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MELDOLA MEDAL LECTURE *

Redox Responsive Macrocyclic Receptor Molecules Containing Transition Metal Redox Centres

By Paul D. Beer
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BIRMINGHAM,
P.O. BOX 363, BIRMINGHAM B15 2TT

1 Introduction

Dibenzo-18-crown-6 (1) was prepared by Pedersen in 1967[1] quite by chance, and the subsequent discovery[1,2] that (1) and other macrocyclic polyethers, the crown ethers, selectively complex biologically relevant alkali and alkaline earth metal cations was the catalyst for the enormous development of the field of synthetic host–guest chemistry. The following inspirational, innovative, and stimulating work of Lehn[3,4] on, in particular, the novel bicyclic cryptands (2) and Cram[5] on chiral crown ethers and the rigid spherands (3) was duly recognized by the award to Pedersen,[2] Lehn,[4] and Cram[5] of the 1987 Nobel Prize for Chemistry. It is beyond the scope of this text to review and discuss the wide variety of molecular hosts that have been prepared since 1967 to complex selectively cationic, anionic, and neutral guest species. Excellent reviews and monographs on the subject may be found in references 6—10.

This review is concerned with a new generation of host molecules, *responsive* macrocyclic receptor molecules whose binding strength and/or selectivity towards guest species can be influenced by physical and chemical means. The stimulus can be pH change, an input of electrochemical, photochemical, or thermal energy *etc.* Interest in this type of host molecule stems from the idea of mimicking 'coupled reactions' *i.e.* reactions that mutually influence each other which are known to play a fundamental role in biological processes such as ion transport and

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* The present text is based upon the lecture delivered on 2 March 1989 at a meeting of the Dalton Division of the Royal Society of Chemistry at the Scientific Societies' Lecture Theatre, Savile Row, London W1.

[1] (*a*) C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017; (*b*) C. J. Pedersen, *Aldrichim. Acta*, 1971, **4**, 1.

[2] C. J. Pedersen, (Nobel Lecture), *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1021.

[3] (*a*) J. M. Lehn, 'Structure and Bonding', Springer Verlag, Berlin, 1973, p. 1; (*b*) B. Dietrich, J. M. Lehn and J. P. Sauvage, *Tetrahedron Lett.*, 1969, 2885.

[4] J. M. Lehn, (Nobel Lecture), *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89.

[5] D. J. Cram, (Nobel Lecture), *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1009.

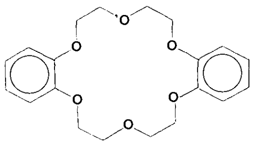
[6] 'Synthesis of Macrocycles', Progress in Macrocyclic Chemistry, Vol. 3, ed. R. M. Izatt and J. J. Christensen, J. Wiley, New York, 1987.

[7] 'Synthetic Multidentate Macrocyclic Compounds', ed. R. M. Izatt and J. J. Christensen, Academic Press, New York, 1978.

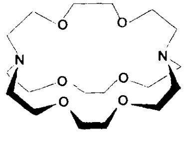
[8] P. D. Beer, in 'Chemical Sensors', ed. T. Edmonds, Blackie Glasgow, London, 1988, Chapter 2, p. 17.

[9] 'Host–Guest Chemistry 1', *Topics Curr. Chem.*, 1980, **98**.

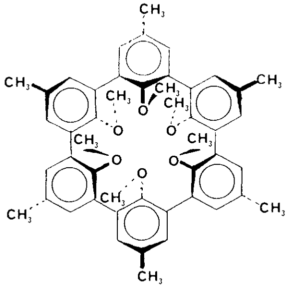
[10] B. Dietrich, in 'Inclusion Compounds', Vol. 2, ed. J. L. Atwood, J. E. D. Davies, and D. MacNicol, Academic Press, London, 1984, p. 337.



(1) Pedersen



(2) Lehn



(3) Cram

oxidative phosphorylation.[11,12] In biological systems such interactions are regarded as *allosteric* when binding at one active site induces conformational changes which alter the receptivity of a remote site. In vision, for instance, a stimulus from the outside world is beautifully transduced in the order: light ⟶ isomerization of retinal ⟶ conformational change in rhodopsin.[13] *Abiotic* responsive macrocyclic hosts are discussed in this review including pH-responsive, photoresponsive, and allosteric crown ethers. Specific attention is focused on our own work and that of others on the synthesis, coordination, and electrochemistry of *redox-responsive* macrocycles that contain transition metal redox active centres.

2 pH-Responsive Crown Ethers

The first examples reported of a class of responsive macrocyclic receptor molecule are the pH-responsive crown ethers[14–17] which contain one or more carboxylic acid functional groups attached to the periphery of crown ether macrocycles (Figure 1). These molecules change their cation binding ability in response to the pH of their environment, *i.e.* in acidic media their ion binding strength is reduced and in basic media it is enhanced.

In an attempt to imitate the ionophoric properties of the polyether antibiotics

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[11] E. Racker, *Acc. Chem. Res.*, 1979, **12**, 338.

[12] L. Stryer, 'Biochemistry', 2nd Edition, Freeman, San Francisco, 1981.

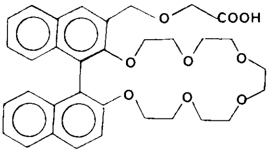
[13] S. Shinkai, *Pure Appl. Chem.*, 1987, **59**, 425.

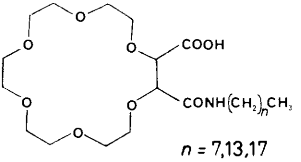
[14] H. Stetter and W. Frank, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 686.

[15] J. P. Desvergne and H. Bouas-Laurent, *J. Chem. Soc., Chem. Commun.*, 1978, 403.

[16] W. Wierenga, B. R. Evans, and J. A. Woltersom, *J. Am. Chem. Soc.*, 1979, **101**, 1334.

[17] L. A. Frederick, T. M. Fyles, V. A. Malik-Diemer, and D. M. Whitfield, *J. Chem. Soc., Chem. Commun.*, 1980, 1211.





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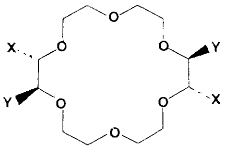

X = COOH
Y = $CON(Pr^n)CH_2CH_2OCH_2CH_2N(Pr^n)CO_2CH_2C_6H_5$

(5)

Figure 1

such as monensin and to demonstrate 'active' or uphill membrane transport by coupling the transportation of metal cations to a proton antiport in a pH gradient, Fyles *et al.*[18,19] have synthesized *lipophilic* crown ethers (4) bearing the carboxylic acid function. Figure 2 illustrates the transport schemes involved in such a membrane system. A related lipophilic dicarboxylic acid–dicarboxamide macrocycle (5), prepared by Lehn *et al.*,[20] demonstrates a very pronounced phenomenon of pH regulation of transport selectivity from preferential K^+ transport to preferential Ca^{2+} transport as the pH increases from 2 to 9 in the starting aqueous phase containing the metal ions.

3 Photoresponsive Crown Ethers

Utilizing the (*E*)–(*Z*) isomerism of the azobenzene moiety as a photoantenna, Shinkai and co-workers[21] have incorporated this chromophore into a variety of macrocyclic polyethers to produce photoresponsive crown ethers. These molecules undergo photoinduced reversible interconversion between the *trans* (*E*) and *cis* (*Z*) azo linkages, resulting in substantial changes in their respective crown ether binding site conformations and hence their cation complexing properties. For example, the influence of photoirradiation on the ion-binding ability of (6) was quite remarkable: (*E*)-(6) extracted Na^+ 5.6 times more efficiently than (*Z*)-(6), whereas (*Z*)-(6) extracted K^+ 42.5 times more efficiently than (*E*)-(6).[22] The

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[18] L. A. Frederick, T. M. Fyles, N. P. Gurprasad, and D. M. Whitfield, *Can. J. Chem.*, 1981, **59**, 1724.

[19] T. M. Fyles, V. A. Malik-Diemer, and D. M. Whitfield, *Can. J. Chem.*, 1981, **59**, 1734.

[20] A. Hriciga and J. M. Lehn, *Proc. Natl. Acad. Sci. USA*, 1983, **80**, 6426.

[21] S. Shinkai and O. Manabe, *Topics Curr. Chem.*, 1984, **121**, 67.

[22] (*a*) S. Shinkai, T. Ogawa, Y. Kusano, and O. Manabe, *Chem. Lett.*, 1980, 283. (*b*) S. Shinkai, T. Nakaji, T. Ogawa, E. Shigematsu, and O. Manabe, *J. Am. Chem. Soc.*, 1981, **103**, 111.

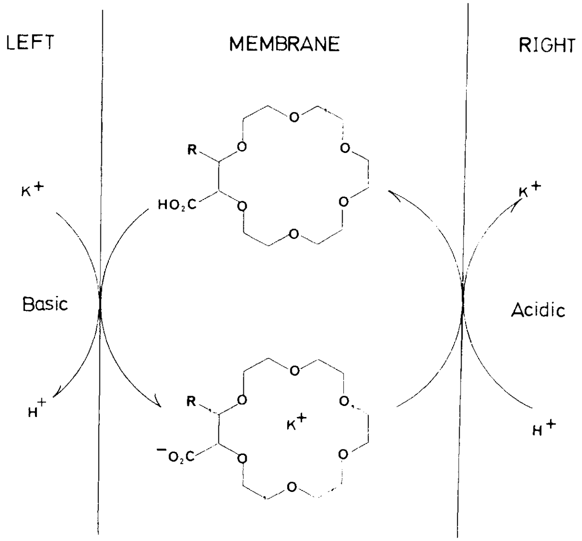
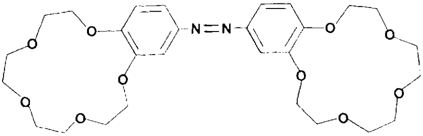


Figure 2 *Active membrane transport; coupling the transportation of* K$^+$ *to a proton antiport in a pH gradient*



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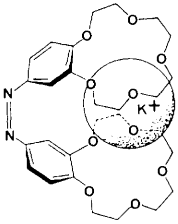

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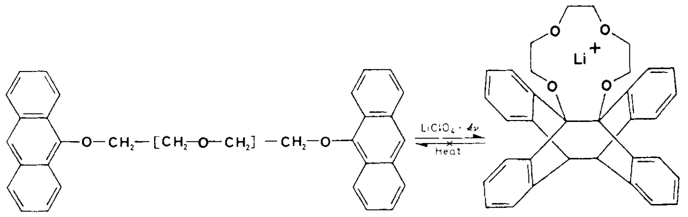
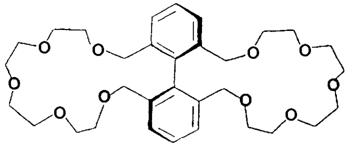


(8) (9)



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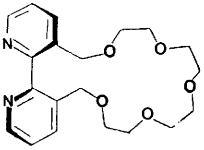

(11)

selectivity expressed by the ratio E/Z of extractabilities for Na^+ against that for K^+ was found to be 238-fold. These experimental results suggest that Na^+ is extracted as a $2Na^+$:(E)-(6) complex while K^+ is extracted as a $1K^+$:(Z)-(6) intramolecular sandwich complex (7).

The photo-dimerization of anthracene was used by Desvergne[23] to design a 'switched on' crown ether (9). Photoirradiation of (8) in the presence of Li^+ gave (9). Addition of a polar solvent to solutions of (9) removed, by preferential solvation, the Li^+ and (8) was reformed.

