SHORT PAPER

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Synthesis of new calix(aza) and calix(aza-thia) crowns

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The synthesis of new calix(aza), calix(aza-thia) crowns and bisbromoacetamides is reported in good yields.

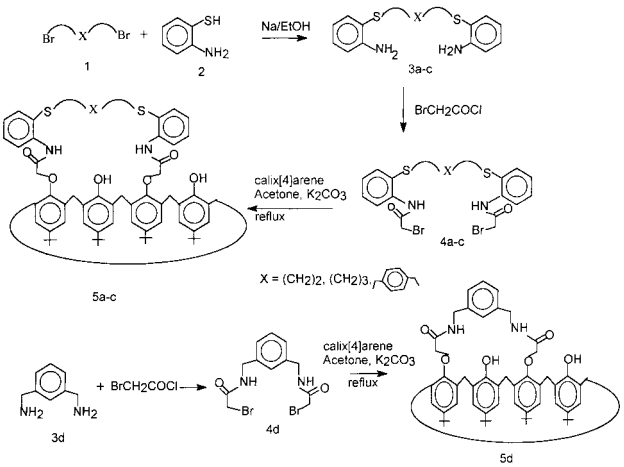
Calixarenes are cyclic oligomers obtained from the base catalysed condensation of *p*-substituted phenols and formaldehyde.[1] A variety of more or less sophisticated compounds have been obtained from these starting materials by carrying out reactions at the phenolic hydroxyl groups or at the *p*-position after the removal of the *p-tert*-butyl groups.[2] The interaction of these derivatives with a particular group of cations is largely dependent on the nature and number of the donor atoms of the ligating arms. In this respect calixcrowns have been shown to be very efficient ionophores for hard ions, such as alkali and alkaline earth metals, and to possess high ion selectivity[3–5] based on immobilization of complementary binding sites on the rigid and preorganized calix[4]arene platform.

However an area of increasing interest is the search for ligands with selective properties for soft metal cations, particularly those of environmental interest such as mercury, lead and cadmium. To achieve the complexing ability of the receptor to 'soft ions', the incorporation of heteroatoms such as nitrogen or sulfur atoms into the macrocycles has been very beneficial. However, the incorporation of both nitrogen and sulfur in calixcrowns have not been reported so far. The synthesis of calix(aza)crowns utilizing the condensation between the distal diesters or diacid dichlorides of calix[4]arene has been reported.[6,7] However, these methods require several steps. Here, we report the synthesis of calix[4](aza) and calix[4](aza-thia)crowns by a simple method. We have used easily prepared bisbromoacetamides and combined them with *p-tert*-butylcalix[4]arene to give calix(axa) and caix(aza-thia)crowns in moderate yields (50-65%). Earlier[8] we have used bisbromoacetates of diols and combined them with *p-tert*-butylcalix[4]arene for preparing calix[4]crown ether-esters. While this work was in progress Huang[9] *et al*. reported the synthesis of calixcrowns containing both nitrogen and sulfur utilizing the condensation between bischloroacetamides and calix[4]arene to obtain the products in 27–47% yield in 12–48 h. In our method the reactions were complete in 18–20 h. and the products were isolated in 50–60% yield.

