A Facile Method for Synthesis of Calix[4]crowns Containing Nitrogen and Sulfur Atoms†

J. Chem. Research (S), 1999, 212–213†

Qi-Yu Zheng, Chuan-Feng Chen and Zhi-Tang Huang*

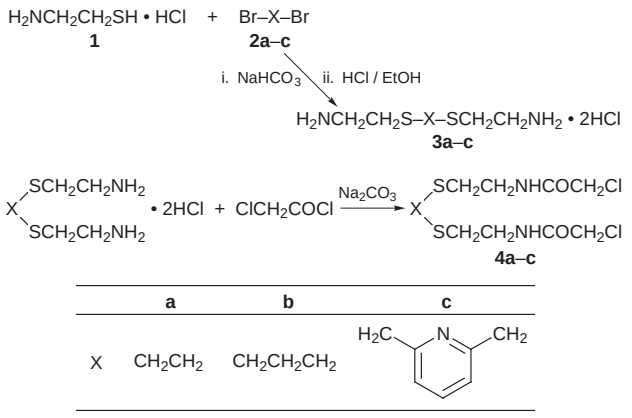
Institute of Chemistry, The Chinese Academy of Sciences, Beijing 100080, China

A synthesis of calix[4]crowns containing nitrogen and sulfur atoms and bischloroacetamides is reported.

Calixarenes are important molecular building blocks for the synthesis of new receptors for 'catching' ions and/or neutral molecules in supramolecular chemistry.[1] Calixcrowns, constructed by introducing a polyether chain into the lower rim of calixarenes, have been shown to be very efficient ionophores for hard ions, such as alkali and alkaline earth metals, and to possess superior ion selectivity and high affinity because of the preorganization effect arising from the calixarene ring.[2–4] To increase the complexation capability of the receptor to 'soft ions', the incorporation of heteroatoms, such as nitrogen or sulfur atoms, into macrocycles has proved efficient.[5,6] However, calixcrowns containing heteroatoms have been studied only to a small extent and calixcrowns containing both nitrogen and sulfur atoms have, as yet, not been reported. We report herein, a facile method for the synthesis of calix[4]crowns, containing both nitrogen and sulfur atoms.

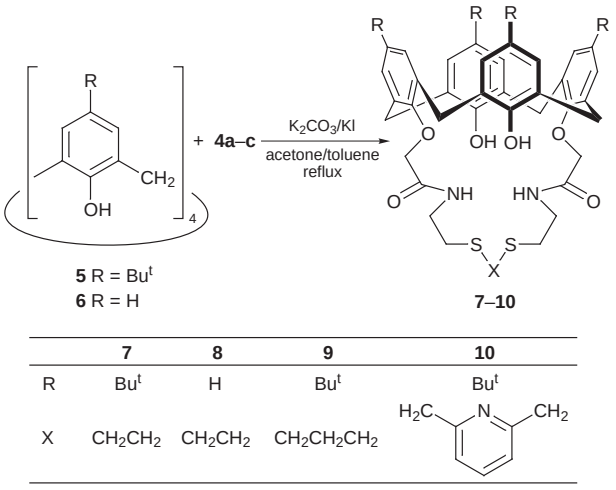
Methods for synthesis of calix[4](aza)crowns containing amide or imine groups (Schiff bases) have been reported.[7–9] They utilized the condensation of distal diesters or acid chlorides of calix[4]arenes with diamines to synthesize calix(aza)crowns containing amide groups in the crown ether subcycles. However, this method requires several steps starting from calix[4]arenes. Here, we use a simple method to synthesize calixcrowns containing both nitrogen and sulfur atoms. It requires only one step starting from calix[4]arenes and another easily prepared reactant, a bischloroacetamide.

Bischloroacetamides **4** were synthesized by the reaction of chloroacetyl chloride with diamines **3**, which can be obtained from 2-aminoethanethiol hydrochloride and dibromides **2** (Scheme 1).



Scheme 1

Calix[4]crowns **7**–**10** containing nitrogen and sulfur atoms were readily synthesized by the reaction of *p-tert*-butylcalix[4]arene **5** or calix[4]arene **6** with **4** in the presence of K_2CO_3 and KI in acetone–toluene; the yields ranged from 27 to 47% (Scheme 2).