4 Allosteric Crown Ethers

Allosteric effects play a critical role in the control and integration of molecular events in biological systems.[24] In enzymology, for example, the regulation of catalytic activity can be accomplished by allosteric effects: the binding of an effector molecule at a remote allosteric site can cause conformational changes at the active site which alters the selectivity and reactivity of the enzyme to its substrate.[24–26] In a recent publication Rebek[27] has elegantly demonstrated the allosteric binding cooperativity of biaryl crown ether systems, such as (10), in solution. The binding of mercury derivatives at one crown ether site reduced the conformational freedom of the adjacent site in a manner that facilitates the positive cooperative binding of a second mercury guest species. In a related system (11)[26] the ion binding ability of the crown ether site is dependent upon the chelation of transition metals at the 2,2′-bipyridyl function. The free ligand

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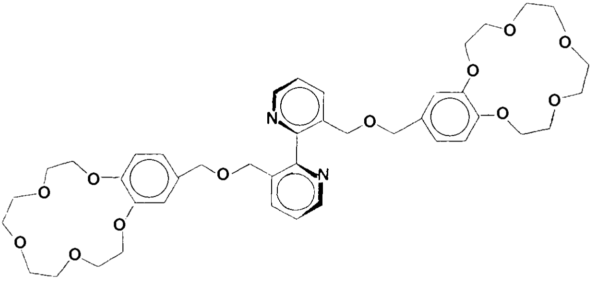
[23] J. P. Desvergne, N. Bitit, and H. Bouas-Laurent, *J. Chem. Res.*, 1984, (*S*) 214; (*M*) 1901.

[24] D. E. Koshland Jr., in 'The Enzymes', Vol. 1, ed. P. Boyer, Academic Press, New York, 1970, p. 341.

[25] J. Rebek, Jr., *Acc. Chem. Res.*, 1984, **17**, 258.

[26] J. Rebek, Jr., J. E. Trend, R. V. Wattley, and S. Chakravorti, *J. Am. Chem. Soc.*, 1979, **101**, 4333.

[27] J. Rebek, Jr., T. Costello, J. Marshall, R. Wattley, R. C. Gadwood, and K. Onan, *J. Am. Chem. Soc.*, 1985, **107**, 7481.



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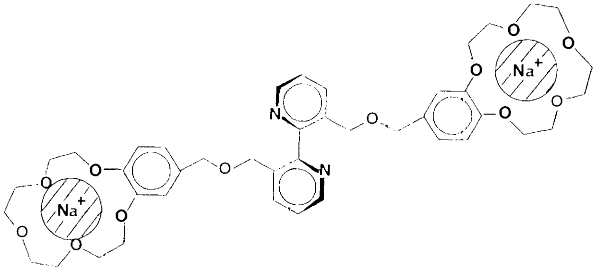

(13)

itself binds K^+ in preference to Na^+, whereas Na^+ is bound more efficiently in the presence of $W(CO)_4$ chelated at the bipyridyl site.

We have also utilized this chelation conformational effect in the synthesis of a new allosteric bis crown ether ligand (12) consisting of the 3,3′-disubstituted-2,2′-bipyridyl fragment and two benzo-15-crown-5 moieties.[28,29] Refluxing (12) with an excess of sodium hexafluorophosphate in methanol led to the successful isolation of a crystalline complex (12)•$2Na^+PF_6^-$, in which the two benzo-15-crown-5 moieties are acting independently of one another, each complexing a sodium cation (13). Molecular models (CPK) suggested that chelation of a transition metal at the bipyridyl nitrogens would force the bipyridyl function towards coplanarity, resulting in the restriction of conformational freedom of the two benzo-crown ether groups in such a way as to favour the formation of an intramolecular sandwich complex with an alkali metal cation (Scheme 1). The reaction of (12) with $(bipy)_2RuCl_2{\cdot}2H_2O$ followed by an excess of sodium hexafluorophosphate gave $[(bipy)_2Ru(12)Na]^{3+}$ $(PF_6^-)_3$ (14). This observed stoicheiometry suggests the sodium guest cation does now form an intramolecular sandwich complex with the two benzo-crown ether groups, aided by this allosteric effect of the chelation of Ru^{II} at the bipyridyl function.

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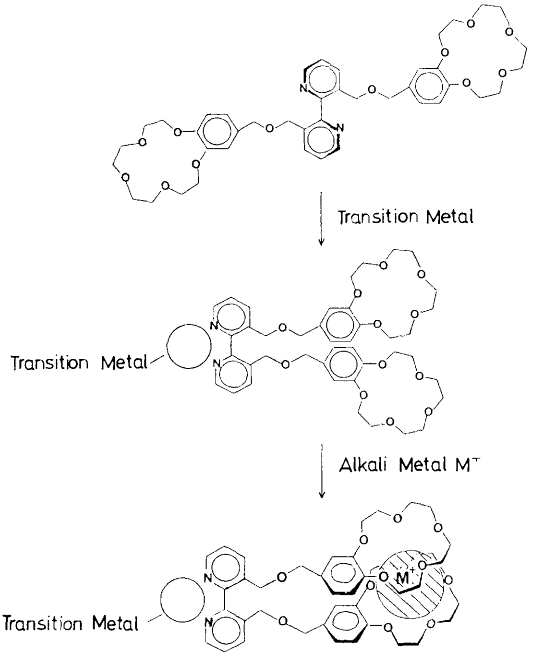
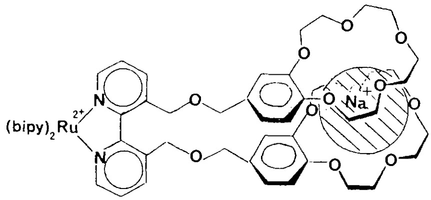
[28] P. D. Beer and A. S. Rothin, *J. Chem. Soc., Chem. Commun.*, 1988, 52.
[29] P. D. Beer and A. S. Rothin, *Polyhedron*, 1988, 7, 137.

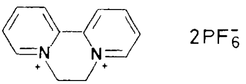


Scheme 1



(14)

The ligand (12) was also shown to bind the planar organic diquat dication guest (15) by intercalation between the two respective electron-rich benzo-crown ethers (16).[28] Chelation of either $(bipy)_2Ru^{II}$ or $Cr(CO)_4$ at the allosteric bipyridyl site 'switched off' the subsequent intercalation binding of diquat. We concluded from these results that the presence of a transition metal at the allosteric bipyridyl nitrogens site of (12) leads to a *rigid* solution conformation of the two benzo-crown ether moieties held in close proximity, cofacial to each other, disfavouring the intercalation of the organic *planar* diquat dication, but favouring the formation of intramolecular sandwich complexes with *spherical* alkali metal cationic guests.



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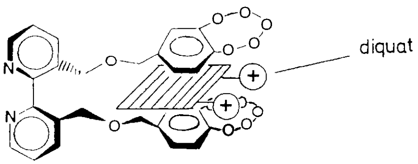

(16)

We have prepared a new Schiff base bis crown ether ligand (17)[30,31] that also exhibits allosteric behaviour. Preliminary complexation studies have revealed that the stoicheiometry of (17) to potassium guest cations is dependent upon the stereochemical requirements of co-bound transition metal guests. In the case of square planar or tetragonal copper(II) bound at the Schiff base–dithia recognition site, the stereochemical requirements of this transition metal allows the subsequent formation of the preferred 1:1 intramolecular sandwich-type complex with K^+ (18). However, with tetrahedrally coordinated copper(I) or Ag^I the subsequent formation of the intramolecular sandwich complex with K^+ is prevented and the polymetallic complex (19) results. Thus, in principle, we have a novel bioinorganic model system that can mimic biological alkali metal physiological processes by reversibly releasing or binding K^+ guest cations into or from the environment, depending on either/or the nature and redox oxidation state of a co-bound transition metal (Scheme 2).

5 Temperature Responsive Crown Ethers

Temperature-regulated release of alkali metal salts from novel polymeric crown ether complexes has been demonstrated by Warshawsky and Kahana.[32] For complexation between cation and crown ether ΔH° and ΔS° values are usually negative and small. Hence the sign and value of the free energy ΔG° may depend on the absolute temperatures, especially in heterogeneous systems such as equilibria between insoluble polymer and solution. The synthesis of the polymeric crown ethers (20) was achieved by condensation of polymer-bound catechol and polyglycol dihalides (Scheme 3). A column packed with polymeric benzo-18-crown-6 (20) $n = 2$ was saturated with KCl at room temperature. A subsequent thermal increase of 40 °C causes a spontaneous release of K^+ ions by this 'thermal shock' resulting in a threefold increase in $[K^+]$ of the eluant. The authors conclude that this phenomena will be of considerable use in water desalination processes, in controlling the temperature of phase-transfer catalysis, and in the thermoregulation of polymeric delivery systems of Na^+/K^+.

6 Redox Responsive Macrocycles

A. Introduction.—With a view to advancing chemical sensor technology,[8] modelling electron transfer processes in biological systems, and producing new

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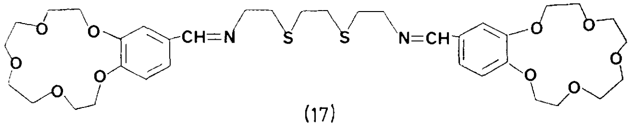
[30] P. D. Beer, *J. Chem. Soc., Chem. Commun.*, 1986, 1678.

[31] P. D. Beer and C. G. Crane, *Polyhedron*, 1988, **7**, 2649.

[32] A. Warshawsky and N. Kahana, *J. Am. Chem. Soc.*, 1982, **104**, 2663.



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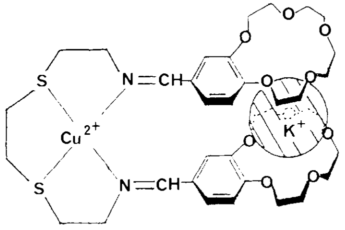

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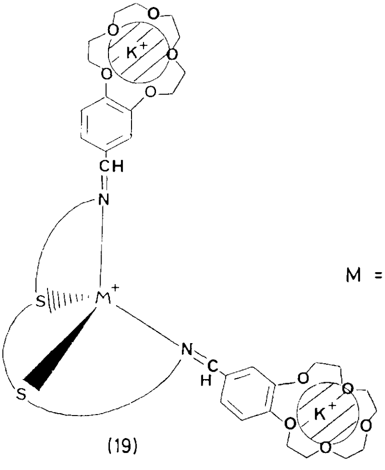

(19)

M = Ag$^+$, Cu$^+$

redox catalysts considerable interest is being shown in the syntheses of redox-active macrocyclic receptor molecules that contain a redox centre in close proximity to a host binding site.[33] In principle, these systems can be designed to recognize electrochemically the binding of (depending on the complementary nature of the host cavity) a cationic, anionic, or neutral inorganic or organic guest species either through space interactions (Figure 3a) or *via* various bond linkages between the receptor site and redox centre (Figure 3b). Obviously *selective* binding of a particular guest species coupled with an electrochemical response is of paramount importance for potential prototypes of new ampero-

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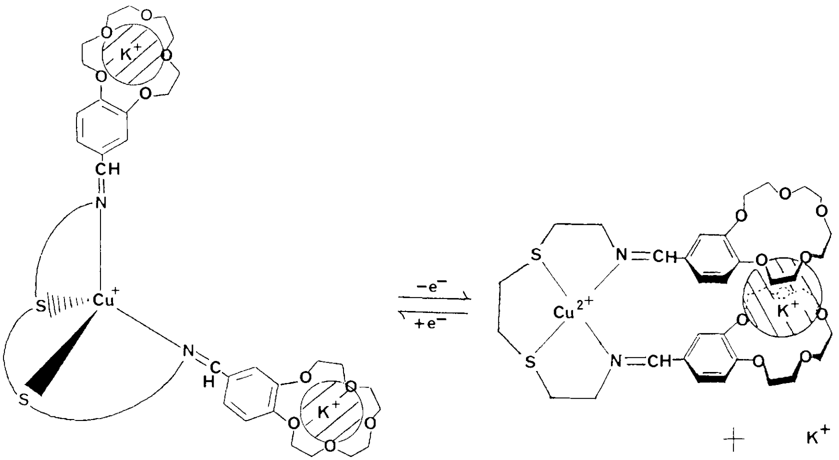
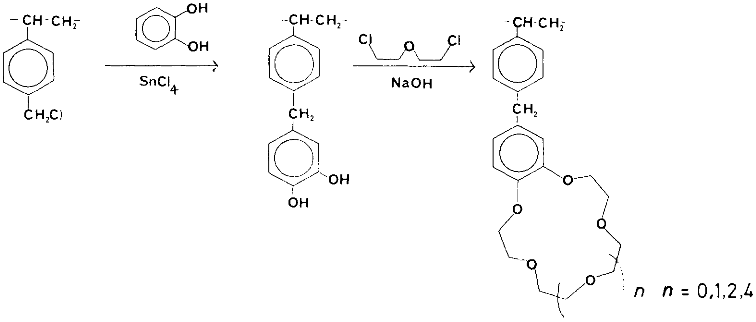
[33] P. D. Beer, *Aldrichim. Acta*, 1989, in press.

