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A Systematic Study to Neutral, Water Soluble Calix[4]arenes

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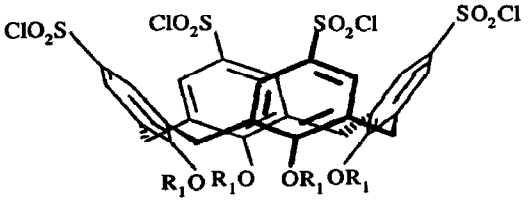
Abstract: A series of neutral water soluble calix[4]arenes was synthesized via direct chlorosulfonylation followed by reaction with hydroxyl group-containing amines. The solubility of these calix[4]arene sulfonamides in water, as determined by means of UV measurements, varies from ~ 10^{-5} to 0.31 M.

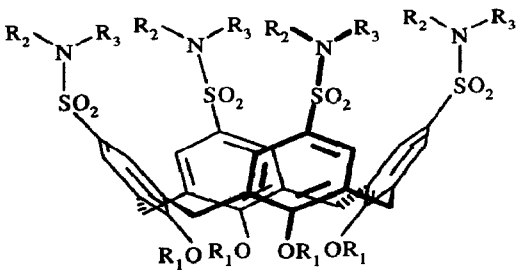
Calix[4]arenes[1,2] have become important hydrophobic building blocks in supramolecular chemistry. We have used (selective) functionalization[3] of calix[4]arenes both at the phenolic OH groups (*lower rim*) and at the para positions of the phenol rings (*upper rim*) for the design of selective receptors for cations,[4] anions,[5] and neutral molecules.[6] Subsequent application of these calix[4]arene based ionophores in ion sensors[7] or ion transport through liquid membranes[8] requires a high hydrophobicity. However, for *in vivo* application of appropriately functionalized calix[4]arenes water solubility is a prerequisite.[9] Hitherto in most cases water soluble calixarenes have been obtained by the introduction of charged moieties. The first report of water soluble calixarenes by Ungaro *et al.*[10] describes a *p-tert*-butylcalix[4]arene tetracarboxylic acid, of which the alkali and ammonium salts are soluble in water (concentrations between 5 x 10^{-4} and 5 x 10^{-3} M depending on the cation used). Shinkai *et al.*[11] reported the pK_a values of a water soluble *p*-tetrasulfonate tetrasodium calix[4]arene. *Lower rim* functionalized *upper rim* sulfonato calix[4]arenes were described by Casnati *et al.*[12] Other methods using charged species to achieve water solubility are the introduction of sulfonato groups at the *lower rim*,[13] phosphonic acid groups[14] or cationic trialkylammonium groups.[15] To avoid unspecific binding of cations by anionic groups, or repulsion by cationic groups in the receptor molecule, we need **neutral**, water soluble, functionalized calix[4]arenes. To the best of our knowledge in literature only two neutral, water soluble calix[4]arenes have been described. Shinkai and Reinhoudt *et al.*[16] reported the pK_a determination of

neutral, water soluble tetrakis[bis-(2-hydroxyethyl)-aminosulfonyl]calix[4]arene. Newkome *et al.*[17] developed the *silvanols* with hydroxyl group-containing amides at the *upper rim*, of which the calix[4]arene derivative contains 36 hydroxyl groups. However, in both cases no quantitative data about the water solubilities are given.

Recently we reported that calix[4]arene sulfonamides can be easily obtained by chlorosulfonylation at the *upper rim* of calix[4]arenes, functionalized at the *lower rim*, followed by reaction with an appropriate amine.[18] In this communication we present our preliminary results of a study towards water soluble calix[4]arenes by systematically increasing the number of hydroxyl groups in calix[4]arene sulfonamides.

As starting compounds we selected two different tetrakis(chlorosulfonylated)calix[4]arenes *viz.* the tetrakis(ethoxymethoxy)- (**1**) and the tetraethyl ester derivative (**2**).[18] Reaction of **1** and **2** with ethanolamine in dichloromethane for 8 h gave the calix[4]arene sulfonamides **3a**[19] and **4a**[20] both in 57% yield. From the corresponding reaction with diethanolamine compounds **3b**[21] and **4b**[22] were obtained in 42 and 49% yield, respectively. For solubility reasons the reactions of **1** and **2** with tris(hydroxymethyl)aminomethane were carried out in DMSO for 8 h to give compounds **3c**[23] and **4c**[24] in 56 and 42% yield, respectively. The ^{1}H-NMR spectra of all compounds **3** and **4**, recorded in solvents more polar than $CDCl_3$, show singlets for the aromatic protons and one AB system for the protons of the methylene bridges, indicating that the substitution reaction of the chloro atoms of compounds **1** and **2** by the amines has taken place completely.





