ELSEVIER

Di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-4 ligands: synthesis and high divalent metal ion extraction selectivity

Chuqiao Tu, Kazimierz Surowiec and Richard A. Bartsch*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

Abstract—Di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-4 ethers in the cone conformation are synthesized with their conformation and regioselectivity verified by NMR spectroscopy. The new ligands are efficient extractants with high selectivity for Ba^{2+} in competitive solvent extraction of alkaline earth metal cations from aqueous solutions into chloroform.
© 2006 Elsevier Ltd. All rights reserved.

Calix[4]arene is an important scaffold for the construction of new metal ion receptors. Introduction of a polyether loop on the lower rim of calix[4]arene not only increases the cation binding ability of the parent calix[4]arene, but allows control of the selectivity through modulation of the crown ether ring size.[1]

Two types of polyether chain bridging on the lower rim of a calix[4]arene molecule are possible: 1,3-bridging of distal phenolic units and 1,2-bridging of proximal phenolic units. To date, the study of calix[4]arene-crown compounds has been heavily focused on the 1,3-bridged isomers. This type of ligand was found to exhibit high binding affinity and selectivity in alkali and alkaline earth metal cation extractions.[2] In contrast, research on 1,2-bridged calix[4]crowns lags far behind. Reported examples are sparse. From the limited available information, 1,2-bridged ligands are expected to exhibit poor binding ability and selectivity toward metal cations.[3]

Earlier work has shown that incorporation of a pendant proton-ionizable group into calix[4]arenes can dramatically enhance their metal ion extraction efficiency compared with non-ionizable analogues. The ionized group not only participates in cooperative metal ion coordination, but also eliminates the need to transfer aqueous phase anions into the organic phase during extraction by operating in a cation-exchange mode with the metal cation.[4]

We now report the preparation of five di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-4 compounds in the cone conformation and evaluation of their alkaline earth metal cation extraction abilities.

p-tert-Butylcalix[4]arene-1,2-crown-4 (**1**) was synthesized by a reported method[3c] and reacted with ethyl bromoacetate and NaH in THF for 48 h to give diester **2** in 70% yield (Scheme 1). Hydrolysis of diester **2** with tetramethylammonium hydroxide in aqueous THF gave diacid **3** in nearly quantitative yield. Di-acid **3** was converted into the corresponding di(acid chloride) by reaction with oxalyl chloride in benzene at 50–55 °C for 12 h. Formation of the di(acid chloride) was verified by IR spectroscopy with the appearance of a strong carbonyl group absorption at 1810 cm^{-1} and disappearance of the carbonyl group absorption for **3** at 1748 cm^{-1}. The di(acid chloride) was reacted with appropriate sulfonamide anions to afford cone, di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-4 compounds **4**–**7** in 42–85% yields.[5,6]

The conformation and regioselectivity of **3**–**7** were verified by NMR spectroscopy. For example, for compound **5**[7] there are no peaks between 36 and 40 ppm in the ^{13}C NMR spectrum, revealing that all four benzene rings have *syn*-arrangements.[8] In the ^1H NMR spectrum, the bridging methylene protons of the calix[4]arene framework are split into three pairs of doublets with relative integrations of 1, 1 and 2, marked as 2, 3, 4
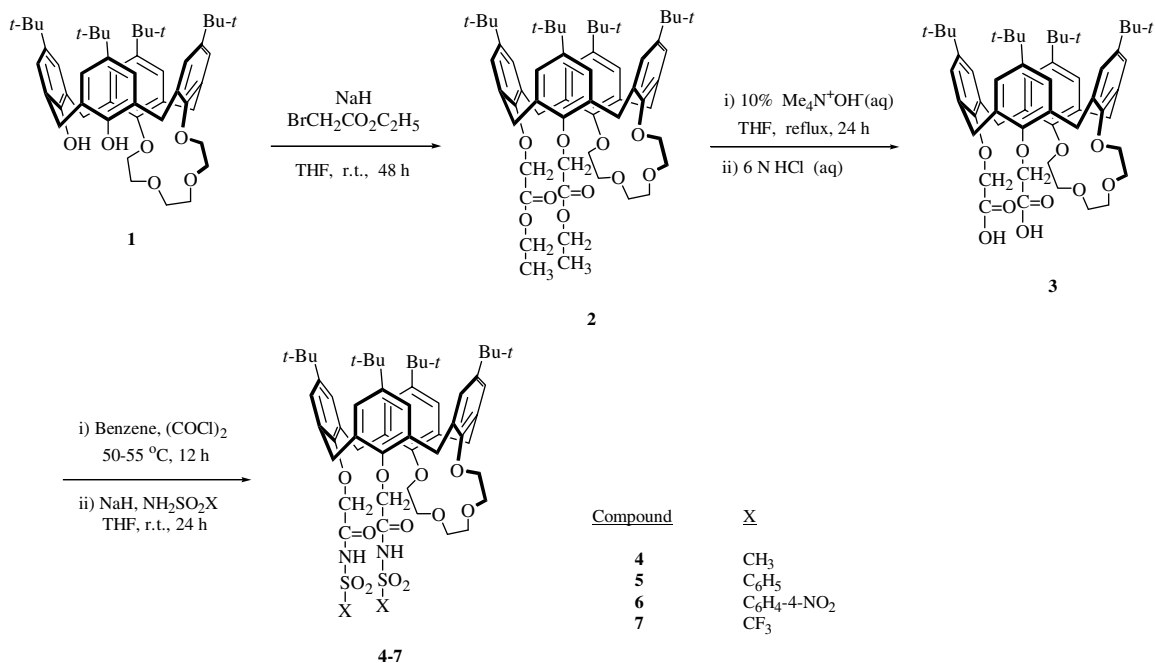
Scheme 1. Synthesis of di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-4 ethers **3**–**7**.