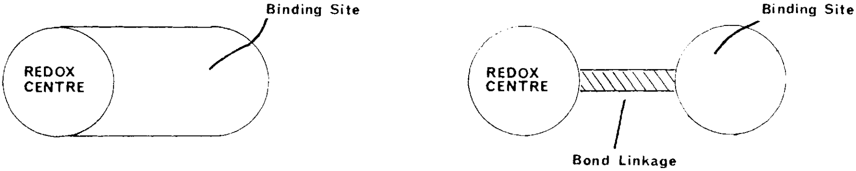


Scheme 2



(20) n = 2

Scheme 3



(a)

(b)

Figure 3 *Depiction of the concept of electrochemical recognition: the binding of a metal guest cation in close proximity to a redox-active centre-electrochemically detectable* (*a*) *through space interactions,* (*b*) *through various bond linkages* metric molecular sensory devices.[34] The majority of redox-active receptors reported to date contain crown ether fragments and are thus targeted at detecting and responding to, in particular, Group IA and IIA metal cationic guests. They may be conveniently subdivided according to whether the redox-active group undergoes electrochemical reduction or oxidation, and these types of system are reviewed first in the following sections. Very recently we have successfully prepared the first types of ammonium cation[35] and bromide *anion*[36] redox-responsive macrocyclic molecules, and hydrophobic redox receptors for inclusion of organic guest substrates.[37–42] Discussion of these results followed by a conclusion and prospects for future development of this area of host–guest chemistry completes this part of the review.

B. Redox Responsive Macrocycles Containing Electrochemically Reducible Moieties for Binding Metal Cations.—The organic redox-active reducible centres quinone[43–50] and nitrobenzene[51,52] have been successfully incorporated into a variety of macrocyclic polyether systems (Figure 4). Upon electrochemical reduction of these host molecules, radical anion species result. The binding site now contains negative charge, and hence metal cation binding strength of the reduced host will be enhanced as compared to the unreduced host. Scheme 4 outlines the respective chemical equilibria involved. Using the simple electrochemical technique of cyclic voltammetry (CV), experimental results have shown that the addition of metal cations to electrochemical solutions of reducible organic macrocyclic systems leads to the observation of either two distinct CV waves or sometimes a single CV wave that is anodically shifted in position relative to the original redox couple. Figure 5 shows an example of the former situation, the effect on the cyclic voltammogram of nitrobenzene lariat crown

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[34] T. E. Edmonds in 'Chemical Sensors', ed. T. E. Edmonds, Blackie Glasgow, London, 1988, Chapter 8, p. 193.

[35] P. D. Beer, D. B. Crowe, and B. Main, *J. Organomet. Chem.*, 1989, **375**, C35.

[36] (*a*) P. D. Beer and A. D. Keefe, Proceedings of XIII Macrocyclic Conference, Hamburg, September 1988, p. 92; (*b*) P. D. Beer and A. D. Keefe, *J. Organomet. Chem.*, 1989, **375**, C40.

[37] P. D. Beer and A. D. Keefe, *J. Inclusion Phenom.*, 1987, **5**, 499.

[38] P. D. Beer, M. G. B. Drew, and A. D. Keefe, *J. Organomet. Chem.*, 1988, **353**, C10.

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[47] K. Maruyama, H. Sohmiya, and H. Tsukube, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2069.

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[50] H. Togo, K. Hashimoto, K. Morihashi, and O. Kikuchi, *Bull. Soc. Jpn.*, 1988, **61**, 3026.

[51] A. Kaifer, L. Echegoyen, D. A. Gustowski, D. M. Goli, and G. W. Gokel, *J. Am. Chem. Soc.*, 1983, **105**, 7168.

[52] A. Kaifer, D. A. Gustowski, L. Echegoyen, V. J. Gatto, R. A. Schultz, T. P. Cleary, C. R. Morgan, D. M. Goli, A. M. Rios, and G. W. Gokel, *J. Am. Chem. Soc.*, 1985, **107**, 1958.

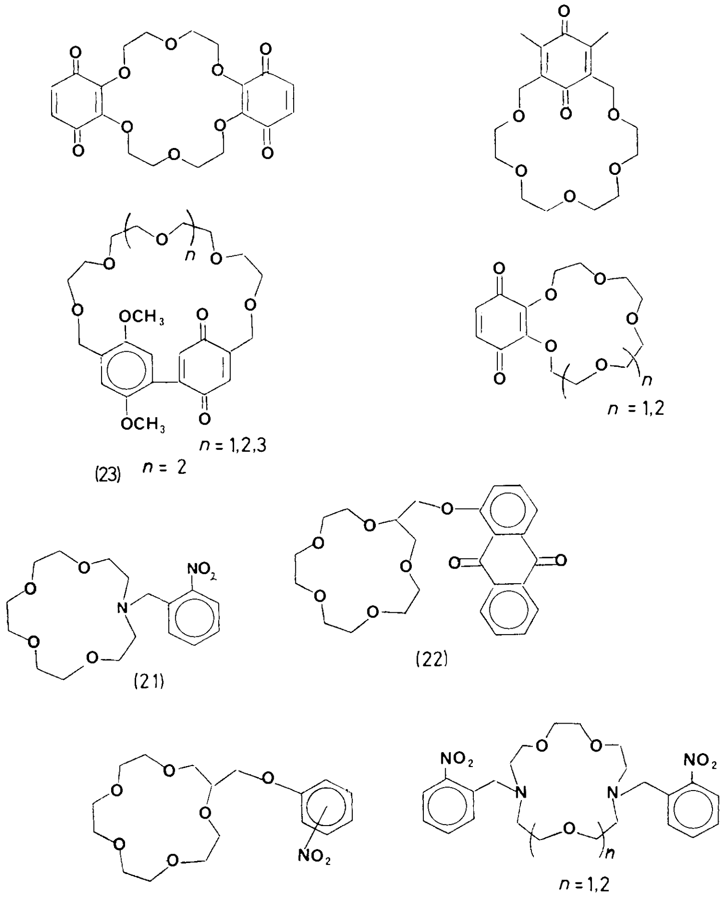

Figure 4

ether (21) on adding successive amounts of $NaClO_4$.[53] Sub-stoicheiometric amounts of sodium cations [Figure 5(b), (c), and (d)] results in two well-resolved redox couples corresponding to the free ligand and the metal complex. The type of electrochemical behaviour observed can be rationalized by considering the binding (stability) constant (K_1) for the neutral unreduced macrocycle–metal cation interaction and the binding constant (K_2) for the reduced macrocycle–cation interaction (Scheme 4). In a recent publication by Gokel *et al.*[53] a computer-based digital simulation scheme has been devised that leads to the conclusion that two distinct waves will be observed only when the initial cation

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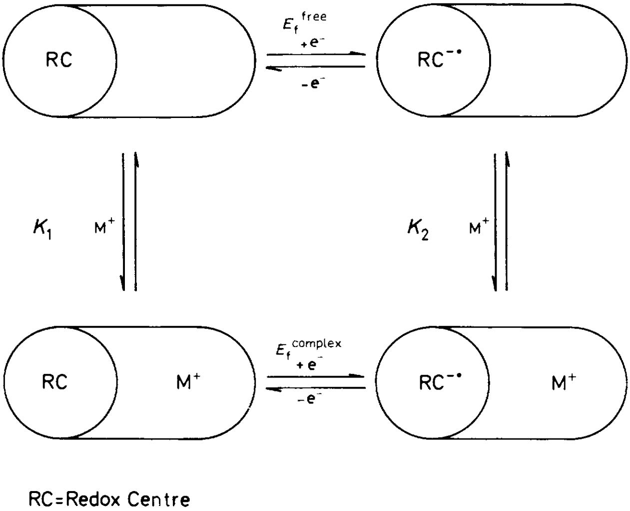
[53] S. R. Miller, D. A. Gustowski, Z. C. Chen, G. W. Gokel, L. Echegoyen, and A. E. Kaifer, *Anal. Chem.*, 1988, **60**, 2021.



Scheme 4

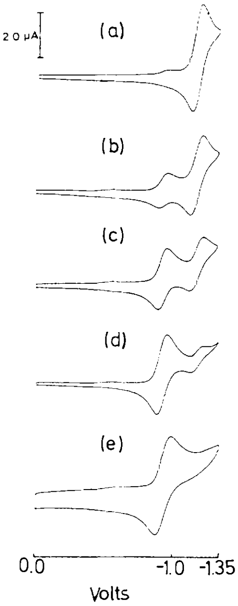


Figure 5 *Experimental cyclic voltammograms for* (21) *in the presence of varying amounts of* $NaClO_4$: (*a*) 0.0 *equivalents;* (*b*) 0.25 *equivalents;* (*c*) 0.50 *equivalents;* (*d*) 0.75 *equivalents; and* (*e*) 1.0 *equivalent of* $NaClO_4$; *scan rate* 100 mVs^{-1}

binding constant K_1 is large, and a shifted wave will result from weaker cation–macrocycle interactions. The authors discuss the important fact that quantitative values of electrochemical binding enhancements of metal cations can be calculated from the differences of formal redox potentials for the free ligand (E_f^{free}) and the complex (E_f^{complex}) using equation 1

$$E_f^{\text{complex}} - E_f^{\text{free}} = \frac{-RT}{nF}\left\{\ln\frac{(K_1)}{(K_2)}\right\} \tag{1}$$

(K_1 = binding constant for unreduced ligand, K_2 = binding constant for reduced ligand)

only in the observed two wave situation (*i.e.* K_1 values are $>10^4$). When K_1 is small ($K_1 < 1$), when only one anodically shifting redox couple is observed at all cation concentrations, equation 1 cannot be applied as it results in substantially underestimated binding enhancement values.

Generally the magnitudes of anodic shifts of quinone and nitrobenzene redox active macrocycles produced by Group IA metal cation binding decrease in the order $Li^+ > Na^+ > K^+$ (see Table 1 for examples) reflecting the order of decreasing charge/radius ratio of alkali metal cation guest. This result suggests that ion pairing between guest metal cation and the respective reduced anion radical redox centre, plus electrostatic stabilization by a proximal crown ether structural framework are essential components for electrochemical recognition to take place in these systems.