The diamines **3** were prepared from 2-aminothiophenol **2** and dibromide **1** (Scheme 1) in absolute ethanol in the presence of sodium metal. Bisbromoacetamides were prepared by the reaction of bromoacetyl chloride with diamines **3** in dry dichloromethane using tetrabutylammonium hydrogen sulfate ($TBHSO_4$) as phase transfer catalyst. The structure of these bisbromoacetamides were confirmed from their ^{1}H NMR and IR spectra. As an example the IR spectrum of **4a** shows absorption bands at 1665cm^{-1} (carbonyl group) and at 3300cm^{-1}(NH). The ^{1}H NMR spectrum of **4a** shows singlets at δ 2.89 (4H,SCH_2) and at 4.10 (4H, $COCH_2Br$); a triplet at δ7.10; a multiplet at δ7.29–7.50 and a doublet at δ 8.41 corresponding to the aromatic protons of the aminothiophenol moiety. A broad singlet corresponding to NH protons appears at δ9.54. These spectroscopic data corroborate the structure **4a** for this compound. The spectral data of other bisbromoacetamides are given in the experimental. A standard procedure adopted for all cyclization reactions involved refluxing together a mixture of calix[4]arene, bisbromoacetamides and potassium carbonate in dry acetone. The products were isolated and purified by chromatography. Mass spectrometric analysis showed that the capped calixarenes were the dominant products. Double or triple calixarenes were not isolated although their formation cannot be ruled out. The ^{1}H NMR spectra of compounds **5a-d** could be assigned completely and are fully consistent with the capped structures all in the cone conformation. The ^{1}H NMR spectral features of the calix[4](aza) and (aza-thia) crowns, for example, for **5a** are: two singlets at δ 0.87 and at δ 1.20 for the *tert*-butyl protons; two singlets at δ 6.74 and at δ 7.00 for the aromatic protons and another singlet at δ7.19 corresponding to the phenolic hydroxyl groups; two doublets centred at δ3.32 and at 4.25 (J = 13.4Hz) for the bridging methylene protons, $ArCH_2Ar$; a singlet at δ4.78 for the OCH_2CO protons; another singlet at δ2.60 (SCH_2); triplets centred at δ = 7.09, 7.33; doublets centred at δ = 7.58 and 7.85 for the protons corresponding to the aminothiophenol moiety. The ^{13}C NMR spectrum further corroborates the structure of this compound. The presence of an AB system in the ^{1}H NMR spectrum for the benzylic protons and a signal at δ = 31.95 in ^{13}C NMR demonstrate that the calx(aza) and calix(aza-thia)crowns exist in the cone conformation. The spectral data of the other compounds are given in the experimental.

Experimental

M.p.s were determined in capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Bruker Acc 200 MHz spectrometer using TMS as an internal standard and $CDC1_3$ as solvent. IR spectra were recorded with a PYE UNICAM SP3-300 infrared spectrophotometer by using $CHC1_3$ or KBr (solid) as medium. FAB Mass spectra were recorded on a JEOL S × 102/DA-6000 mass spectrometer using Xenon (6KV, 10mA) as the FAB gas, at Central Drug Research Institute, Lucknow. *p-tert*-Butylcalix[4]arene was prepared by the



Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

reported method.[1a] Elemental analysis of solid samples were performed at the microanalytical laboratory RSIC, Chandigarh.

General procedure for the preparation of diamines **3***:* A solution of dibromide (30 mmol) in absolute ethanol (20ml) was added during 20 minutes to a solution of 2-aminothiophenol (60 mmol) and sodium in absolute ethanol (30 ml). The reaction mixture was refluxed for half an hour, then cooled to room temperature and then poured in ice water to obtain precipitates. The precipitates were filtered off and recrystallized from ethanol.

1,2-bis(o-aminophenylthio) ethane **3a**: Yield 80%; m.p. 76°C (lit. [10]78°C).

1,3-bis(o-aminophenylthio) propane **3b**: Yield 75%; m.p. thick liquid; δ_H ($CDCl_3$) 1.78(2H, qnt, *J*=7Hz, –CH_2–), 2.83(4H, t, *J*=7Hz, SCH_2), 3.74(br, s, 4H, NH_2), 6.64(2H, d, *J*=7.4Hz, ArH), 6.71(2H, d, *J*=7.4Hz, ArH), 7.11(2H, t, *J*=7.8 Hz, ArH), 7.31(2H, t, *J*=7.6Hz, ArH).

1,4-bis(2-aminophenylthiomethyl)benzene **3c**: Yield 65%; m.p. 102–104°C; IR$\nu_{max.}$ 3250 cm^{-1} (NH); δ_H ($CDCl_3$) 3.85(4H, s, benzylic), 4.20(4H, br, s, NH_2), 6.85–6.71(4H, m, ArH), 7.00(4H, s, ArH), 7.08–7.22((4H, m, ArH); MS *m/z* 352(M^+).

General procedure for the preparation of bisbromoacetamides: A solution of bromoacetyl chloride (42 mmol) in dry dichloromethane was added dropwise to a stirred solution of diamine **3** anhydrous potassium carbonate (40 mmol) as base and tetrabutylammonium hydrogen sulfate as catalyst. After completion of the reaction (2h, TLC) the solid was filtered and the filtrate distilled off to give pure bisbromoacetamides.

1,2-bis[0-(bromoacetamido)phenylthio]ethane **4a**: Yield 70%; $\nu_{max.}$ ($CHCl_3$) 1665 cm^{-1} (CO) 3300cm^{-1}(NH); δ_H($CDCl_3$) 2.89(4H, s, SCH_2), 4.10,(4H, s, $COCH_2Br$), 7.11(2H, t, *J*=7.4Hz, ArH), 7.29-7.51(4H, m, ArH), 8.41(2H, d, *J*=8.2Hz, ArH), 9.54(2H, br, s, NH, exchanges with D_2O).

