Selectivity in Redox-switched Calix[4]arene Cationophores: Electrochemical Detection of a Conformational Change on Cation Binding

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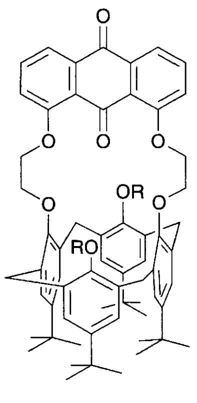
Three 4-*tert*-butylcalix[4]arenes bearing a 1,8-bis(ethyleneoxy)anthraquinone bridge between alternate phenolic oxygen atoms, on one-electron reduction, show enhanced binding of alkali-metal cations with selectivities dependent upon the groups attached at the other phenolic oxygens; for one of the compounds, binding of potassium but not sodium is accompanied by a conformational change of the calixarene from cone to partial cone.

Until recently, the design and synthesis of redox-switched ionophores for sensing and ion transport had been restricted to crown ethers and aza-crowns incorporating electroactive groups, usually quinones or nitroaromatics, either within the macrocycle or attached to it (so-called lariat systems).[1] Calix[4]arenes, particularly ones bearing methylenecarboxylate and related carbonyl-containing groups on the phenolic oxygen atoms, show good cation-binding qualities in the preorganised binding cavities of their cone conformations, and moderate selectivities between different alkali-metal cations have been reported.[2] Better selectivities have been observed with ethyleneoxy-bridged calix[4]arenes.[3] Redox-switchable calix[4]arenes in which one of the phenolic rings has been converted into a *p*-benzoquinone moiety, have only just been described[4] and these, upon reduction, show large binding enhancements towards alkali-metal and alkaline earth cations. We now report three examples of redox-switched calix[4]arenes having a basic structure **1** that allows for much more flexible design of the binding cavity, its donor atoms and the nature of the redox-switch.

Compounds **1a**, **1b** and **1c** have been synthesised *via* the anthraquinone-bridged parent structure **1d**. This was obtained by reaction of *p*-*tert*-butylcalix[4]arene (1 equiv.) with 1,8-bis(2′-bromoethoxy)anthraquinone (1 equiv.) in butyronitrile containing 8 equiv. each of sodium carbonate and sodium iodide. The free phenolic groups in **1d** were derivatised using sodium hydride in dry THF and dimethyl sulfate giving **1a** (50% yield), ethyl bromoacetate giving **1b** (71% yield) and *N,N*-diethylchloroacetamide giving **1c** (25% yield). All three compounds exist in solution as the cone conformer as evidenced by the characteristic single pair of doublets assignable to the methylene protons between the *tert*-butylphenoxy-groups of the calixarene. The choice of methoxy-groups in **1a** was based on modelling studies which suggested that the highly preorganised cavity of the molecule in its cone conformation would provide a significantly tighter and, it was hoped, better fit for the potassium cation than for sodium. The other groups were chosen as ones likely, in the neutral state, to give improved cation binding compared to **1a**,[2] a situation that could give rise to differences in electrochemical response.[5]



1a R = Me
b R = CH_2CO_2Et
c R = CH_2CONEt_2
d R = H

Cyclic voltammetry was employed to evaluate the binding enhancements towards alkali-metal cations on one-electron reduction of the ionophores using the relationship $\log (K^*/K) = F(E_p - E_p^\circ)/2.303RT$ relating the ratio of binding constants of the ligand in the neutral (K) and reduced state (K^*) to the shift in peak potential in the presence of the metal cation, added as their perchlorates, relative to that observed in the presence of the tetrabutylammonium perchlorate supporting electrolyte alone (E_p°). Experiments were conducted in MeCN solution at 20 °C using concentration ratios $[M^+]/[\text{ligand}]$ of 0, 0.5 and 1.0. Potential scan rates were in the range 50–5000 mV s^{-1}, a range of values being used so as to establish that peak shifts were independent of scan rate. In all cases, the presence of the alkali-metal cation (0.5 equiv.) led to the appearance of additional peaks corresponding to the first and second reduction step of the ligand–metal ion complex at potentials shifted considerably in the anodic direction compared with values for the corresponding reduction of the free ligand. With 1 equiv. of the added alkali-metal salt, only reduction and reoxidation waves for the complex could be detected at scan rates below 1 V s^{-1}. Values of $\log (K^*/K)$ calculated from the peak shifts of the first reduction waves are shown in Fig. 1 as a function of the radius of the bound cation.