Scheme 2

Products **7**–**10** were characterized by ^1H and ^{13}C NMR spectroscopy, FAB-MS, IR and elemental analysis. In the ^1H NMR spectra of calix[4]crowns **7**–**10**, the signal of the methylene protons between aromatic rings showed a typical AB pattern ($J = 13.0$ Hz), whilst in the ^{13}C NMR spectra of **7**–**10**, there was only one corresponding methylene signal ($\delta \approx 31$). This demonstrates that these calix[4]crowns exist in cone conformations and that the molecules are in high symmetry.

Experimental

Mps are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 200 spectrometer with $CDCl_3$ as solvent and TMS as internal reference. IR spectra were recorded with a Perkin-Elmer 782 spectrometer. Mass spectra were recorded on a KYKY-ZHT-5 instrument. Elemental analyses were performed by the Analytical Laboratory of the institute. *p-tert*-Butylcalix[4]arene **5**[10] and calix[4]arene **6**[11] were prepared according to literature procedures.

General Procedure for the Preparation of Bischloroacetamides **4**.—A solution of dibromides **2** (35 mmol) in ethanol (60 ml) was added dropwise under a nitrogen atmosphere to a solution of 2-aminoethanethiol hydrochloride (70 mmol) and $NaHCO_3$ (70 mmol) in water (130 ml). The mixture was stirred at room temperature for 30 min and refluxed for 3 h, and then concentrated *in vacuo*. The residue was treated with ethanol and hydrochloric acid, and cooled in an ice bath to obtain a precipitate. After filtering this off and washing with anhydrous ethanol (40 ml), the product **3** was dissolved in water (20 ml) and the pH of solution was adjusted to **7** by addition of a saturated aqueous solution of K_2CO_3. Then $CHCl_3$ (30 ml) was added and chloroacetyl chloride (70 mmol) in chloroform (70 ml) and K_2CO_3 (35 mmol) in water (250 ml) were added separately through dropping funnels to the above stirred solution at 0–5 °C over 3 h. The mixture was stirred for an additional 3 h at room temperature. The organic phase was separated and washed several times with water. After removal of solvent *in vacuo*, the product was crystallized from ethanol in an ice bath.

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

1,8-*Bis*(*chloroacetamido*)-3,6-*dithiaoctane* (**4a**). Yield 69%; mp 116–118°C (ethanol). ($CDCl_3$) 2.73 (t, 4 H, $NHCH_2CH_2S$), 2.77 (s, 4 H, SCH_2CH_2S), 3.55 (q, 4 H, $NHCH_2$), 4.06 (s, 4 H, $ClCH_2CO$), 7.07 (br, 2 H, N*H*).

1,9-*Bis*(*chloroacetamido*)-3,7-*dithianonane* (**4b**). Yield 30%; mp 63–64 °C (ethanol). δ_H ($CDCl_3$) 1.90 (qnt, 2 H, $CH_2CH_2CH_2$), 2.66 (t, 4 H, $NHCH_2CH_2S$), 2.73 (t, 4 H, $SCH_2CH_2CH_2S$), 3.52 (q, 4 H, $NHCH_2$), 4.08 (s, 4 H, $ClCH_2CO$), 7.04 (br, 2 H, N*H*).

2,6-*Bis*(4′-*chloroacetamido*-2′-*thiabutyl*) *pyridine* (**4c**). Yield 30%; mp 65–66 °C (ethanol). δ_H ($CDCl_3$, 2.69 (t, 4 H, $NHCH_2CH_2S$), 3.52 (q, 4 H, $NHCH_2$), 3.89 (s, 4 H, SCH_2Py), 4.05 (s, 4 H, $ClCH_2CO$), 7.24 (br, 2 H, N*H*), 7.31 (d, 2 H, Py*H*), 7.72 (t, 1 H, Py*H*).

General procedure for the preparation of aza- and thiacalix[4]*crowns* **7**–**10**.—To a solution of bischloroacetamides **4** (2.5 mmol) and *p-tert*-butylcalix[4]arene **5** or calix[4]arene **6** (2 mmol) in acetone (50 ml)–toluene (20 ml) were added K_2CO_3 (2 mmol) and KI (4 mmol). After the reaction mixture was stirred under reflux for 12–48 h, the solvent was removed *in vacuo* and the residue was dissolved in 0.2 M HCl (50 ml) and $CHCl_3$ (50 ml). The organic layer was washed with water, concentrated and then chromatographed on a silica gel column using $CHCl_3$–petroleum ether (bp 60–90 °C) (2 : 1 v/v) as eluent to afford a white solid which was recrystallized from $CHCl_3$–CH_3OH to give pure compounds **7**–**10**.

