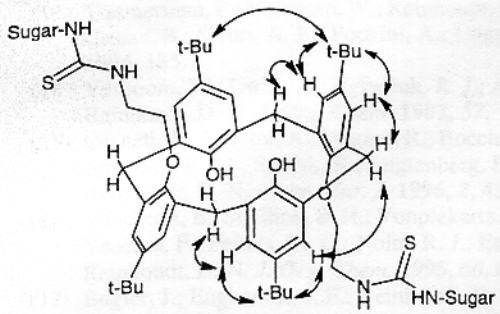


Scheme

new class of carbohydrate containing calixarenes using the Suzuki reaction. Related macrocylic sugar clusters have also been described by Aoyama et al.[28-30]

On the other hand, calixarenes functionalised with urea and thiourea moieties have been synthesised and exploited as a new class of neutral ligands for selective anion complexation.[31,32] In addition, these derivatives of calixarenes have proved to dimerize reversibly in organic solvent by intermolecular hydrogen-bonds forming dimeric capsules.[33,34]

Continuing our efforts in the synthesis of new cluster glycosides,[35,36] we report here the synthesis of bisthiourea-bridged calix[4]arenes substituted by carbohydrates units (D-glucose, D-mannose, D-galactose and lactose) at the narrow rim.



nOe experiments for calix-sugars

Figure

Table 3 Selected ^{13}C NMR Chemical Shifts (ppm) of **2a-h** at Room Temperature

Compound	C=S	C-1	ArCH_2Ar
2a[a]	184.7	82.5	32.5, 31.8
2b[a]	184.5	82.7	32.5, 31.8
2c[a]	183.9	79.8	32.4, 31.6
2d[a]	185.3	83.1	33.2, 32.4
2e[b]	185.0	84.5	32.8
2f[b]		85.5	32.8, 32.5
2g[c]	185.2	83.6	32.5, 32.3
2h[c]		80.6	32.6, 32.1

[a] Cl_3CD as solvent; [b] Acetone-d_6 as solvent
[c] MeOH-d_4 as solvent

The assembling of the sugars into the calixarene scaffold was performed by the reaction of per-acetylated mono- as well as disaccharide glycosyl isothiocyanates with bis(aminoethoxy)calix[4]arene **1**[37]. The reactions of this compound with the D-gluco, D-galacto, D-manno, and lacto glycopyranosyl isothiocyanates derivatives[38] were carried out using pyridine as solvent at room temperature giving the corresponding thiourea-bridge calix-sugars **2a-d** in good yields (57-82%)[39]. Zemplen de-*O*-acetylation of these compounds with MeOH and a catalytic amount of NaOMe at room temperature lead to the corresponding hydroxylated derivatives **2e-h** in high yields (>80%).

The structure of the calix-sugar **2a-h** was established on the basis of the spectroscopical data. The IR spectra contained absorption for the NH streching band of the thiourea group. The ^1H NMR spectra in $CDCl_3$ showed that the Ar-H proton of the calixarene appeared as four separated doublets (see Table 2) with coupling constants of ~2.0 Hz typical for protons in meta-position. Under the same conditions the hydrogens of the methylenes connecting the aromatic rings appear as two AX systems. In addition two signals are observed for the carbon atoms of this methylene groups. These data together with the substitution pattern of the aromatic rings point to a 1,2-alternate cone conformation in $CDCl_3$. NOE effects obtained after the irradiation of the signals corresponding to the aromatic and *tert*-butyl hydrogens were consistent with this 1,2-alternate cone conformation (see Figure).

Proofs were also obtained that support the intermolecular assembling of the described calix-sugars in $CDCl_3$. The ^1H NMR spectra in this solvent for **2a-d** showed chemical shifts for the thiourea NH protons at δ 8.3±0.4 and 6.9±0.4 and the phenolic OH appearing at δ 8.7±0.4 (see Table 2). None of these signals shift upon dilution and this is a good indication of a strong association. Compound **2c** was further studied in mixtures of $CDCl_3$ and DMS*O*-d_6, a strong hydrogen-bond acceptor. The monomer was observed only at $\chi_{DMSO} \geq 0.05$ by ^1H NMR spectroscopy; the NH and OH protons gave broad signals centred at δ 8.0 and 7.7. The monomer was the only species observed in DMS*O*-d_6 as supported by the observed simplification of the spectra where only two singlets for the aromatic calixarene protons were found (see Table 2). Additional evidence for the dimeric structure of **2a-d** came from the mass spectrometry. In addition to a peak at m/z 1536 for **2a-c** and 2112 for **2d** (100% rel. intensity) ascribable to the monomer $[M+Na]^+$, the positive-ion FAB spectra of **2a-c** showed another for the dimers at m/z 3049 (2-4%).

Molecular recognition studies of the described calix-sugars are currently under investigation in our laboratory.