Despite the work on these and other organic redox systems[54] such as Flavin[54a,c] and NADH[54b] the effect of metal cation binding on the electrochemical properties of reducible transition metal redox centres in macrocyclic polyether systems is not well documented. We have recently prepared[55,56] a series of novel macrocycles (24)—(31) which contain a reducible transition metal redox-active 16-electron molybdenum nitrosyl $\{Mo(NO)\}^{3+}$ group incorporated into a cyclic polyether moiety. The compounds (24)—(28) were prepared from the reactions between $[Mo(NO)LX_2]$, L^- = tris(3,5-dimethylpyrazolyl)hydroborate, X = Cl or I, and the appropriate amine-substituted benzo-crown ether. The compounds (29)—(31) were synthesized from the reactions between $[Mo(NO)LI_2]$ and tetra-, penta-, or hexaethylene glycol respectively in the presence of triethylamine. A crystal structure determination[57] of (30) is shown in Figure 6.

The electrochemistry of (24)—(31) in the presence and absence of stoicheiometric amounts of Na^+ and K^+ guest cations was investigated in acetonitrile

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[54] Although other organic redox active moieties such as flavin and NADH have been recently incorporated into macrocyclic structures their *electrochemical* properties have not been reported. See, for example: (*a*) S. Shinkai, Y. Ishikawa, H. Shinkai, T. Tsuno, H. Makishima, K. Ueda, and O. Manabe, *J. Am. Chem. Soc.*, 1984, **106**, 1801; (*b*) J. D. De Vries and R. M. Kellog, *J. Chem. Soc.*, 1979, **101**, 2759; (*c*) E. Seward and F. Diederich, *Tetrahedron Lett.*, 1987, **28**, 5111.

[55] P. D. Beer, N. Al-Obaidi, J. P. Bright, C. J. Jones, J. A. McCleverty, and S. S. Salam, *J. Chem. Soc., Chem. Commun.*, 1986, 239.

[56] P. D. Beer, C. J. Jones, J. A. McCleverty, and S. S. Salam, *J. Inclusion Phenom.*, 1987, **5**, 504.

[57] P. D. Beer T. A. Hamor, N. Al-Obaidi, C. J. Jones, and J. A. McCleverty, unpublished results.

Table 1 *Electrochemical cation-dependence of reducible quinone and nitroaromatic crown ether macrocycles*

Compound	*Cation* (1 equivalent added)	ΔE/mV[a] ($E_f^{\text{complex}} - E_f^{\text{free}}$)	*Binding* enhancement (K_2/K_1) calculated from equation 1[b]
(21)	Li^+	200[c]	2.4×10^3
	Na^+	140[c]	2.3×10^2
(22)	Li^+	380[c]	8.2×10^5
	Na^+	280[c]	5.4×10^4
	K^+	200[c]	2.4×10^3
(23)	Li^+	260[d]	—
	Na^+	80[d]	—
	K^+	30[d]	—

[a] Shift in reduction potential produced by presence of metal cation. [b] Can be calculated only in two-wave case, see ref. 53. [c] Two-wave situation. [d] One wave anodically shifted, 30 equivalents of alkali metal salt added

solution by cyclic voltammetry with $[Bu^n_4N]BF_4$ as the supporting electrolyte. Table 2 shows that addition of alkali metal salt in 1:1 molar ratio produces anodic shifts (ΔE) in the original redox couple of 40—320 mV in the reduction potentials of the respective host's molybdenum redox centre. Comparing (29)—(31) to the quinone macrocyclic systems of Cooper[43] and Tsukube,[47] in the case of Na^+ guest cation these ΔE values are generally much larger in magnitude, suggesting that the transition metal molybdenum redox centre is more electrochemically *sensitive* to the presence of a closely bound metal cation than the quinone redox-active moiety.

It is noteworthy in the case of (25)—(27) that the magnitudes of the anodic shifts (ΔE) produced by cation addition appear relatively insensitive to the size of the macrocyclic polyether ring, and also that a consistent difference is found between the ΔE values for Na^+ and K^+ guest cations. The larger potassium ion having the smaller charge/radius ratio produces approximately half the shift of the Na^+ ion suggesting that, as with the organic reducible redox systems, the polarizing power of the cation guest is of great importance in determining the magnitude of the anodic shift in E_f^{free} produced by cation binding.

C. Redox Responsive Macrocycles Containing Electrochemically Oxidizable Moieties.—In contrast to the alkali metal coordination studies of electrochemically reducible redox-active macrocyclic systems, until quite recently little has been reported about the effects of cation binding on the oxidation potential of redox-active macrocycles containing oxidizable moieties such as ferrocenyl.

Ferrocene Crown and Bis Crown Ethers Designed to Bind Group I*A*, II*A Metal Cations.* Saji[58] reported the first evidence of anodic shifts in the oxidation

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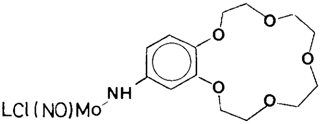
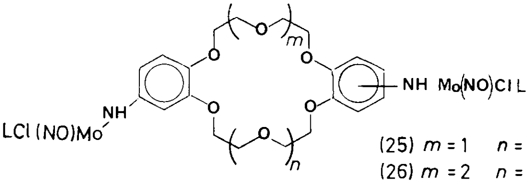
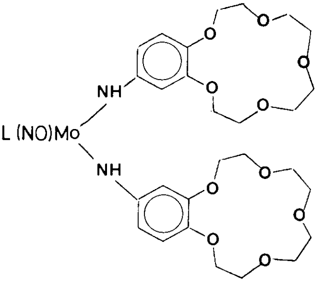
[58] T. Saji, *Chem. Lett.*, 1986, 275.



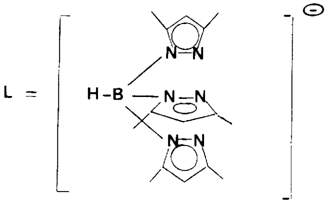
(24)

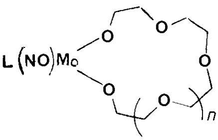


(25) $m = 1$ $n = 1$ *trans*
(26) $m = 2$ $n = 1$ *cis/trans*
(27) $m = 2$ $n = 2$ *cis/trans*



(28)





(29) $n = 1$
(30) $n = 2$
(31) $n = 3$

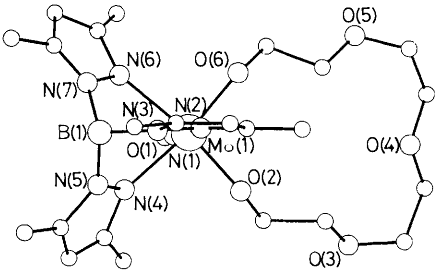
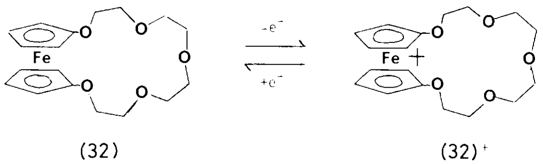


Figure 6 *Crystal structure of* (30)

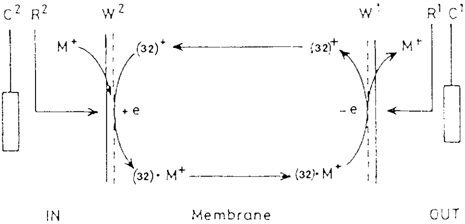
Table 2 *Electrochemical data and cation-dependence of reducible molybdenum macrocycles*

Compound	$E_f^{\text{free}\,a}$/V	$E_f^{\text{complex}\,a}$/V	ΔE^b/mV ($E_f^{\text{complex}} - E_f^{\text{free}}$)
(24)	−0.95		
(24) + Na^+		−0.89	60
(25)	−0.96		
(25) + Na^+		−0.89	70
(25) + K^+		−0.92	40
(26)	−0.94		
(26) + Na^+		−0.855	85
(26) + K^+		−0.90	40
(27)	−0.92		
(27) + Na^+		−0.835	85
(27) + K^+		−0.88	40
(28)	−1.36		
(28) + Na^+		−1.25	90
(28) + K^+		−1.32	40
(29)	−1.32		
(29) + Na^+		−1.00	320
(30)	−1.28		
(30) + Na^+		−1.00	280
(31)	−1.24		
(31) + Na^+		−1.06	180

[a] Obtained in MeCN solution containing 0.2 M $[Bu^n_4]BF_4$ as supporting electrolyte. Solutions were *ca.* 2×10^{-3} M in complex, and potentials were determined with reference to ferrocene as internal standard but are quoted relative to the SCE. [b] Shift in reduction potential produced by the presence of Na^+ or K^+ added as their BPh_4 salts, in solution, and in aliquots to provide up to 2 molar equivalents with less than 5% volume change in the solution. Broadening of the cyclic voltammogram trace was observed when between 0.2 and 1.0 equivalents of Na^+ or K^+ had been added. After *ca.* 1.2 equivalents had been added the trace returned to its original shape and no further changes were observed on adding an additional 0.8 equivalents to give a cation/complex molar ratio of 2. These shifts may be compared with the effects of adding aliquots of $NaBPh_4$ to solutions containing $[Mo(NO)LCl\{NHC_6H_4\text{-}3,4\text{-}(OMe)_2\}$ or $[Mo(NO)L\{NHC_6H_4\text{-}3,4\text{-}(OMe)_2\}_2]$ for which shifts in reduction potential of less than 10 mV were found under similar conditions



Scheme 5



Scheme 6

potential of pentaoxa[13]ferrocenophane (32) resulting from the addition of alkali metal salts, corresponding to a *decrease* of the binding constant of (32) as compared to (32^+) towards metal cations (Scheme 5). Two distinct electrochemical waves corresponding to complexed and uncomplexed (32) were observed for both Na^+ and Li^+ guest cations. The *decrease* of the binding constants for Na^+ and Li^+ calculated from equation 1 are 40 and 2, respectively, and result from the electrostatic repulsion between the positive charge on the ferrocene moiety and that of the guest alkali metal cation. This ability to switch on and switch off cation binding electrochemically has been applied by Saji and Kinoshita[59] to the electrochemical ion transport across a liquid membrane containing (32) as a carrier. The mechanism of electrochemical redox-driven metal ion transport is shown in Scheme 6. Initially at the left aqueous–CH_2Cl_2 phase interface (32) extracts a metal ion to form the complex (32)·M^+. Diffusion across the membrane followed by electrochemical oxidation by electrode W^1 at the right phase interface releases the metal ion to the aqueous phase. The $(32)^+$ then diffuses back to the left interface where it is electrochemically reduced by electrode W^2 back to (32). Very recently, electrochemical cation transport using reducible anthraquinone-derived lariat crown ethers has also been demonstrated by Gokel and co-workers.[60]

We have been synthesizing a variety of novel metallocene macrocyclic molecules designed not only to be redox responsive but also *selective* to the host binding of metal guest cations. On account of simple bis crown ether receptor molecules being known to exhibit remarkable selectivity for alkali metal cations[61–63] our initial efforts focused on the preparation of amido-linked

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[59] T. Saji and I. Kinoshita, *J. Chem. Soc., Chem. Commun.*, 1986, 716.

[60] L. E. Echegoyen, H. K. Yoo, V. J. Gatto, G. W. Gokel, and L. Echegoyen, *J. Am. Chem. Soc.*, 1989, **111**, 2440.