1,8-[(5,11,17,23-*tetra*-tert-*Butyl*-25,27-*dihydroxycalix*[4]*arene*-26,28-*diyl*)*bis*(*oxyacetamido*)]-3,6-*dithiaoctane* (**7**). Reaction time 12 h; yield 33%; mp 175 °C (decomp.) ($CHCl_3$–CH_3OH). IR (ν/cm^{-1}): 3370 (NH), 1670 (CO), 1540, 1495. δ_H ($CDCl_3$) 0.92 [s, 18 H, $C(CH_3)_3$], 1.31 [s, 18 H, $C(CH_3)_3$], 2.84 (s, 4 H, SCH_2CH_2S), 2.85 (t, 4 H, $NHCH_2CH_2S$), 3.38 (d, 4 H, J_{AB} 13.0, $ArCH_2Ar$), 3.65 (q, 4 H, $NHCH_2$), 4.20 (d, 4 H, J_{AB} 13.0, $ArCH_2Ar$), 4.52 (s, 4 H, $ArOCH_2$), 6.72 (s, 2 H, O*H*), 6.76 (s, 4 H, Ar*H*), 7.10 (s, 4 H, Ar*H*), 8.03 (br, 2 H, N*H*); δ_C ($CDCl_3$) 30.82, 30.84, 31.61, 31.72, 32.32, 33.87, 33.89, 39.79, 74.25, 125.35, 125.90, 127.74, 131.88, 142.65, 147.79, 149.71, 149.76, 169.07. FAB-MS: *m/z* 907 ($[M - 1]^+$). Anal. Calc. for $C_{54}H_{72}N_2O_6S_2$: C, 71.33, H, 7.98, N, 3.08. Found: C, 70.81, H, 7.89, N, 3.43%.

1,8-[(25,27-*Dihydroxycalix*[4]*arene*-26,28-*diyl*)*bis*(*oxyacetamido*)]3,6-*dithiaoctane* (**8**). Reaction time 48 h; yield 44%; mp 270 °C (decomp.) ($CHCl_3$–CH_3OH). IR (ν/cm^{-1}): 3350 (NH), 1665, (CO), 1540, 1465. δ_H ($CDCl_3$) 2.84 (t, 4 H, $NHCH_2CH_2S$), 2.85 (s, 4 H, SCH_2CH_2S), 3.44 (d, 4 H, J_{AB} 13.0, $ArCH_2Ar$), 3.71 (q, 4 H, $NHCH_2$), 4.25 (d, 4 H, J_{AB} 13.0, $ArCH_2Ar$), 4.55 (s, 4 H, $ArOCH_2$), 6.73 (t, 2 H, Ar*H*), 6.78 (t, 2 H, Ar*H*), 6.89 (d, 4 H, Ar*H*), 7.10 (d, 4 H, Ar*H*), 7.53 (s, 2 H, O*H*), 7.74 (br, 2 H, N*H*); δ_C ($CDCl_3$) 30.75, 31.42, 32.15, 39,75, 74.35, 119.84, 126.05, 127.71, 128.80, 129.37, 132.62, 151.84, 152.52, 168.51. FAB-MS: *m/z* 683 ($[M - 1]^+$). Anal. Calc. for $C_{38}H_{40}N_2O_6S_2$: C, 66.64, H, 5.89, N, 4.09. Found: C, 65.89, H, 5.82, N, 4.04%.

1,9-[(5,11,17,23-*tetra*-tert-*Butyl*-25,27-*dihydroxycalix*[4]*arene*-26,28-*diyl*)*bis*(*oxyacetamido*)]-3,7-*dithianonane* (**9**). Reaction time 48 h; yield 47%; mp 215–216 °C ($CHCl_3$–CH_3OH). IR (ν/cm^{-1}): 3370 (NH), 1670 (CO), 1540, 1490. δ_H ($CDCl_3$) 0.91 [s, 18 H, $C(CH_3)_3$], 1.31 [s, 18 H, $C(CH_3)_3$], 1.92 (qnt, 2 H, $CH_2CH_2CH_2$), 2.73 (t, 4 H, $NHCH_2CH_2S$), 2.83 (t, 4 H, SCH_2CH_2S), 3.38 (d, 4 H, J_{AB} 13.0, $ArCH_2Ar$), 3.69 (q, 4 H, $NHCH_2$), 4.20 (d, 4 H, J_{AB} 13.0, $ArCH_2Ar$), 4.53 (s, 4 H, $ArOCH_2$), 6.55 (s, 2 H, O*H*), 6.74 (s, 4 H, Ar*H*), 7.10 (s, 4 H, Ar*H*), 7.98 (br, 2 H, N*H*); δ_C ($CDCl_3$) 29.37, 30.33, 30.81, 30.92, 31.55, 32.09, 33.86, 34.07, 38.95, 74.80, 125.58, 126.16, 127.23, 132.34, 143.10, 148.31, 149.04, 149.34, 168.30. FAB-MS: *m/z* 921($[M - 1]^+$). Anal. Calc. for $C_{55}H_{74}N_2O_6S_2$: C, 71.54, H, 8.08, N, 3.03. Found: C, 71.29, H, 8.11, N, 3.01%.