Acknowledgement

We thank the Dirección General de Enseñanza Superior for financial support (Project nº PB97/1207) and Dr. Ali Haidour for recording the NMR spectra

References and Notes

(1) Visiting Professor at the University of Granada. Permanent Adress: Departamento de Química Orgánica y Físico Química. Facultad de Ciencias Químicas y Farmaceúticas. Universidad de Chile, Casilla 233, Santiago, Chile
(2) Gutsche, C. D., *Calixarenes;* Stoddart, J. F. Ed.; Royal Society of Chemistry: London, 1989
(3) *Calixarenes. A versatile Class of Macrocylcic Compounds;* Vicens, J.; Böhmer, V. Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991
(4) *Calixarenes 50th Anniversay: Commemorative Volume;* Vicens, J.; Asfari, Z.; Harrowfield, J. M. Eds.; Kluwer Academic Publishers: Dordecht, The Netherlands, 1994
(5) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 3.
(6) Bohmer, V. *Angew. Chem. Int. Ed. Eng* **1995**, *34*, 713.
(7) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933.
(8) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713.
(9) Denamor, A. F.; Cleverley, R. M.; Zapata-Ormachea, M. L. *Chem. Rev.* **1998**, *98*, 2495.
(10) Neri, P.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1995**, *60*, 4126.
(11) Vandienst, E.; Bakker, W. I.; Engbersen, J. F.; Verboom, W.; Reinhoudt, D. N. *Pure Appl. Chem.* **1993**, *65*, 387.
(12) Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527.

(13) Timmerman, P.; Verboom, W.; Reinhoudt, D. N.; Arduini, A.; Grandi, S.; Sicuri, A. R.; Pochini, A.; Ungaro, R. *Synthesis* **1994**, 185.
(14) Verboom, W.; Durie, A.; Egberink, R. J.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 1313.
(15) Casnati, A.; Pochini, A.; Ungaro, R.; Bocchi, C.; Ugozzoli, F.; Egberink, R. M.; Struijk, H.; Lugtenberg, R.; Dejong, F.; Reinhoudt, D. N. *Chem. Eur. J.* **1996**, *2*, 436.
(16) Vandienst, E.; Snellink, B. H.; Vonpiekartz, I.; Gansey, M. H.; Venema, F.; Feiters, M. C.; Nolte, R. J.; Engbersen, J. F.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6537.
(17) Bugler, J.; Engbersen, J. F.; Reinhoudt, D. N. *J. Org. Chem.* **1998**, *63*, 5339.
(18) Nagasaki, T.; Fujishima, H.; Shinkai, S. *Chem. Lett.* **1994**, 989.
(19) Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, *35*, 7131.
(20) Arimura, T.; Brown, C. T.; Springs, S. L.; Sessler, J. L. *Chem. Commun.* **1996**, 2293.
(21) Casnati, A.; Fabbi, M.; Pelizzi, N.; Pochini, A.; Sansone, F.; Ungaro, R.; Dimodugno, E.; Tarzia, G. *Bioorg. Medicinal Chem. Letter.* **1996**, *6*, 2699.
(22) Marra, A.; Scherrmann, M. C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2479.
(23) Dondoni, A.; Marra, A.; Scherrmann, M. C.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Eur. J.* **1997**, *3*, 1774.
(24) Sansone, F.; Barboso, S.; Casnati, A.; Fabbi, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 897.
(25) Meunier, S. J.; Roy, R. *Tetrahedron Lett.* **1996**, *37*, 5469.
(26) Roy, R.; Kim, J. M. *Angew. Chem. Int. Ed.* **1999**, *38*, 369.
(27) Felix, C.; Parrot-López, H.; Kalchenko, V.; Coleman, A. W. *Tetrahedron Lett.* **1998**, *39*, 9171.
(28) Fujimoto, T.; Shimizu, C.; Hayashida, O.; Aoyama, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6676.
(29) Hayashida, O.; Shimizu, C.; Fujimoto, T.; Aoyama, Y. *Chem. Lett.* **1998**, 13.
(30) Hayashida, O.; Nishiyama, K.; Matsuda, Y.; Aoyama, Y. *Tetrahedron Lett.* **1999**, *40*, 3407.
(31) Scheerder, J., Fochi, M., Engbersen, J. F., and Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815.
(32) Scheerder, J., Engbersen, J. F., Casnati, A., Ungaro, R., and Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448.
(33) Mogck, O., Bohmer, V., and Vogt, W. *Tetrahedron* **1996**, *52*, 8489.
(34) Castellano, R. K. and Rebek, J. *J. Am. Chem. Soc.* **1998**, *120*, 3657.
(35) Garcia-Lopez, J. J.; Hernandez-Mateo, F.; Isac-Garcia, J.; Kim, J. M.; Roy, R.; Santoyo-Gonzalez, F. *J. Org. Chem.* **1999**, *64*, 522.
(36) Garcia-Lopez, J. J.; Santoyo-Gonzalez, F.; Vargas-Berenguel, A.; Giménez Martínez, J. J. *Chem. -Eur. J.* **1999**, *5*, 1775.
(37) Zhang, W. C.; Huang, Z. T. *Synthesis* **1997**, 1073.
(38) García-Fernández, J. M.; Ortiz-Mellet, C. *Sulfur Repts.* **1996**, *19*, 61.
(39) *General Procedure for the synthesis of calix-sugars* **2a-d**: To a solution of **1** (0.5 mmol) in anhydrous pyridine (10 mL) was added the glycopyranosyl isothiocyanate (1.1 mmol). The reaction mixture was left at rt for 24 h. The solvent was then removed by evaporation under vacuum and coevaporated with toluene (2 x 10 mL). Ether was added and when crystallisation of the corresponding calix-sugar happened the product was filtered. In those cases in which crystallisation was not observed the solvent was evaporated and the product purified by column chromatography (AcOEt-Hexane 1:1).