1,3-bis[0-(bromoacetamido)phenylthio]propane **4b**: Yield 60%; $\nu_{max.}$ ($CHC1_3$) 1665 cm^{-1} (CO) 3300cm^{-1}(NH); δ_H($CDC1_3$) 1.80(2H, qnt, J = 7Hz, CH_2), 2.85(4H, s, SCH_2), 4.10(4H, s, $COCH_2Br$), 7.10(2H, t, *J* = 7.8Hz, ArH), 7.28–7.50(4H, m, ArH), 8.40(2H, d, *J* = 8.2Hz, ArH), 9.56(2H, br, s, NH, exchanges with D_2O).

1,4-bis(bromoacetamidophenylthiomethyl)benzene **4c**: Yield 60%; ν_{max} (KBr) 1664 cm^{-1} (CO); δ_H($CDCl_3$) 3.83, (4H, s, benzylic), 3.91, (4H, s, $COCH_2Br$), 6.61–6.81(4H, m, ArH), 7.00(4H, s, ArH), 7.08–7.38(2H, m, ArH), 8.32(2H, br, s, ArH).

1,3-bis(bromoacetamidmethyl)benzene **4d**: Yield 65%; ν_{max} (KBr) 1680 cm^{-1} (CO); δ_H($CDCl_3$) 3.93, (4H, s, $COCH_2Br$), 4.47(2H, d, *J*=9Hz, $NHCH_2$), 4.50(2H, d, *J*=8Hz, $NHCH_2$), 7.19–7.38(4H, m, ArH).

General procedure for the synthesis of calix(aza) and calix(azathia)crowns: A solution of *p-tert*-butylcalix[4]arene (1.54 mmol), compound **4** (3.08 mmol) and potassium carbonate (3.30 mmol) in dry acetone was refluxed for 20 h. After the reaction was complete (t.l.c.) the solution was filtered through celite. The filtrate and dichloromethane washings of the celite were combined and distilled to remove the solvent. The solid residue was purified by column chromatography over silica gel using petroleum ether and ethyl acetate as eluent.

1,2[(5,11,17,23-tetra-tert-butyl-25,27-dihydroxycalix[4]arene-26,28diyl)bis(oxyacetamido –o- phenylthio)]ethane **5a**. Reaction time 18h; yield 60%; m.p.202–205°C; IR(ν/cm^{-1}): 3320(NH), 1690(CO); δ_H($CDCl_3$) 0.87[18H, s, C(CH_3)], 1.20[18H, s, C(CH_3)], 2.60(4H, s, SCH_2), 3.32(4H, d, *J*=13.4Hz, $ArCH_2Ar$), 4.25(4H, d, *J*= 13.4Hz, $ArCH_2Ar$), 4.78(4H, s, 4H, $ArOCH_2$), 6.74(4H, s, Ar), 7.00(4H, s, Ar), 7.09(2H, t, *J*=8.4Hz, Ar), 7.19(2H, s, ArOH), 7.33(2H, t, *J*=7.2Hz, ArH), 7.58(2H, d, *J*=7.6Hz, ArH), 7.85(2H, d, *J*=8Hz, ArH), 10.76(2H, s, NHCO); δ_C(DEPT)($CDCl_3$) 30.81(+ve), 31.57(+ve), 31.95(–ve), 33.84(absent), 38.85(–ve), 75.39(–ve), 124.49(+ve), 125.14(+ve), 126.07(+ve), 126.42(+ve), 127.14(+ve), 127.72(+ve), 130.17(+ve), 132.10 (absent), 137.89(+ve), 140.46(absent), 142.65(absent), 147.91(absent), 149.92(absent), 150.83(absent), 167.75(absent); FAB-MS *m/z* 1005 ($[M+1]^+$ calcd. 1004.5 for $C_{62}H_{72}N_2O_6S_2$). Anal. Calc. For $C_{62}H_{72}N_2O_6S_2$: C, 74.06; H, 7.21; N, 2.78. Found: C, 73.77; H, 7.01; N, 2.93%.