2,6-[4′-(5,11,17,23-*tetra*-tert-*Butyl*-25,27-*dihydroxycalix*[4]*arene*-26,28-*diyl*)*bis*(*oxyacetamido*-2′-*thiabutyl*)]*pyridine* (**10**). Reaction time 48 h; yield 27%; mp 150–152 °C ($CHCl_3$–CH_3OH). IR (ν_{max}/cm^{-1}): 3365 (NH), 1680 (CO), 1540, 1485. δ_H ($CDCl_3$) 1.05 [s, 18 H, $C(CH_3)_3$] 1.29 [s, 18 H, $C(CH_3)_3$], 2.77 (t, 4 H, $NHCH_2CH_2S$), 3.43 (d, 4 H, J_{AB} 13.0, $ArCH_2Ar$), 3.48 (s, 4 H, $NHCH_2$), 3.93 (s, 4 H, SCH_2Py), 4.15 (d, 4 H, J_{AB} 13.0, $ArCH_2Ar$), 4.56 (s, 4 H, $ArOCH_2$), 6.90 (s, 4 H, Ar*H*), 7.10 (s, 4 H, Ar*H*), 7.29 (d, 2 H, Py*H*, 7.71 (t, 1 H, Py*H*), 7.67 (s, 2 H, O*H*), 8.87 (br, 2 H, NH); δ_C ($CDCl_3$) 29.86, 30.89, 31.54, 32.13, 33.87, 34.04, 37.34, 39.62, 74.78, 121.51, 125.57, 126.17, 127.37, 132.21, 138.19, 143.34, 148.31, 149.22, 149.30, 158.23, 167.82. FAB-MS: *m/z* 984($[M - 1]^+$). Anal. Calc. for $C_{59}H_{75}N_3O_6S_2$: C, 71.84, H, 7.66, N, 4.26; Found: C, 71.58, H, 7.61, N, 4.48%.

This work was supported by the National Natural Science Foundation of China.

Received, 3rd November 1998; Accepted, 30th November 1998
Paper E/8/08527G

References

1 For recent review, see: A. Ikeda and S. Shinkai, *Chem. Rev.,* 1997, **97**, 1713.
2 H. Yamamoto, T. Sakaki and S. Shinkai, *Chem. Lett.,* 1994, 469.
3 A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.-J. Schwing, R. J. M. Egberink, F. de Jong and D. N. Reinhoudt, *J. Am. Chen. Soc.,* 1995, **117**, 2767.
4 A. Casnati, A. Pochini, R. Ungaro, S. Bocchi, F. Ugozzoli, R. J. M. Egberink, H. Struijk, R. Lugtenberg, F. de Jong and D. N. Reinhoudt, *Chem. Eur. J.,* 1996, **2**, 436.
5 A. T. Yordanov, J. T. Mague and D. M. Roundhill, *Inorg. Chem.,* 1995, **34**, 5084.
6 A. T. Yordanov, J. T. Mague and D. M. Roundhill, *Inorg. Chim. Acta,* 1995, **240**, 441.
7 V. Boehmer, G. Ferguson, J. F. Gallagher, A. J. Lough, M. A. McKervey, E. Madigan, M. B. Moran and J. Phillips, *J. Chem. Soc., Perkin Trans. 1,* 1993, 1521.
8 I. Bitter, A. Grün, G. Tóth, B. Balázs and L. Tõke, *Tetrahedron,* 1997, **53**, 9799.
9 R. Seangprasertkij, Z. Asfari, F. Arnaud and J. Vicens, *J. Org. Chem.,* 1994, **59**, 1741.
10 C. D. Gutsche, *Org. Synth.,* 1989, **68**, 234.
11 C. D. Gutsche and L.-G. Lin, *Tetrahedron,* 1986, **42**, 1633.