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New isocyanatomethoxycalix[4]arenes in the design of anion receptors

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New bis and tetrakis(isocyanatomethoxy)calix[4]arenes and their urea derivatives capable of binding anions have been described.

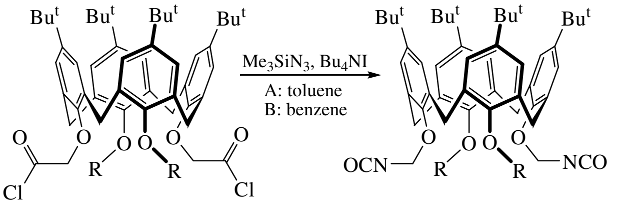
Artificial anion receptors are of great interest. For example, macrocyclic quaternary ammonium hosts are known to bind anions in polar media by electrostatic interactions.[1] Neutral proton-donative receptors are most like natural systems, which act in polar and non-polar media and selectively bind anions with different geometries due to the spatially organised system of hydrogen bonds.[2,3]

Calixarenes have been successfully used for the design of anion hosts.[4] Wide rim amidocalix[4]arenes are capable of binding to benzoate and acetate anions in [$^2H_6$]acetone solutions in the presence of chloride, iodide, nitrate and dihydrophosphate anions.[5] Lower rim (thio)ureacalixarenes bind rigid halide ions ($Cl^- > Br^- > I^- > NCS^-$) in $CDCl_3$ solutions[6] and can form stable complexes with dicarboxylate anions in DMSO.[7]

Here we report on the synthesis of new bis and tetrakis isocyanatomethoxycalix[4]arenes **2** and the anion binding capability of urea derivatives **3** and **4** obtained by simple nucleophilic addition reactions.

Calix[4]arenes with iso(thio)cyanate groups at the *para* positions of benzene rings[8] and with isothiocyanate groups attached at the narrow rim through the ethylene spacer[9] are known. All of these species were obtained by the treatment of amines with (thio)phosgene.

Our approach to the synthesis of bis and tetrakis(isocyanatomethoxy)calix[4]arenes **2** is based upon the modified Curtius reaction. Easily accessible acid chlorides **1** react with a 50% excess of trimethylsilyl azide in boiling toluene (**1a**) or benzene (**1b**) (Scheme 1).



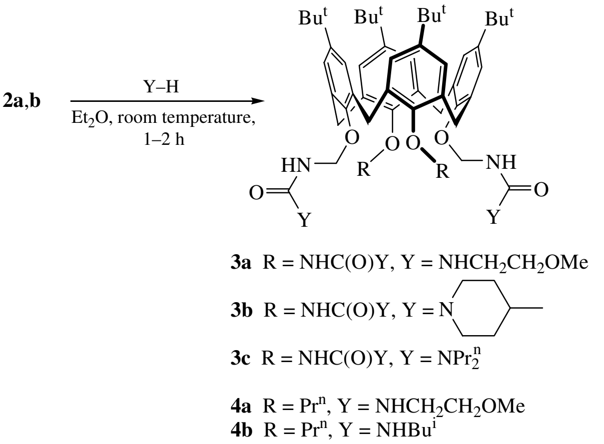
1a R = $CH_2C(O)Cl$
1b R = Pr^n

2a R = CH_2NCO
2b R = Pr^n

Scheme 1

The reactions were carried out for 20–30 min in the presence of a catalytic amount of tetrabutylammonium iodide facilitating the replacement of chlorine by the azide anion and an azide solution should be added to an acid chloride solution at 70 °C. Analytically pure isocyanates **2** were obtained after solvents and an excess of azide were evaporated under vacuum and the substances were treated with diethyl ether (**2a**) or hexane (**2b**) to make them crystalline. The ^{1}H NMR spectra of isocyanates **2** reveal a cone conformation of the macrocyclic skeleton, as evidenced by the characteristic doublets of the AB spin system.[†]

Compounds **2a**,**b** are stable in solutions and a solid state in a dry atmosphere for a long time and do not trimerise under reaction conditions. However, phenoxymethylisocyanate quickly trimerises under these conditions.[11]



3a R = NHC(O)Y, Y = $NHCH_2CH_2OMe$
3b R = NHC(O)Y, Y = N
3c R = NHC(O)Y, Y = NPr$^n_2$
4a R = Pr^n, Y = $NHCH_2CH_2OMe$
4b R = Pr^n, Y = NHBu^i

Scheme 2

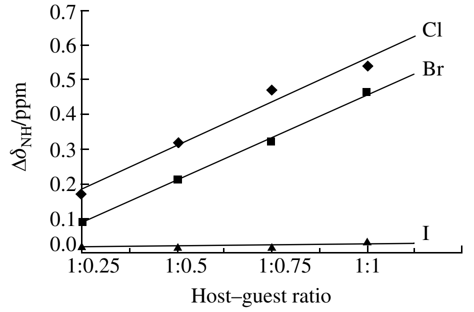


Figure 1 Dependence of the effective shift of NH protons of compound **3c** on the host–guest ratio in $CDCl_3$ at 298 K.