[61] K. Kimura, H. Sakamoto, Y. Koseki, and T. Shono, *Chem. Lett.*, 1985, 1241.

[62] M. Bourgoin, K. H. Wong, J. Y. Hui, and J. Smid, *J. Am. Chem. Soc.*, 1975, **97**, 3462.

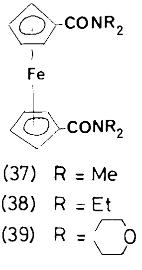
[63] K. Kikukawa, G. X. He, A. Abe, T. Goto, R. Arata, T. Ikeda, F. Wada, and T. Matsuda, *J. Chem. Soc., Perkin Trans. 2*, 1987, 135.

metallocene bis crown ethers[64–68] prepared by the synthetic routes shown in Scheme 7. ^{13}C N.m.r. titration of (33) and (34) with Na^+, K^+, and Cs^+ alkali metal salts gave titration curves suggesting 1:1 stoicheiometry, the benzo-15-crown-5 moieties are acting cooperatively to form intramolecular sandwich complexes with the alkali metal cation guest species.[66] Refluxing aqueous methanolic solutions of (33) with an excess amount of sodium or potassium hexafluorophosphate led to the successful isolation of the respective $[(33)M]PF_6{\cdot}H_2O$, M = Na, K complexes, the single-crystal structure of the potassium complex[66] is illustrated in Figure 7 with the space-filling representation of the structure in Figure 8. The potassium guest cation is coordinated to all ten oxygen atoms of the two benzo-crown ether moieties in an irregular pentagonal antiprismatic configuration with K–O contact distances ranging from 2.82—2.97 Å.

The corresponding sodium and potassium complexes of the ferrocene bis amido aza crown ether compound (36) were of 1:2 ligand:alkali metal cation stoicheiometry[67] in which each macrocyclic ring acts independently of the other (Figure 9). However, (35) containing two aza-15-crown-5 moieties forms a 1:1 intramolecular sandwich complex with K^+ and 1:2 complex with Na^+.

Fast atom bombardment (f.a.b.) mass spectrometry, a new powerful semi-quantitative technique has been used to study the selectivity of monocyclic crown ethers for Group IA metal cations in competition experiments.[69] We applied this technique for the first time to bis crown ethers.[64,66] Individual f.a.b. mass spectrometric experiments of the metallocene bis crown ethers with the alkali metal nitrates gave gas-phase [metallocene bis crown ether + metal]$^+$ ions at *m/z* values corresponding to the respective complexes. Analogous competition experiments of each compound with a mixed aqueous solution of lithium, sodium, potassium, and caesium nitrates revealed that (33) and (34) showed *exclusive* selectivity for potassium (Figure 10) and (35), (36) no selectivity for any particular alkali metal cation.

Subsequent electrochemical investigations of (33) proved disappointing. Addition of sodium or potassium salts to electrochemical solutions of (33) had little



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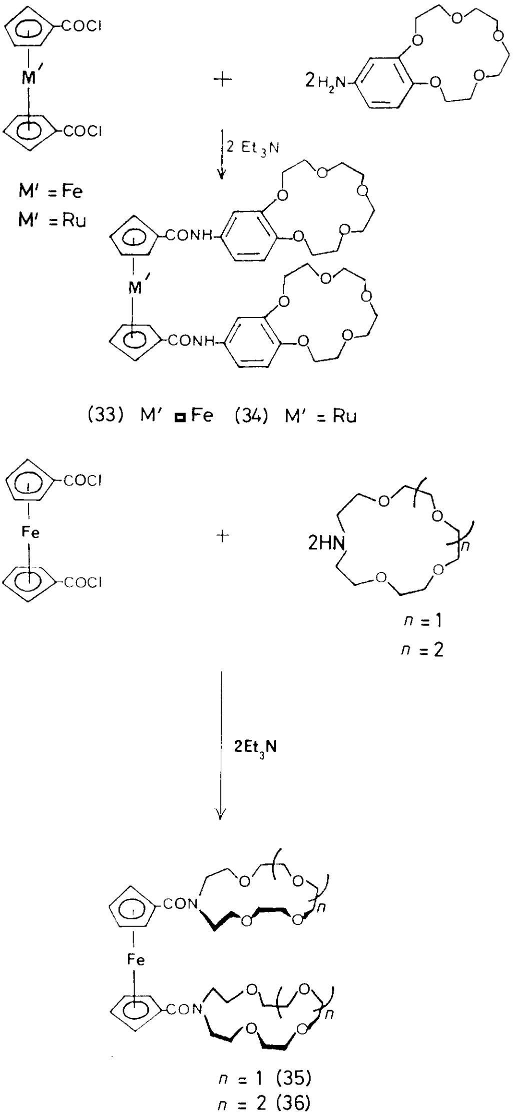
[64] P. D. Beer, *J. Chem. Soc., Chem. Commun.*, 1985, 1115.
[65] P. D. Beer, *J. Organomet. Chem.*, 1985, **297**, 313.
[66] P. D. Beer, H. Sikanyika, A. M. Z. Slawin, and D. J. Williams, *Polyhedron*, 1989, **8**, 879.
[67] P. D. Beer and H. Sikanyika, *J. Organomet. Chem.*, unpublished results.
[68] P. D. Beer and A. D. Keefe, *J. Organomet. Chem.*, 1986, **306**, C10.
[69] R. A. W. Johnstone and M. E. Rose, *J. Chem. Soc., Chem. Commun.*, 1983, 1268.



Scheme 7

effect on the reversible ferrocenyl oxidation wave, suggesting that the complexed alkali metal cation is too far away to influence the electron density at the ferrocene iron atom, either inductively or through space. Significant one-wave

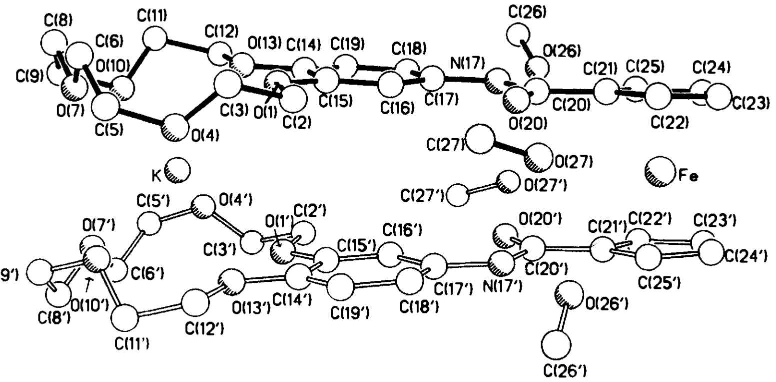


Figure 7 *The skeletal representation of the solid-state structure of* [(33)K]PF_6·4MeOH

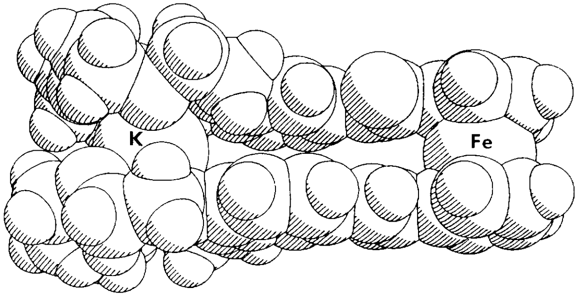
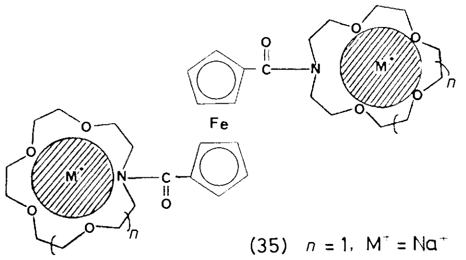


Figure 8 *The space-filling representation of the solid-state structure of the* 1:1 *complex formed between* (4) *and potassium*



(35) $n = 1$, $M^+ = Na^+$
(36) $n = 2$, $M^+ = Na^+, K^+$

Figure 9 *Ferrocene bis amido aza crown ether* 1:2 *ligand:alkali metal cation complexes*

anodic shifts were obtained, however, for (35) and (36),[67] and the electrochemical results of Group IA cation binding on these and 'model' compounds (37)—(39) are summarized in Table 3. Again the magnitude of the shift (ΔE) is dependent upon the polarizing power of the particular cationic guest. It is noteworthy from

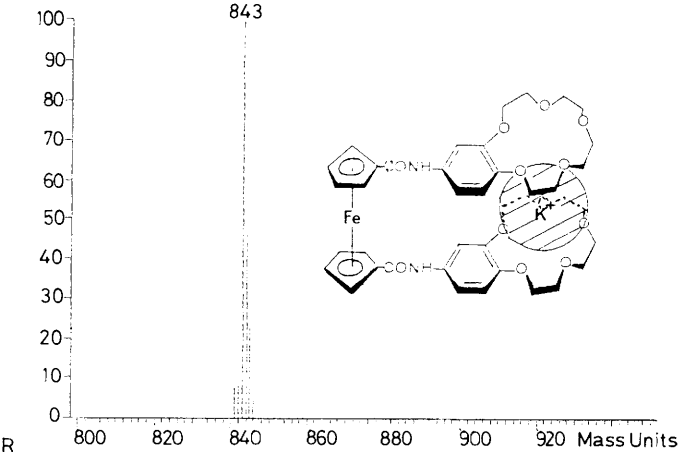


Figure 10 *FAB mass spectrum of* [(33) + *potassium*]$^+$

Table 3 that although the 'model' compounds (37)—(39) are electrochemically insensitive to the presence of Na^+ and K^+ the addition of Li^+ to these simple acyclic ferrocene bis-tertiary amides results in a large anodic shift of the respective ferrocene oxidation wave and the appearance of a new redox couple associated with a Li^+ complex (Figure 11) in which only the respective carbonyl oxygen donor atoms of (37)—(39) are coordinating to the Li^+ metal cation.[70]

As an alternative to 'through space' interactions we and others have been studying the electrochemical recognition of metal ion binding *via* conjugated[71,72] and direct[73] bond linkages between benzo crown ethers and the ferrocenyl redox centre using the compounds (40)—(47) prepared by synthetic routes outlined in

Table 3 *Electrochemical data and cation-dependence of ferrocene amide crown ethers and 'model' analogues*

Compound	(35)	(36)	(37)	(38)	(39)
E_f/V^a	+0.67	+0.67	+0.68	+0.62	+0.60
$\Delta E(Na^+)/mV^b$	40	35	<10	<10	<10
$\Delta E(K^+)/mV^b$	20	20	<10	<10	<10
$\Delta E(Li^+)/mV^c$	70	75	360	390	320

[a] Obtained in acetonitrile solution containing 0.2 M $[Bu^n_4N]BF_4$ as supporting electrolyte. Solutions were *ca.* 2 × 10^{-3} M in complex, and potentials were determined with reference to SCE. [b] One-wave shift in oxidation potential produced by presence of metal cation (4 equivalents) added as their perchlorate salts. [c] Two-wave situation; ΔE quoted is difference between E_f^{free} and position of new redox couple associated with a Li^+ complex

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[70] P. D. Beer, H. Sikanyika, C. Blackburn, and J. F. McAleer, *J. Organomet. Chem.*, 1988, **350**, C15.

[71] M. P. Andrews, C. Blackburn, J. F. McAleer, and V. D. Patel, *J. Chem. Soc., Chem. Commun.*, 1987, 1122.