1,3[(5,11,17,23-tetra-tert-Butyl-25,27-dihydroxycalix[4]arene-26,28-diyl)bis(oxyacetamido –o- phenylthio)]propane **5b**. Reaction time 22h; yield 65%; m.p.218–220°C; IR(ν/cm^{-1}): 3320(NH), 1690(CO); δ_H($CDCl_3$) 0.89[18H, s, C(CH_3)], 1.22[18H, s, C(CH_3)], 1.82(2H, qnt, *J*=7Hz, CH_2), 2.62 (4H, s, SCH_2), 3.34(4H, d, *J*=13.4Hz, $ArCH_2Ar$), 4.28(4H, d, *J*=13.4Hz, $ArCH_2Ar$), 4.81(4H, s, $ArOCH_2$), 6.76(4H, s, Ar), 7.03(4H, s, Ar), 7.11(2H, t, *J*=8.4Hz, Ar), 7.21(2H, s, ArOH), 7.35(2H, t, J = 7.2Hz, ArH), 7.60(2H, d, *J*=7.6Hz, ArH), 7.87(2H, d, *J*=8Hz, ArH), 10.76(2H, s, NHCO); FAB-MS *m/z* 1019 ($[M+1]^+$ calcd. 1018.5 for $C_{63}H_{74}N_2O_6S_2$). Anal. Calc. For $C_{63}H_{74}N_2O_6S_2$: C, 74.22; H, 7.31; N, 2.74. Found: C, 73.93; H, 7.02; N, 2.89%.

1,4[(5,11,17,23-tetra-tert-Butyl-25,27-dihydroxycalix[4]arene-26,28-diyl)bis(oxyacetamido –o-phenylthio)]benzene **5c***:* Time 22h; Yield 50%; m.p.212–215°C; IR(ν/cm^{-1}): 3390(NH), 1685(CO); δ_H($CDC1_3$) 0.85[18H, s, C(CH_3)], 1.25[s, 18H, C(CH_3)], 3.40(4H, d, *J*=13.2Hz, $ArCH_2Ar$), 4.00(4H, s, benzylic), 4.39(4H, s, $ArOCH_2$), 4.48(4H, d, *J*=13.4Hz, $ArCH_2Ar$), 6.67(4H, s, Ar), 6.94(s, 4H, Ar), 7.13-7.19(m, 2H, Ar) 7.14(s, 4H, Ar), 7.27–7.40(m, 4H, ArH), 8.24(2H, d, *J*=8Hz, Ar), 8.92(2H, s, NHCO); FAB-MS *m/z* 1081 ($[M+1]^+$ calcd. 1080.5 for $C_{68}H_{76}N_2O_6S_2$). Anal. Calc. For $C_{68}H_{76}N_2O_6S_2$: C, 75.52; H, 7.08; N, 2.59. Found: C, 75.27; H, 6.80; N, 2.39%.

1,3[(5,11,17,23-tetra-tert-Butyl-25,27-dihydroxycalix[4]arene-26,28-diyl)bis(oxyacetamidomethyl)]benzene **5d***:* Time 18h; Yield 50%; m.p.252–255°C; IR(ν/cm^{-1}): 3390(NH), 1670(CO); δ_H($CDC1_3$) 1.17 [s, 9H, C(CH_3)], 1.20[s, 9H, C(CH_3)], 1.28(s, 18H, C(CH_3)], 3.38(d, J = 13.4Hz, 4H, $ArCH_2Ar$), 4.17(d, *J*=13.4Hz, 4H, $ArCH_2Ar$), 4.47(s, 4H, $ArOCH_2$), 4.62(s, 2H, $ArCH_2$), 4.65(s, 2H, $ArCH_2$), 6.67(s, 4H, Ar), 7.13(s, 4H, Ar), 7.25(s, 4H, Ar); δ_C(DEPT)($CDC1_3$) 30.81(+ve), 31.20(–ve), 31.67(+ve), 33.95(absent), 41.89(-ve), 74.98(–ve), 122.86(+ve), 125.52(+ve), 125.88(+ve), 126.36(+ve), 128.00(absent), 128.70(+ve), 131.60(absent), 132.98(absent), 143.20(absent), 148.05(absent), 148.83(absent), 149.64(absent), 168.21(absent); ES–MS *m/z* 865.5($[M+1]^+$ calcd. 864.5 for $C_{56}H_{68}N_2O_6$). Anal. Calc. For $C_{56}H_{68}N_2O_6$: C, 77.75; H, 7.92; N, 3.23. Found: C,77.48; H, 7.70; N, 3.43%.

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