1 $R_1 = CH_2CH_2OCH_3$
2 $R_2 = CH_2CO_2CH_2CH_3$

3a $R_1 = CH_2CH_2OCH_3$, $R_2 = H$, $R_3 = CH_2CH_2OH$
3b $R_1 = CH_2CH_2OCH_3$, $R_2 = R_3 = CH_2CH_2OH$
3c $R_1 = CH_2CH_2OCH_3$, $R_2 = H$, $R_3 = C(CH_2OH)_3$
4a $R_1 = CH_2CO_2CH_2CH_3$, $R_2 = H$, $R_3 = CH_2CH_2OH$
4b $R_1 = CH_2CO_2CH_2CH_3$, $R_2 = R_3 = CH_2CH_2OH$
4c $R_1 = CH_2CO_2CH_2CH_3$, $R_2 = H$, $R_3 = C(CH_2OH)_3$

The water solubility of sulfonamides **3a-c** and **4a-c** was determined by means of UV measurements[26] (Table 1). These data clearly demonstrate that by variation of the number of hydroxyl groups the water solubility of calix[4]arenes can be dramatically altered. Introduction of one additional hydroxyl group per

aromatic unit of the calix[4]arene leads roughly to a hundred fold increase of the water solubility. This method may be useful for obtaining neutral, *lower rim* functionalized, water soluble calix[4]arenes that can be applied in biological systems.

Table 1: Water solubility of neutral calix[4]arenes at 25 °C

Compound	Water solubility (M)
3a	$\sim 10^{-5}$
3b	$(2.5 \pm 0.2) \times 10^{-3}$
3c	0.23 ± 0.02
4a	$\sim 10^{-5}$
4b	$(8.8 \pm 0.1) \times 10^{-4}$
4c	0.31 ± 0.02