(axial) and 2′, 3′, 4′ (equatorial) in Figure 1. These absorptions are correlated with each other, which demonstrates that the polyether ring is attached to the calix[4]arene scaffold through proximate phenolic oxygens. The correlated peaks are separated by more than

1 ppm, which verifies that the calix[4]arene molecule is in the cone conformation.[3f,8] The two methylene protons in the ionizable side arms (–OCH_2C(O)–), marked as 1 and 1′ in Figure 1, are diastereotopic. They are correlated with each other.
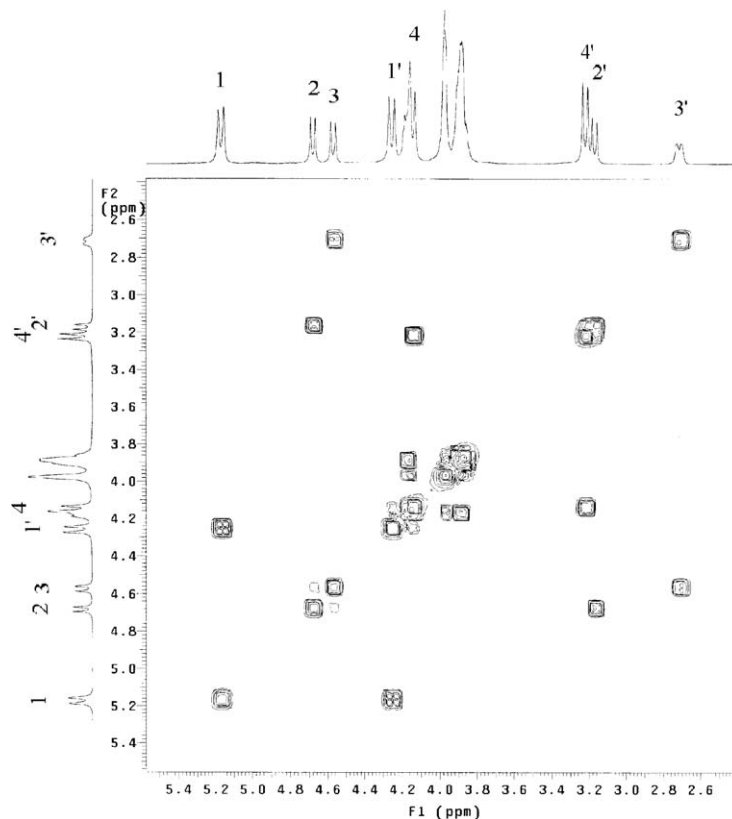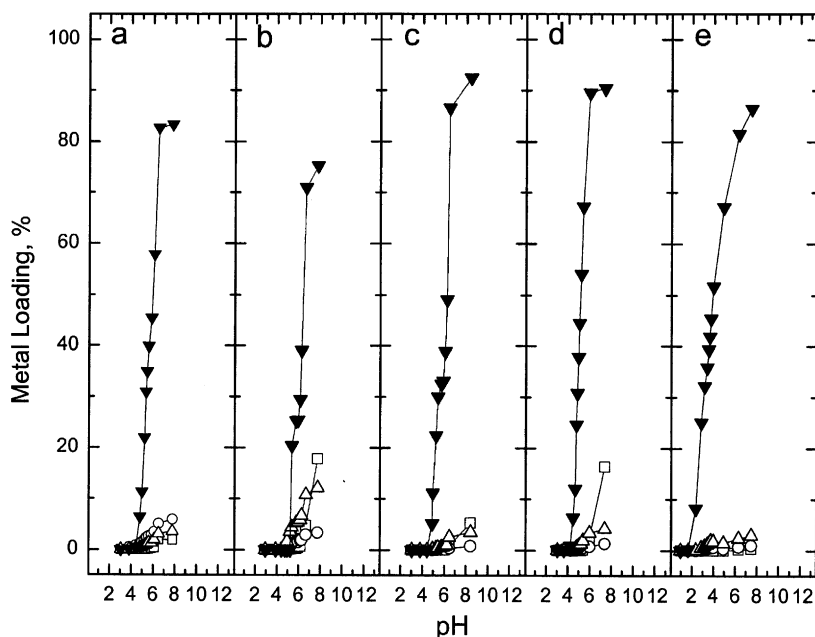