Isocyanates **2** easily react with primary and secondary amines yielding tetrakisureas **3** and bisureas **4** (Scheme 2). The reactions were carried out in dry diethyl ether at room temperature with an excess of amine and were complete within 2 h. The yields of ureas **3a**–**c** and **4a**,**b** (colourless crystals) were 49–67% after recrystallization from acetonitrile.[‡]

The number of proton-donating NH groups in ureas **3** and **4** has a dramatic influence on association in deuterochloroform.[12] For instance, urea **3a**, with eight NH groups, is strongly associated and reveals a broadened ^{1}H NMR spectrum at 298 K in deuterochloroform. In deuteropyridine, the molecules of **3a** are monomeric and the ^{1}H NMR spectrum is sharp. Bis(ureas) **4a**,**b** and *N*,*N*-dialkylureas **3b**,**c** having only four NH groups are monomeric in deuterochloroform solutions.

The complexation of ureas **3b**,**c** with guest anions was studied by an NMR titration procedure in deuterochloroform solutions at 298 K. The effective downfield shift of 0.54 ppm of urea **3c**

[†] All the syntheses were carried out in dry freshly distilled solvents and a dry atmosphere. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (299.94 MHz), with HMDSO as internal standard; IR spectra of solutions were measured on a UR-20 spectrometer in KBr cells (0.13 mm). Acid chlorides **1a**,**b** were prepared according to a published procedure.[10]

5,11,17,23-Tetra-tert-*butyl-25,26,27,28-tetrakis(isocyanatomethoxy)-calix[4]arene* **2a**: yield 96%, mp > 140 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ: 1.08 (s, 36H, Bu^t), 3.29 (d, 4H, e-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 13.4 Hz), 4.36 (d, 4H, a-Ar–CH_2–Ar, $^2J_{\text{H-H}}$ 13.4 Hz), 5.29 (s, 8H, –OCH_2–), 6.83 (s, 8H, ArH). IR (toluene, ν/cm^{-1}): 2265 (NCO, asymmetric stretch). Found (%): C, 71.73; H, 6.93; N, 6.64. Calc. for $C_{52}H_{60}N_4O_8$ (%): C, 71.87; H, 6.96; N, 6.45.

5,11,17,23-Tetra-tert-*butyl-25,27-bis(isocyanatomethoxy-26,28-dipropoxy)calix[4]arene* **2b**: yield 94%, mp 105–106 °C. ^{1}H NMR ($CDCl_3$) δ: 0.80 (s, 18H, Bu^t), 1.06 (t, 6H, Me), 1.34 (s, 18H, Bu^t), 1.93 (m, 4H, –CH_2–), 3.19 (d, 4H, e-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 13.2 Hz), 3.68 (t, 4H, –CH_2-), 4.40 (d, 4H, a-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 13.2 Hz), 5.49 (s, 4H, OCH_2), 6.41 (s, 4H, ArH), 7.14 (s, 4H, ArH). IR (benzene, ν/cm^{-1}): 2260 (NCO, asymmetric stretch). Found (%): C, 76.12; H, 8.37; N, 3.32. Calc. for $C_{54}H_{70}N_2O_6$ (%): C, 75.07; H, 8.63; N, 3.35.

[‡] *5,11,17,23-Tetra*-tert-*butyl-25,26,27,28-tetrakis(methyloxyethylaminocarbonylaminomethoxy)calix[4]arene* **3a**: yield 51%, mp > 250 °C. ^{1}H NMR ([$^2H_5$]pyridine) δ: 1.19 (s, 36H, Bu^t), 3.27 (s, 12H, OMe) 3.36 (d, 4H, e-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 13.8 Hz), 3.52 (t, 8H, CH_2), 3.64 (t, 8H, CH_2), 4.92 (d, 4H, a-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 13.8 Hz), 5.63 (d, 8H, OCH_2), 7.04 (s, 8H, ArH). Found (%): C, 65.24; H, 8.34; N, 9.61. Calc. for $C_{64}H_{96}N_8O_{12}$ (%): C, 65.79; H, 8.27; N, 9.58.

5,11,17,23-Tetra-tert-*butyl-25,26,27,28-tetrakis(4'-methylpiperidino)-aminocarbonylaminomethoxycalix[4]arene* **3b**: yield 60%, mp 180 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ: 0.90 (d, 12H, Me), 0.94 (m, 8H, CH_2), 1.05 (s, 36H, Bu^t), 1.56 (m, 12H, CH_2 + CH), 2.71 (m, 8H, CH_2), 3.11 (d, 4H, e-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 12.9 Hz), 4.04 (m, 8H, CH_2), 4.57 (d, 4H, a-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 12.9 Hz), 5.21 (d, 8H, OCH_2), 6.76 (s, 8H, ArH), 6.84 (br. t, 4H, NH). Found (%): C, 71.84; H, 8.79; N, 8.62. Calc. for $C_{76}H_{112}N_8O_8$ (%): C, 72.12; H, 8.92; N, 8.85.