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19. m.p. 167-168 °C; ^{1}H-NMR (DMSO-d_6): δ 7.27 (s, 8H, ArH), 7.00 (t, 4H, NH), 4.54 (t, 4H, OH), 4.52 (part of ABq, 4H, $ArCH_2Ar$),[25] 4.16 (t, 8H, OCH_2), 3.79 (t, 8H, OCH_2), 3.5-3.4 (m, 12H, CH_2OH and part of ABq, 4H, $ArCH_2Ar$),[25] 3.31 (s, 12H, OCH_3), 2.56 (q, 8H, NCH_2); ^{13}C-NMR (DMSO-d_6): δ 158.8 (s, ArC-O), 135.0 (s, ArC-SO_2), 134.4 (s, Ar*C*-CH_2), 126.8 (d, ArC-H), 73.6 (t, OCH_2), 71.2 (t, OCH_2), 60.0 (t, CH_2OH), 58.0 (q, OCH_3), 44.9 (t, NC), 29.8 (t, $ArCH_2Ar$); FAB mass spectrum, *m/e* 1149.6 [(M + H)$^+$, calcd 1149.3].
20. m.p. 237-239 °C; ^{1}H-NMR (DMSO-d_6): δ 7.29 (s, 8H, ArH), 7.07 (bs, 4H, NH), 4.84 (s, 8H, $OCH_2C(O)$), 4.79 and 3.49 (ABq, 8H, J = 13.5 Hz, $ArCH_2Ar$), 4.57 (bs, 4H, OH), 4.15 (t, 8H, OCH_2Me), 3.35 (t, 8H, CH_2OH), 2.57 (bt, 8H, NCH_2), 1.22 (t, 12H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 169.1 (s, C(O)), 157.8 (s, ArC-O), 135.0 (s, ArC-SO_2), 134.5 (s, Ar*C*-CH_2), 127.0 (d, ArC-H), 71.1 (t, $OCH_2C(O)$), 60.5 (t, OCH_2Me), 59.9 (t, CH_2OH), 44.9 (t, NC), 30.7 (t, $ArCH_2Ar$), 13.9 (q, CH_3); FAB mass spectrum, *m/e* 1261.7 [(M + H)$^+$, calcd 1261.3].
21. m.p. 215-216 °C; ^{1}H-NMR (DMSO-d_6): δ 7.33 (s, 8H, ArH), 4.80 (t, 8H, OH), 4.47 and 3.55 (ABq, 8H, J = 12.5 Hz, $ArCH_2Ar$), 4.16 (t, 8H, OCH_2), 3.80 (t, 8H, OCH_2), 3.48 (q, 16H, CH_2OH), 3.32 (s, 12H, OCH_3), 2.86 (t, 16H, NCH_2); ^{13}C-NMR (DMSO-d_6): δ 159.0 (s, ArC-O), 135.1 (s, ArC-SO_2), 132.1 (s, Ar*C*-CH_2), 127.3 (d, ArC-H), 73.6 (t, OCH_2), 71.1 (t, OCH_2), 60.1 (t, CH_2OH), 58.0 (q, OCH_3), 51.5 (t, NC), 30.0 (t, $ArCH_2Ar$); FAB mass spectrum, *m/e* 1325.4 [(M + H)$^+$, calcd 1325.4].
22. m.p. 211-213 °C; ^{1}H-NMR (DMSO-d_6): δ 7.36 (s, 8H, ArH), 4.86 (s, 8H, $OCH_2C(O)$), 4.78 (t, 8H, OH), 4.75 (ABq, 8H, J = 13.4 Hz, $ArCH_2Ar$), 4.16 (q, 8H, OCH_2Me), 3.48 (bt, 16H, CH_2OH), 2.86 (bt, 16H, NCH_2), 1.22 (t, 12H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 169.0 (s, C(O)), 158.1 (s, ArC-O), 134.8 (s, ArC-SO_2), 132.7 (s, Ar*C*-CH_2), 127.6 (d, ArC-H), 71.0 (t, $OCH_2C(O)$), 60.5 (t, OCH_2Me), 60.1 (t, CH_2OH), 51.5 (t, NC), 30.5 (t, $ArCH_2Ar$), 13.9 (q, CH_3); FAB mass spectrum, *m/e* 1438.6 [(M + H)$^+$, calcd 1438.7].
23. m.p. 153-155 °C; ^{1}H-NMR (D_2O): δ 7.29 (s, 8H, ArH), 4.51 and 3.44 (ABq, 8H, J = 13.3 Hz, $ArCH_2Ar$), 4.25 (t, 8H, OCH_2), 3.92 (t, 8H, OCH_2), 3.68 (s, 24H, CH_2OH), 3.38 (s, 12H, OCH_3); ^{13}C-NMR (D_2O): δ 158.5 (s, ArC-O), 137.3 (s, ArC-SO_2), 135.1 (s, Ar*C*-CH_2), 126.1 (d, ArC-H), 73.2 (t, OCH_2), 72.1 (t, OCH_2), 61.7 (t, CH_2OH), 59.8 (s, NC), 58.1 (q, OCH_3), 30.8 (t, $ArCH_2Ar$); FAB mass spectrum, *m/e* 1099.4 [(M - $SO_2NHC(CH_2OH)_3$ - $C(CH_2OH)_3$)$^+$, calcd 1099.3].
24. m.p. 166-168 °C; ^{1}H-NMR (D_2O): δ 7.32 (s, 8H, ArH), 4.90 (s, 8H, $OCH_2C(O)$), 4.72 and 3.49 (ABq, 8H, J = 13.6 Hz, $ArCH_2Ar$), 4.22 (q, 8H, OCH_2Me), 3.68 (s, 24H, CH_2OH), 1.26 (t, 12H, CH_3); ^{13}C-NMR (D_2O): δ 172.0 (s, C(O)), 157.4 (s, ArC-O), 138.1 (s, ArC-SO_2), 134.7 (s, Ar*C*-CH_2), 126.5 (d, ArC-H), 71.6 (t, $OCH_2C(O)$), 62.4 (t, OCH_2Me), 61.7 (s, NC), 59.6 (t, CH_2OH), 31.3 (t, $ArCH_2Ar$), 13.6 (q, CH_3); FAB mass spectrum, *m/e* 1133.4 [(M - 2 x $SO_2NHC(CH_2OH)_3$ + H)$^+$, calcd 1133.3].
25. The coupling constant could not be determined due to overlap of signals.
26. Solutions of the compounds in doubly distilled water were measured at 25 °C. The concentrations were chosen to give absorbances between 0.2 and 0.8 and a plot was drawn of the absorbance against the concentration. A saturated solution was filtered and diluted with a known amount of water to give an absorbance in the same region and the concentration of the saturated solution could be calculated using the plot.

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