Figure 1. ^{1}H–^{1}H COSY spectrum for compound **5**.

Figure 2. Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal ions into chloroform by di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-4 ethers (a) **3**, (b) **4**, (c) **5**, (d) **6**, and (e) **7**. ($\square = Mg^{2+}$; $\bigcirc = Ca^{2+}$; $\triangle = Sr^{2+}$; $\blacktriangledown = Ba^{2+}$).[9]

Competitive solvent extractions of alkaline earth metal cations from aqueous solutions into chloroform by ligands **3–7** were performed by a reported procedure[2d] with determination of the alkaline earth metal cation concentrations in the acidic aqueous strippant by ion chromatography. Results for competitive extractions of aqueous solutions containing 2.0 mM (in each) of Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} with 1.0 mM chloroform solutions of **3–7** are presented in Figure 2.[9]

Ligands **3–7** exhibit high selectivity for Ba^{2+} over the three lighter alkaline earth metal cations and 100% maximum metals loading (for formation of a 1:1 metal ion-ionized ligand complex). For **4** and **6**, the total metals loading somewhat exceeded 100% at the most basic pHs. This is attributed to extraction of colloidal $Mg(OH)_2$ at the higher pH values. The extraction selectivity order is $Ba^{2+} \gg Sr^{2+} > Ca^{2+} > Mg^{2+}$, the same as the order of decreasing metal cation sizes. The Ba^{2+}/Sr^{2+} selectivity reaches 35 under conditions of high loading. With variation of the X group in order of CH_3, C_6H_5, C_6H_4-4-NO_2, and CF_3, the ligand acidity is expected to increase as the electron-withdrawing power of the X group is enhanced. The pH for half loading, $pH_{0.5}$, is a qualitative measure of ligand acidity. For compounds **4–7**, the $pH_{0.5}$ values are 6.26, 6.22, 5.12, and 3.84, respectively, which is in accord with the electron-withdrawing power of the X group. To our knowledge, this is the first report of calix[4]arene-1,2-crown ethers that are efficient and selective in metal ion separations.

Since Ba^{2+} is too large to be accommodated within the crown-4 cavity, we envision extraction complexes in which on one side the metal ion perches on the polyether oxygen atoms and the other interacts with the two ion-ized groups. Why this arrangement is especially favorable for Ba^{2+} complexation relative to the lighter alkaline earth metal cations remains unclear at this time. Further investigations of the metal ion separation properties of novel di-ionizable calix[4]arene-1,2-crown ethers are in progress.

References and notes

1. (a) Gutsche, C. D. Calixarenes. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1989; (b) Gutsche, C. D. Calixarenes Revisited. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1998; (c) Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Netherlands, 2001; pp 365–384.
2. (a) Dijkstra, P. J.; Brunink, J. A.; Bugge, K.-E.; Renhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567–7575; (b) Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1990**, *112*, 6979–6985; (c) Lamare, V.; Dozol, J.-F.; Ugozzoli, F.; Casnati, A.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 1559–1568; (d) Zhou, H.; Surowiec, K.; Purkiss, D. W.; Bartsch, R. A. *Org. Biomol. Chem.* **2005**, *3*, 1676–1684.
3. (a) Arduini, A.; Casnati, A.; Doni, L.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1597–1598; (b)

Arduini, A.; Casnati, A.; Fabbi, M.; Minari, P.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Supramol. Chem.* **1993**, *1*, 235–246; (c) Arduini, A.; Domiano, L.; Pochini, A.; Secchi, A.; Ungaro, R.; Ugozzoli, F.; Struck, O.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1997**, *53*, 3767–3776; (d) Arnaud-Neu, F.; Caccamese, S.; Fuangswasdi, S.; Pappalardo, S.; Parisi, M. F.; Petringa, A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041–8048; (e) Arnaud-Neu, F.; Ferguson, G.; Fuangswasdi, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Petringa, A. *J. Org. Chem.* **1998**, *63*, 7770–7779; (f) Mathieu, A.; Asfari, Z.; Thuery, P.; Nierlich, M.; Faure, S.; Vicens, J. *J. Incl. Phenom. Macrocycl. Chem.* **2001**, *40*, 173–181.