[72] P. D. Beer, H. Sikanyika, C. Blackburn, and J. F. McAleer, *Inorg. Chem.*, in press.

[73] P. D. Beer, H. Sikanyika, C. Blackburn, J. F. McAleer, and M. G. B. Drew, *J. Organomet. Chem.*, 1988, **356**, C19.

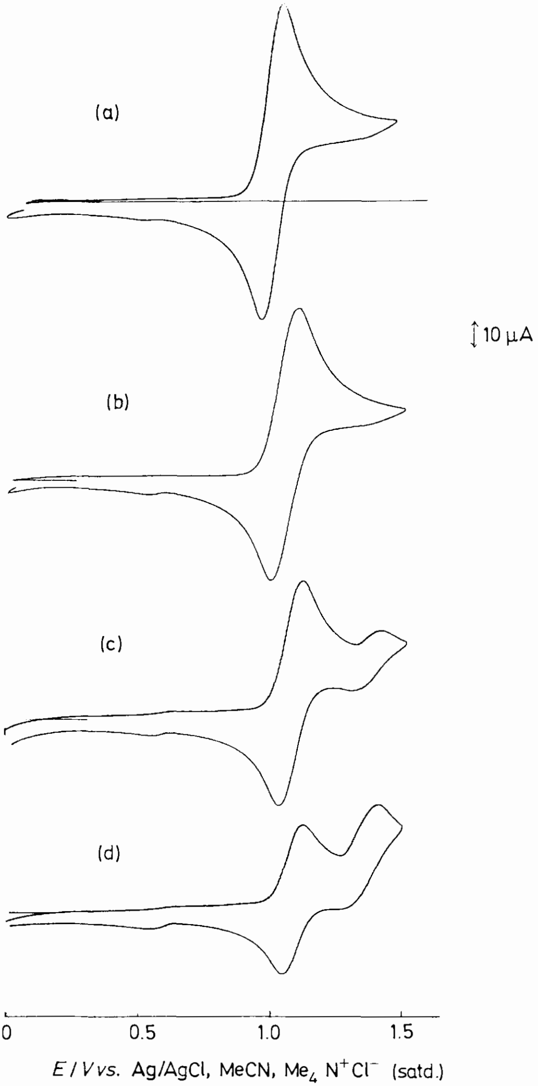
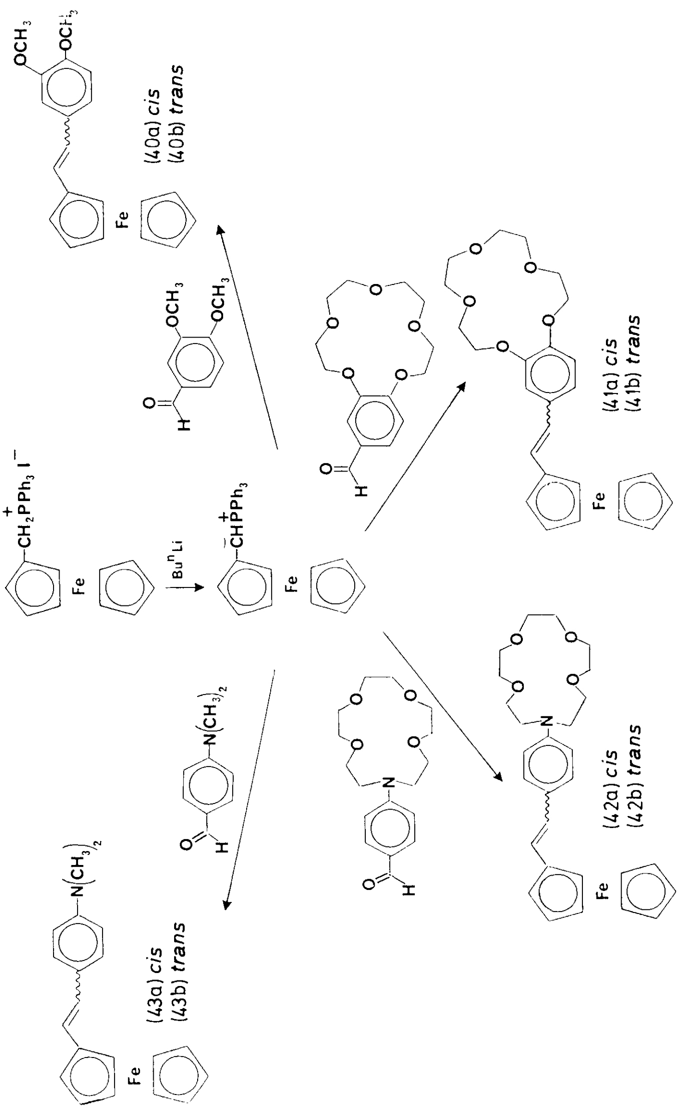


Figure 11 *Cyclic voltammetry in acetonitrile solution of:* (*a*) (37), (*b*) (37) + 0.5 *equivalents* Li^+, (*c*) (5) + 2 *equivalents* Li^+, (*d*) (37) + 4 *equivalents* Li^+. *Sweep rate* 50 mVs^{-1} *scanning from* 0 *to* 1.5 V

Schemes 8 and 9. The sodium cation forms 1:1 stoicheiometric complexes with (41), (42), (45), and (46)—the crystal structure of $[(45)Na]PF_6$ is shown in Figure 12[73]—whereas potassium produces 1:2 intermolecular sandwich complexes with



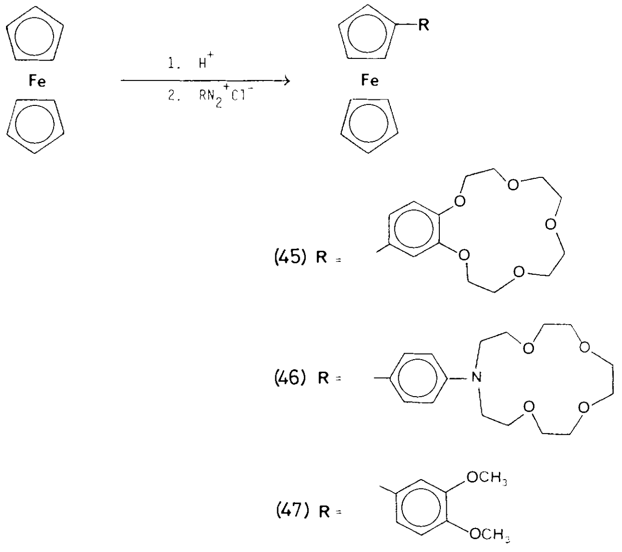
(40a) *cis*
(40b) *trans*

(41a) *cis*
(41b) *trans*

(42a) *cis*
(42b) *trans*

(43a) *cis*
(43b) *trans*

Scheme 8



Scheme 9

$$\begin{tikzcd}
\mathrm{FcI} + \mathrm{M}^{n+} \arrow[r, shift left, "K_1"] \arrow[d, shift left] & \mathrm{FcIM}^{n+} \arrow[l, shift left] \arrow[d, shift left, "E_{1c}"] \\
\mathrm{Fc^+I} + \mathrm{M}^{n+} \arrow[u, shift left, "E_{1f}"] \arrow[r, shift left, "K_2"] \arrow[d, shift left] & \mathrm{Fc^+IM}^{n+} \arrow[u, shift left] \arrow[l, shift left] \arrow[d, shift left, "E_{2c}"] \\
\mathrm{Fc^+I^+} + \mathrm{M}^{n+} \arrow[u, shift left, "E_{2f}"] \arrow[r, shift left, "K_3"] & \mathrm{Fc^+I^+M}^{n+} \arrow[u, shift left] \arrow[l, shift left]
\end{tikzcd}$$

Scheme 10 *Redox and complexation equilibria for a ferrocene-substituted ionophore, FcI; f denotes free (uncomplexed) ionophore, c denotes complexed species;* $K_j = \overrightarrow{k}_j\overleftarrow{k}_j$

the same ferrocenyl ionophores. The bis-olefinic compound 44 forms a 1:1 intramolecular sandwich complex with K$^+$ and a (44)·2Na$^+$ complex.[74]

Electrochemical investigations reveal that addition of Li$^+$ or Mg^{2+} to solutions of (42a,b) lead to the appearance of a new ferrocene redox couple at more positive potentials (Figure 13) (Table 4) associated with oxidation of a complex FcIM^{n+} (Scheme 10), whereas addition of Na$^+$ or K$^+$ gave only one-wave shift behaviour. With the benzo-15-crown-5 olefinic derivatives (41) and (44), and directly linked ionophores (45) and (46) gradual anodic shifts of the ferrocene wave were observed with all the cations Na$^+$, K$^+$, and Mg^{2+} with shift

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[74] P. D. Beer, H. Sikanyika, C. Blackburn, and J. A. McAleer, unpublished results.

Table 4 *Electrochemical data and cation-dependence of ferrocene olefinic linked crown ethers and 'model' analogues*

Compound	(40a)	(40b)	(41a)	(41b)	(42a)	(42b)	(43a)	(43b)	(44)	(48)	(49)
E_f/V[a]	+0.43	+0.43	+0.43	+0.40	+0.33 +0.61[d]	+0.34 +0.64[d]	+0.34 +0.63[d]	+0.35 +0.63[d]	+0.35	+0.45	+0.36 +0.79[d]
$\Delta E(Na^+)$mV[b]	<10	<10	30	30	50	65	<5	<5	55	—	<5
$\Delta E(K^+)$/mV[b]	<10	<10	20	20	20	20	<5	<5	35	—	<5
$\Delta E(Mg^{2+})$/mV[c]	<10	<10	70[b]	60[b]	100	110	120	100	110	—	<20
$\Delta E(Li^+)$/mV[c]	<10	<10	—	—	110	110	110	110	—	—	<5

[a] Obtained in acetonitrile solution containing 0.2 M $[Bu^n{}_4N]BF_4$ as supporting electrolyte. Solutions were *ca.* 2 × 10^{-3} M in complex, and potentials were determined with reference to SCE. [b] One-wave shift in oxidation potential produced by presence of metal cation (4 equivalents) added as their perchlorate salts. [c] Two-wave situation; ΔE quoted is difference between E_f^{free} and position of new redox couple associated with Li^+ or Mg^{2+} complex. [d] Dialkylaniline oxidation wave

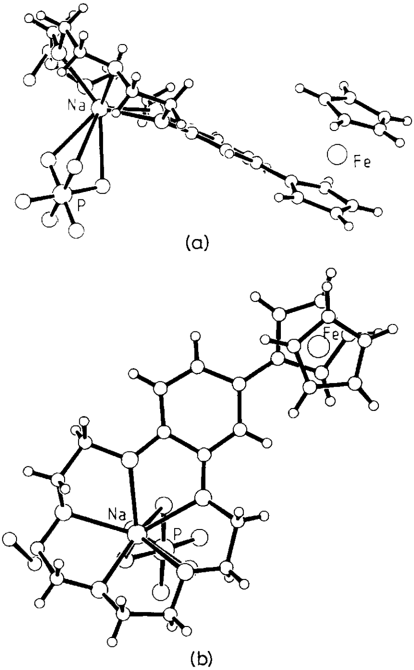
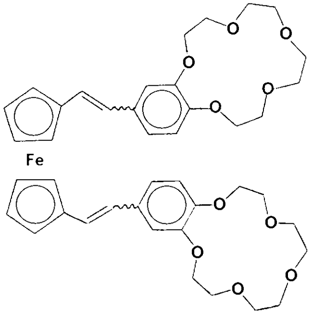