The pattern of results in Fig. 1 shows interesting features. The binding enhancement factors on one-electron reduction are highest for **1a**, the compound having OR groups that are the least likely to promote strong cation binding to the neutral ligand. Moreover, **1a** also shows binding enhancements that decrease much more slowly with increasing cation radius than the other two calixarenes and when compared with similar observations on anthraquinone-switched crown ethers.[1,6] Indeed, the binding enhancements for **1a** are among the highest observed for Na^+ and K^+ using switchable ligands.

Using potential scan rates ≥ 1 V s^{-1}, it was observed that cyclic voltammograms for the reduction of **1a** in the presence of

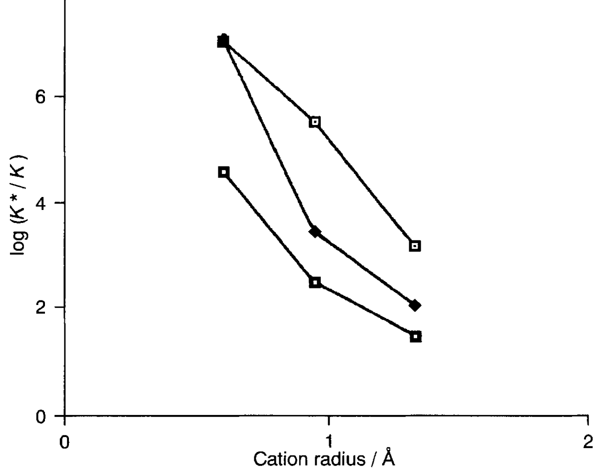


Fig. 1 Binding enhancements (K^*/K) on one-electron reduction of compounds **1** in MeCN solution at 20 °C: **1a** □; **1b** ◆; **1c** ■

one equivalent of potassium perchlorate changed from the clean pattern of reversible one-electron reduction to the more complex pattern illustrated in Fig. 2. The current response becomes resolved into two at the highest scan rates, the peak potentials corresponding closely to those observed at low sweep rates for the free ligand (1.154 V *vs.* Ag/AgCl) and the potassium complex (0.968 V). Such behaviour was not observed in the reduction of **1a** with Li$^+$ or Na$^+$, nor in the reduction of **1b** and **1c** in the presence of any of the three alkali-metal cations examined here. We interpret this behaviour as indicating that binding of K$^+$ to neutral **1a** is incomplete at the low concentrations (1.5 mmol dm^{-3}) used in the voltammetric experiments and is slow enough on the CV timescale that it can be outrun at the highest potential scan rates. The response at the highest scan rate thus represents the position of the binding equilibrium prior to reduction; we estimate a binding constant of approximately 4000 dm^3 mol^{-1} and, from the potential scan rate required to resolve the current response in the presence of K$^+$, that the half life of the binding process is *ca.* 100 ms. The binding constant of the reduced ligand is *ca.* 6 × 10^6 dm^3 mol^{-1}.

We believe this slow binding process is due to a conformational change in the ligand when cation binding takes place. The following evidence supports our view that this change is from the cone conformation in the free ligand to a partial cone conformation in the potassium complex, a conformational change already described in non-switchable bridged calix[4]arenes.[4b,7]

At concentrations tenfold higher than in the CV experiments, the ^{1}H NMR spectrum of **1a** in CD$_3$CN solution containing 1 equiv. of KClO$_4$ is mainly that of the complex and shows three singlets (intensity ratio 1 : 1 : 2) for the *tert*-butyl groups and four pairs of doublets indicative of two different bridging methylene groups in the calixarene as required for the partial cone conformation; for comparison, the free ligand and the Na$^+$-complex both show only one pair of doublets for the calixarene methylene protons, characteristic of the cone conformation and simpler signals for the *tert*-butyl protons [free ligand, 2 singlets (intensity ratio 2 : 2); Na$^+$-complex, 1 singlet corresponding to 4 *tert*-butyl groups].