4. (a) Arduini, A.; Pochini, A.; Reverberi, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981–982; (b) Ogata, M.; Fujimoto, K.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, *116*, 4505–4506; (c) Talanov, V. S.; Talanova, G. G.; Gorbunova, M. G.; Bartsch, R. A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 209–215.

5. The general procedure for the conversion of diacid **3** into ligands **4–7** is as follows: Dry benzene (40 mL), diacid **3** (2.19 g, 2.49 mmol) and oxalyl chloride (5.06 g, 39.84 mmol) were stirred at 50–55 °C for 12 h. The benzene was evaporated in vacuo to give the corresponding di(acid chloride), which was used directly in the next step. A solution of the appropriate sulfonamide (5.48 mmol) in THF was added over a 10-min period to a mixture of NaH (0.60 g, 24.9 mmol) and THF (30 mL) under nitrogen at room temperature. The mixture was stirred for 1.5 h followed by addition of a solution of the di(acid chloride) in THF (10 mL). The mixture was stirred for 24 h after which 10 mL of H_2O was added carefully to destroy the excess NaH. The solvent was evaporated in vacuo and CH_2Cl_2 was added to the residue. The resulting solution was dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2–MeOH (19:1) or hexanes–EtOAc (1:2 or 3:2) as eluent. The product was dissolved in CH_2Cl_2 and the solution was shaken with 6 N HCl. The organic layer was separated, dried over $MgSO_4$, and evaporated in vacuo to provide ligands **4–7** in 42–85% yields.

6. Satisfactory combustion analysis results were obtained for new compounds **2–7**.

7. Compound **5**. Yield: 49%; Mp: 164–165 °C; IR: v_{max} (deposit from CH_2Cl_2 solution onto a NaCl plate)/cm^{-1} 3236 (N–H), 1717 (C=O), 1361, 1160 (SO_2), 1251, 1124, 1058 (C–O); ^{1}H NMR (500 MHz, CDCl$_3$, ppm): 10.58 (s, 2H, NH), 8.17 (d, *J* 7.6, 4H, ArH), 7.60 (t, *J* 7.1, 2H, ArH), 7.50 (t, *J* 7.4, 4H, ArH), 6.82 (s, 2H, ArH), 6.74 (s, 4H, ArH), 6.60 (s, 2H, ArH), 5.17 (d, *J* 14.6, 2H, O*CH*$_2$C(O)), 4.68 (d, *J* 12.3, 1H, Ar*CH*$_2$Ar, *ax*), 4.57 (d, *J* 12.9, 1H, Ar*CH*$_2$Ar, *ax*), 4.26 (d, *J* 14.4, 2H, O*CH*$_2$C(O)), 4.18 (d, *J* 13.2, 2H, OCH$_2$), 4.15 (d, *J* 13.8, 2H, Ar*CH*$_2$Ar, *ax*), 3.98 (s, 4H, OCH$_2$), 3.94–3.80 (m, 6H, OCH$_2$), 3.22 (d, *J* 13.3, 2H, Ar*CH*$_2$Ar, *eq*), 3.17 (d, *J* 12.4, 1H, Ar*CH*$_2$Ar, *eq*), 2.72 (d, *J* 10.0, 1H, Ar*CH*$_2$Ar, *eq*), 1.06 (s, 18H, C(*CH*$_3$)$_3$), 1.05 (s, 18H, C(*CH*$_3$)$_3$); ^{13}C NMR (126 MHz, CDCl$_3$, ppm): 169.10 (C=O), 153.24, 153.14, 145.26, 145.20, 138.64, 133.72, 133.54, 133.46, 132.54, 131.30, 131.27, 128.88, 128.64, 126.05, 125.34, 125.12 (Ar), 74.00 (O*CH*$_2$C(O)), 73.52, 70.27, 68.61 (OCH$_2$), 33.81, 33.76 (*C*(CH$_3$)$_3$), 31.96, 31.79 (Ar*CH*$_2$Ar), 31.34, 31.26 (C(*CH*$_3$)$_3$), 29.89 (Ar*CH*$_2$Ar). Anal. Calcd for C$_{66}$H$_{80}$O$_{12}$S$_2$N$_2$: C, 68.49; H, 6.97; N, 2.42. Found: C, 68.64; H, 7.26; N, 2.45.

8. Talanov, V. S.; Bartsch, R. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1957–1961.

9. An alternative way to present such solvent extraction data is as distribution ratios, DM, defined as $[M]_{org}/[M]_{aq}$. To transform the vertical axis in Figure 2 from 'Metals Loading, %' to 'DM', multiply the values given by 0.0010.