Figure 12 *Crystal structure of* [(45)Na]PF_6 *showing:* (*a*) *the* Na^+ *lying above the* 15-*crown*-5 *ligand coordinated to* PF_6^-; (*b*) *the* Na^+ *bound to all five oxygens of the benzo-crown ether*



(44)

magnitudes increasing with increasing charge (polarizing power) of the guest cation (Tables 4 and 5). Interestingly, the electrochemistry of the 'model' amines (43a,b) was unaffected by Na^+ or K^+ ions but Li^+ or Mg^{2+} addition led to the evolution of a new ferrocene wave. This observation, of similar behaviour to the aza crown compounds (42a,b) indicates the importance of the nitrogen atom in the complexation process of these two particular cations. The redox potentials of

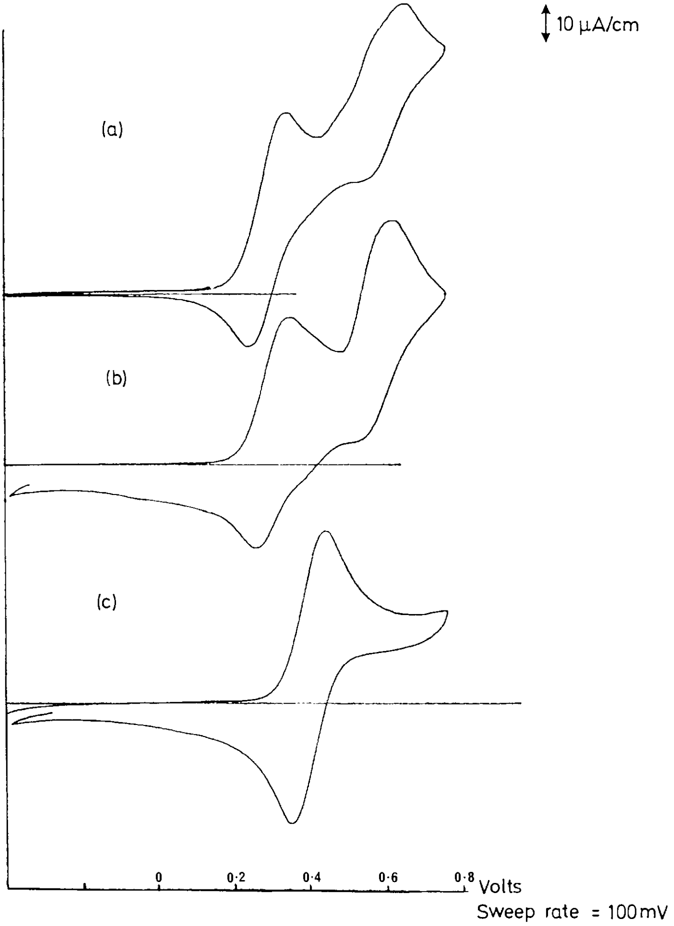


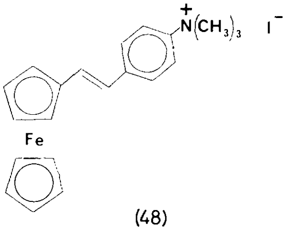
Figure 13 *Cyclic voltammetry of:* (*a*) *compound* (42a); (*b*) (42a) + 0.75 *equivalents of* Mg^{2+}; (*c*) (42a) + 1.5 *equivalents of* Mg^{2+}

the ferrocene wave for complexes formed between (42) or (43) and Li^+ Mg^{2+} are close to that observed for the methiodide (48), suggesting that ions of high charge density induce a positive charge near unity on the nitrogen atom. Compound (49) which contains a saturated linkage between the aza-crown system and the ferrocenyl redox centre was unaffected by the presence of any metal cation. In conclusion with this type of system anodic shifts in the ferrocene oxidation wave are observed if a conjugated π-electron system links the heteroatoms of the crown ionophore to the redox centre and clearly the charge/radius ratio or polarizing power of the guest cation is of great importance in determining the

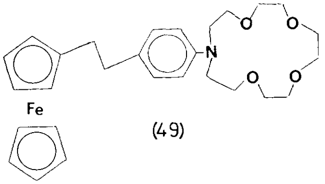
Table 5 *Electrochemical data and cation-dependence of ferrocene crown ethers containing a direct linkage*

Compound	(45)	(46)	(47)
E_f/V^a	+0.54	+0.58	+0.55
$\Delta E(\mathrm{Na}^+)/\mathrm{mV}^b$	60	90	<10
$\Delta E(\mathrm{K}^+)/\mathrm{mV}^b$	20	40	<10
$\Delta E(\mathrm{Mg}^{2+})/\mathrm{mV}^b$	70	110	<10

[a] Obtained in acetonitrile solution containing 0.2 M $[\mathrm{Bu^n{}_4N}]\mathrm{BF_4}$ as supporting electrolyte. Solutions were *ca.* 2 × 10^{-3} M in complex, and potentials were determined with reference to SCE. [b] One-wave shift in oxidation potential produced by presence of metal cation (4 equivalents) added as their perchlorate salts



(48)



(49)

magnitude and type (one or two wave) of the shift in redox potential of the ferrocenyl redox centre.

Ferrocene Cryptand Molecules. Although a number of ferrocene cryptand molecules (50)—(52) have been reported in the literature,[75-81] until very recently their electrochemical coordination properties had not been disclosed. We have synthesized potassium-selective metallocene cryptands[81] (50) and (51); the electrochemistry of the former in the presence of K^+ guest ions proved

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[75] P. J. Hammond, A. P. Bell, and C. D. Hall, *J. Chem. Soc., Perkin Trans. 1*, 1983, 707.

[76] P. D. Beer, P. J. Hammond, and C. D. Hall, *J. Chem. Soc., Chem. Commun.*, 1983, 1161.

[77] P. D. Beer, J. Elliot, P. J. Hammond, C. Dudman, and C. D. Hall, *J. Organomet. Chem.*, 1984, **263**, C37.

[78] P. D. Beer, P. J. Hammond, C. Dudman, I. P. Danks, C. D. Hall, J. Kynchala, and M. C. Grossel, *J. Organomet. Chem.*, 1986, **306**, 367.

[79] P. D. Beer, C. D. Bush, and T. A. Hamor, *J. Organomet. Chem.*, 1988, **339**, 133.

[80] M. C. Grossel, M. R. Goldspink, J. P. Kynchala, A. K. Cheetham, and J. A. Hriljac, *J. Organomet. Chem.*, 1988, **352**, C13.

[81] P. D. Beer, C. G. Crane, A. D. Keefe, and A. R. Whyman, *J. Organomet. Chem.*, 1986, **314**, C9.

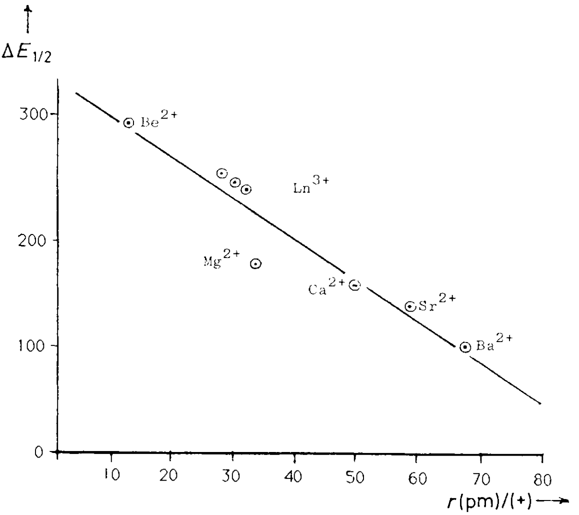

Figure 14 *Plot of* $\Delta E_{\frac{1}{2}}$ versus *radius, r* (in pm) *ionic charge, for the complexation of* (52) *with a series of alkaline earth and lanthanide metal cations*

unfortunately irreversible.[82] Using cyclic voltammetry Hall *et al.*[83] have investigated the coordination of alkaline-earth and lanthanide metal cations by the ferrocene cryptand (52). They note that large anodic shifts of the ferrocenyl redox couple are produced with these metal cations and that there exists a broad correlation between the $\Delta E_{\frac{1}{2}}$ value and the charge/radius ratio of cationic guest (Figure 14). As with the ferrocenyl crown ether ionophores discussed previously, as the charge density of the metal guest cation increases so does the observed shift in redox potential of the cryptate complex compared to the free cryptand ligand. Interestingly, with Be^{2+} and Dy^{3+} the respective cyclic voltammogram traces suggest evidence that, once oxidized, the respective complex $[(52^{+}); M^{n+}]$ ($M^{n+} = Be^{2+}, Dy^{3+}$) *ejects* the bound metal cation rapidly, presumably as a result of mutual electrostatic repulsion.

Di-η-cyclopentadienyl-molybdenum(IV) *and -tungsten*(IV) *Crown Ether Complexes.* Green and co-workers[84,85] have recently prepared ionophoric ligands incorporating the oxidative, redox-active bent d^2 di-η-cyclopentadienyl-molybdenum(IV) or -tungsten(IV) fragments into a macrocyclic structural framework. Compounds (53)—(55) were prepared from the reaction of $[M(\eta\text{-}C_5H_5)_2Cl_2]$ (M = Mo or W)

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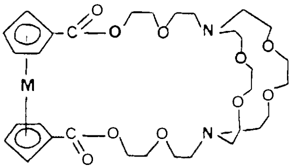
[82] P. D. Beer and A. D. Keefe, unpublished results.

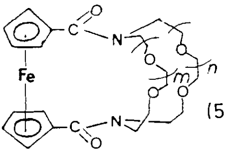
[83] C. D. Hall, N. W. Sharpe, I. P. Danks, and Y. P. Sang, *J. Chem. Soc., Chem. Commun.*, 1989, 419.

[84] E. Fu, M. L. H. Green, V. J. Lowe, and S. R. Marder, *J. Organomet. Chem.*, 1988, **341**, C39.

[85] E. Fu, J. Granell, M. L. H. Green, V. J. Lowe, S. R. Marder, G. C. Saunders, and M. Tuddenham, *J. Organomet. Chem.*, 1988, **355**, 205.



(50) M = Fe
(51) M = Ru



m = 1,2,3
n = 1,2,3
m = n, m ≠ n
(52) m = 1, n = 1

and the appropriate sodium thiolate, and (56)—(57) from reaction of the same organometallic precursors with 4′-carboxybenzo-15-crown-5.

Although the respective reversible one-electron oxidation couples of (53), (56), and (57) proved insensitive to the presence of alkali metal cations, replacing the Et_4NPF_6 supporting electrolyte with either $NaPF_6$, KPF_6, or $LiClO_4$ resulted in significant one-wave anodic shifts with compounds (54) and (55), of up to 110 mV with Na^+ and (55).

Ammonium Redox Responsive Ferrocenyl Aza Crown Ethers. In contrast to the alkali metal coordination studies of electrochemically reducible and oxidizable redox-active macrocycles discussed previously, the design and syntheses of prototype amperometric *ammonium* cation sensor systems have yet to be reported. Lehn and co-workers[86,87] first described the synthesis of 4,10,16-triaza-18-crown-6 (58) and subsequently showed that this macrocycle forms very stable ammonium and primary ammonium complexes by the formation of three complementary $\overset{+}{N}H\cdots N$ hydrogen bonds between host and guest. Utilizing this precedent we have incorporated ferrocenyl redox-active centres into this type of macrocyclic system[35] by preparing (59), (60), and 'model' compounds (61) and (62) *via* synthetic routes shown in Scheme 11.