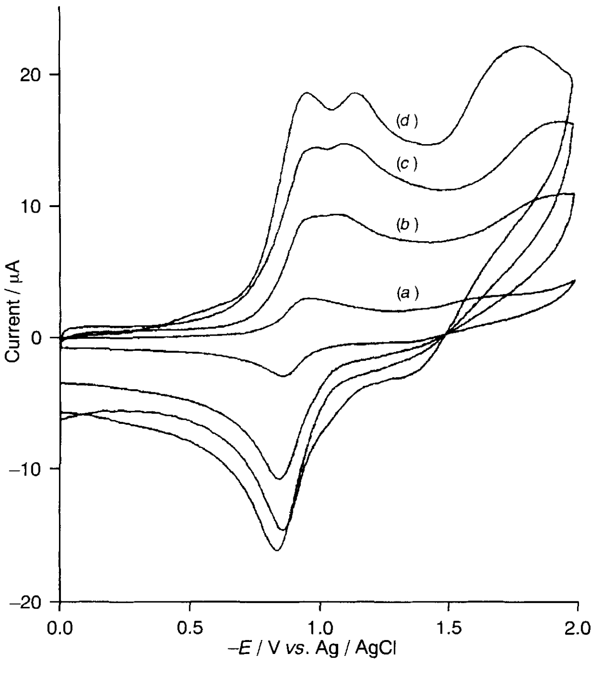


Fig. 2 Sweep rate dependence of the peak potentials for the **1a**/KClO$_4$ interaction; (*a*) 200 mV s^{-1}, (*b*) 1 V s^{-1}, (*c*) 4 V s^{-1}, (*d*) 5 V s^{-1}

Molecular modelling of the K$^+$/ligand complex using both the PC Model (Serena Software) and Sybyl (Tripos Associates) programs indicates that the minimised energy of the cone conformation is less than 1 kcal mol^{-1} (1 cal = 4.184 J) lower than that of a distorted partial cone conformation which allows the methoxy oxygen atom of the inverted methoxyphenyl moiety to coordinate to the underside of the metal cation held in close proximity to the redox switch and the remaining donor atoms. Similar calculations on the Na$^+$ complex yields an energy for the cone conformation more than 3 kcal mol^{-1} below that of the partial cone.

This investigation provides valuable new insights into the factors that must be taken into account in designing effective and selective redox-switched ionophores. It has also provided the first example of a system in which the kinetics of metal-ion binding can be directly investigated by electrochemical means.

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References

1 For a review, see G. W. Gokel, *Crown ethers and Cryptands*, Monographs in Supramolecular Chemistry, ed. J. F. Stoddart, The Royal Society of Chemistry, Cambridge, 1991, p. 145; examples: anthraquinone-containing crowns, M. Delgado, D. Gustowski, H. Yoo, V. J. Gatto, G. W. Gokel and L. Echegoyen, *J. Am. Chem. Soc.*, 1988, **112**, 119; anthraquinone-containing cryptands, Z. Chen, O. F. Schall, M. Icalá, Y. Li, G. W. Gokel and L. Echegoyen, *J. Am. Chem. Soc.*, 1992, **114**, 444; switchable lariat crowns, L. Echegoyen, D. A. Gustowski, V. J. Gatto and G. W. Gokel, *J. Chem. Soc., Chem. Commun.*, 1986, 220.

2 S. K. Chang and I. Cho, *Chem. Lett.*, 1984, 477; *J. Chem. Soc., Perkin Trans. 1*, 1986, 211; S. K. Chang, S. K. Kwon and I. Cho, *Chem. Lett.*, 1987, 947; A. Arduini, A. Pochini, S. Reverberi and R. Ungaro, *Tetrahedron*, 1986, **42**, 2089; F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. M. Marques, B. L. Ruhl, M. J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.*, 1989, **111**, 8681.

3 C. Alfieri, E. Dradi, A. Pochini, R. Ungaro and G. G. Andreetti, *J. Chem. Soc., Chem. Commun.*, 1983, 1075; D. N. Reinhoudt, P. J. Dijkstra, P. J. A. in't Veld, K. E. Bugge, S. Harkema, R. Ungaro and E. Ghidini, *J. Am. Chem. Soc.*, 1987, **109**, 4761; H. Yamamoto and S. Shinkai, *Chem. Lett.*, 1994, 1115.

4 (*a*) M. Gomez-Kaifer, P. A. Reddy, C. D. Gutsche and L. Echegoyen, *J. Am. Chem. Soc.*, 1994, **116**, 3580; P. D. Beer, Z. Chen, M. G. B. Drew and P. A. Gale, *J. Chem. Soc., Chem. Commun.*, 1994, 2207.

5 S. R. Miller, D. A. Gustowski, Z. Chen, G. W. Gokel, L. Echegoyen and A. E. Kaifer, *Anal. Chem.*, 1988, **60**, 2021; see also E. Laviron and L. Roullier, *J. Electroanal. Chem.*, 1985, **186**, 1.

6 See, for example, J. M. Caridade Costa, B. Jeyashri and D. Bethell, *J. Electroanal. Chem.*, 1993, **351**, 259.

7 E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A. A. El-Fadl and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1990, **112**, 6979; W. I. I. Bakker, M. Haas, C. Khoo-Beattie, R. Ostaszewski, S. M. Franken, H. J. den Hertog, W. Verboom, D. de Zeeuw, S. Harkema and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1994, **116**, 123.