5,11,17,23-Tetra-tert-*butyl-25,26,27,28-tetrakis(*N,N-*dipropyl)aminocarbonylaminomethoxycalix[4]arene* **3c**: yield 64%, mp 195–197 °C. ^{1}H NMR ($CDCl_3$) δ: 0.82 (t, 24H, Me), 1.05 (s, 36H, Bu^t), 1.43 (m, 16H, CH_2), 3.08 (d, 4H, e-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 13.5 Hz), 3.14 (t, 16H, CH_2), 4.59 (d, 4H, a-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 13.5 Hz), 5.27 (d, 8H, OCH_2), 6.75 (s + br. t, 12H, ArH + NH). Found (%): C, 71.58; H, 9.51; N, 8.92. Calc. for $C_{76}H_{120}N_8O_8$ (%): C, 71.66; H, 9.49; N, 8.80.

5,11,17,23-Tetra-tert-*butyl-25,27-bis(methyloxyethylaminocarbonylaminomethoxy)-26,28-dipropoxycalix[4]arene* **4a**: yield 49%, mp > 250 °C. ^{1}H NMR ($CDCl_3$) δ: 0.80 (s, 18H, Bu^t), 0.94 (t, 6H, Me), 1.33 (s, 18H, Bu^t), 1.83 (m, 4H, CH_2), 3.12 (d, 4H, e-Ar–CH_2–Ar, $^2J_{\text{H-H}}$ 12.8 Hz), 3.32 (s, 6H, OMe), 3.35 (t, 4H, CH_2), 3.48 (t, 4H, CH_2), 3.69 (t, 4H, CH_2), 4.36 (d, 4H, a-Ar–CH_2–Ar, $^2J_{\text{H–H}}$ 12.8 Hz), 5.26 (d, 4H, OCH_2), 5.66 (br. m, 2H, NH), 6.39 (br. m, 2H, NH), 6.41 (s, 4H, ArH), 7.11 (s, 4H, ArH). Found (%): C, 72.23; H, 8.90; N, 5.62. Calc. for $C_{60}H_{88}N_4O_8$ (%): C, 72.55; H, 8.93; N, 5.64.

5,11,17,23-Tetra-tert-*butyl-25,27-bis(isobutylaminocarbonylaminomethoxy-26,28-dipropoxy)calix[4]arene* **4b**: yield 54%, mp 171–172 °C. ^{1}H NMR ($CDCl_3$) δ: 0.79 (s, 18H, Bu^t), 0.92 [d + t, 18H, Me(Pr) + Me(Bu^i)], 1.33 (s, 18H, Bu^t), 1.83 [2m, 6H, CH_2(Pr) + CH(Bu^i)], 3.09 and 3.11 [2d, 8H, e-Ar–CH_2–Ar + CH_2(Bu^i), $^2J_{\text{H–H}}$ 12.4 Hz, $^3J_{\text{H-H}}$ 13.1 Hz], 3.69 (t, 4H, CH_2), 4.37 (d, 4H, a-Ar–CH_2–Ar, $^2J_{\text{H-H}}$ 12.4 Hz), 5.27 (d, 4H, OCH_2), 5.39 (br. m, 2H, NH), 6.26 (br. m, 2H, NH), 6.41 (s, 4H, ArH), 7.11 (s, 4H, ArH). Found (%): C, 75.34; H, 9.29; N, 5.60. Calc. for $C_{62}H_{92}N_4O_6$ (%): C, 75.26; H, 9.37; N, 5.66.

Table 1 Association constants (dm^3 mol^{-1}) of urea **3c** complexes in $CDCl_3$ at 298 K.

Bu_4NI	Bu_4NBr	$C_6H_4CH_2NMe_3Cl$
23(±5)[a]	221(±6)[a]	230(±5)[a]
—	240(±7)[b]	244(±5)[b]

[a]Calculated based on NH shifts. [b]Calculated based on ArH shifts.

NH protons has been observed in the presence of trimethylbenzylammonium chloride (Figure 1). Only one set of signals for both receptor and guest implying that the complexes formed are kinetically unstable in the NMR timescale.

As is shown in Figure 1, compound **3c** effectively binds Cl^- and Br^- in solution. Association constants (Table 1) of complexes were calculated based on a 1:1 complexation model with the Levenberg–Marquardt procedure.[13]

During the NMR titration of urea **3b**, only a slight shift, within a 0.03 ppm range, was observed.

In conclusion, new isocyanatomethoxycalix[4]arenes are promising for the design of urea-type anion receptors. *N*,*N*-Dipropoxyurea derivative **3c** binds chloride and bromide anions ten times stronger than iodide in deuterochloroform at 298 K.

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