Significant one-wave anodic shifts were produced on addition of NH_4^+ to electrochemical solutions of (59) and (60) only,[35] suggesting the crown ether structural framework containing tertiary amine nitrogen donor atoms are

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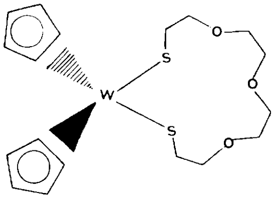
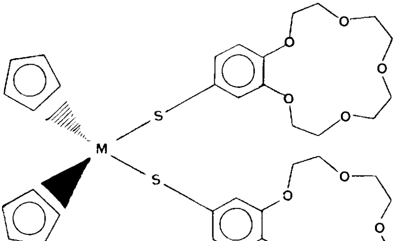
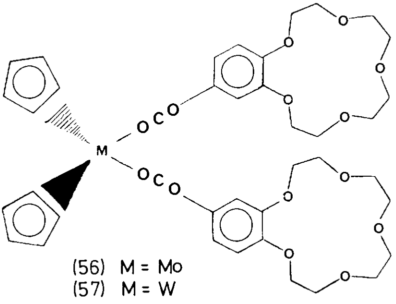
[86] E. Graf and J. M. Lehn, *J. Am. Chem. Soc.*, 1975, **97**, 5022.
[87] E. Graf and J. M. Lehn, *Helv. Chim. Acta*, 1981, **64**, 1040.



(53)



(54) M = Mo
(55) M = W

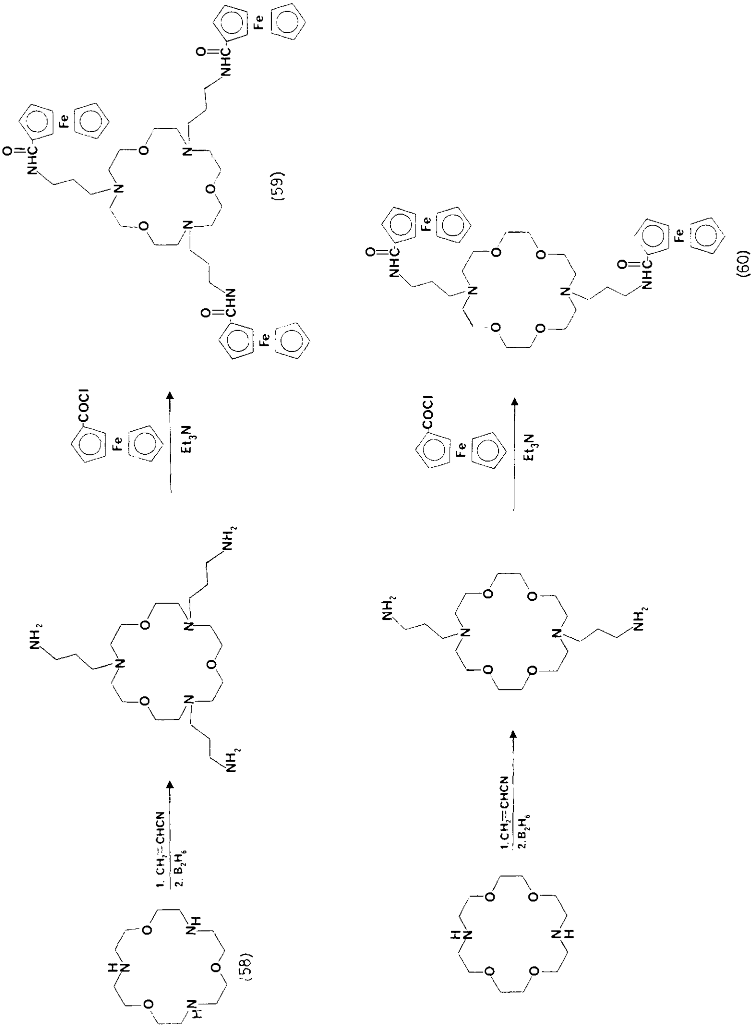


(56) M = Mo
(57) M = W

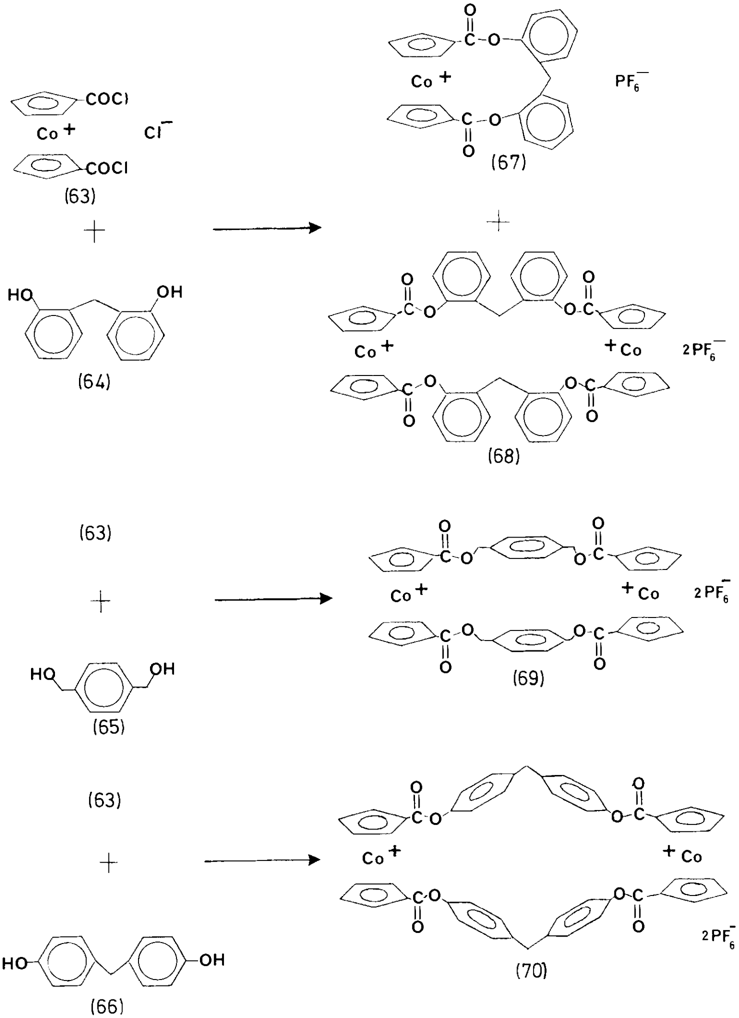
essential components for successful NH_4^+ binding. It was noteworthy that the complementary bound NH_4^+ cation exhibits the *largest* magnitude of shift, of up to 220 mV with (60). The nature of the communication between cationic ammonium guest and redox-active host probably results from a through-space electrostatic perturbation effect similar to those reported by Gokel for reducible quinone[45,46] and nitroaromatic[51,52] lariat crown ethers with alkali metal guest cations discussed in Section 6B.

D. Anion Redox Responsive Polycobalticinium Macrocyclic Receptor Molecules.—Anion coordination chemistry, the complexation of anionic species by organic receptor molecules, has only recently been recognized and developed as a new field of coordination chemistry.[10,88] This is somewhat surprising in view of the fundamental role played by anions in chemical as well as in biological processes.[89] Several classes of anion ligands have been reported, including Lewis acidic bicyclic tin cryptands,[90] organomercury[91] and silicon[92] macrocycles, and quaternary ammonium,[93] polyguanidinium, and polyammonium macrocyclic

[88] J. M. Lehn, *Pure Appl. Chem.*, 1978, **50**, 871.
[89] J. J. R. Frausto da Silva and R. J. P. Williams, *Struct. Bonding* (*Berlin*), 1976, **29**, 67.
[90] M. Newcomb, J. H. Horner, and M. T. Blanda, *J. Am. Chem. Soc.*, 1987, **109**, 7878.
[91] J. P. West and B. Zacharie, *J. Am. Chem. Soc.*, 1987, **109**, 4714.
[92] M. E. Jung and H. Xia, *Tetrahedron Lett.*, 1988, **29**, 297.
[93] F. P. Schmidtchen, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 720.

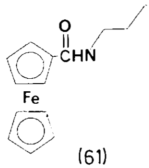


Scheme 11

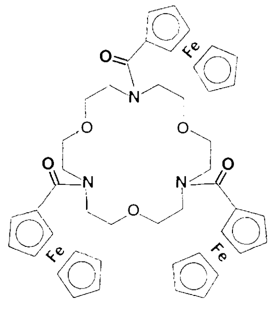

COCl
Co +
Cl⁻
COCl
(63)
HO
OH
(64)
O
C
O
Co +
PF₆⁻
(67)
Co +
+ Co
2PF₆⁻
(68)
(63)
HO
OH
(65)
Co +
+ Co
2PF₆⁻
(69)
(63)
HO
OH
(66)
Co +
+ Co
2PF₆⁻
(70)

Scheme 12

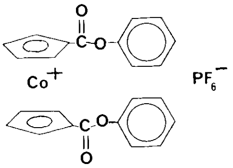
molecules.[94–96] The latter, positively charged and pH-dependent hosts, form strong and sometimes selective complexes with a variety of anions, including the binding of linear carboxylates with chain-length selectivity.[97] We have recently reported[36] the synthesis and electrochemistry of the *first* redox-responsive class of anion receptors, polycobalticinium macrocycles, which are designed to utilize the (pH-independent, positively charged, eighteen-electron, air stable, organometallic, and redox-active) cobalticinium fragment to coordinate and respond electrochemically to the binding of anionic guest species.



(61)



(62)



(71)

The condensation of 1,1′-bis(chlorocarbonyl)cobalticinium chloride (63) with respectively 2,2′-bis(hydroxyphenyl)methane (64), 1,4-benzene dimethanol (65), and 4,4′-bis(hydroxyphenyl)methane (66) followed by column chromatography and excess ammonium hexafluorophosphate gave the macrocycles (67)—(70) as yellow powders (Scheme 12). The first evidence indicating that these receptors would complex anionic guests came from fast atom bombardment mass spectrometry (FABMS) and fourier transform infra red (FTIR) investigations. For example, the hexafluorophosphate salt of (68) gave an ester carbonyl stretch at 1747 cm^{-1}, whereas the analogous chloride salt absorbed at 1739 cm^{-1}. Interestingly, this effect was *not* observed with the hexafluorophosphate and chloride salts of the acylic model (71), suggesting the presence of a macrocyclic effect in these systems.

The addition of stoicheiometric amounts of tetrabutyl ammonium bromide to electrochemical solutions of (68) led to gradual *cathodic* shifts in the reduction wave of the host. A maximum shift of 45 mV was observed after four equivalents had been added. No cathodic shifts were observed with (71) which suggests that

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[94] C. H. Park and H. E. Simmons, *J. Am. Chem. Soc.*, 1968, **90**, 2431.

[95] J. M. Lehn, E. Sonveaux, and A. K. Willard, *J. Am. Chem. Soc.*, 1978, **100**, 4914.

[96] J. M. Lehn and D. Heyer, *Tetrahedron Lett.*, 1986, **27**, 5869.

[97] M. W. Hosseini and J. M. Lehn, *Helv. Chim. Acta*, 1986, **69**, 587.

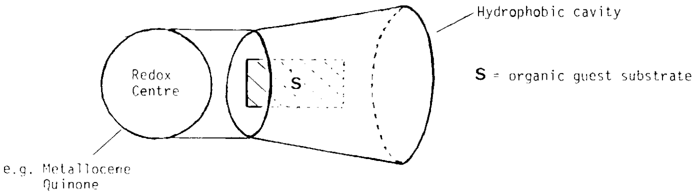
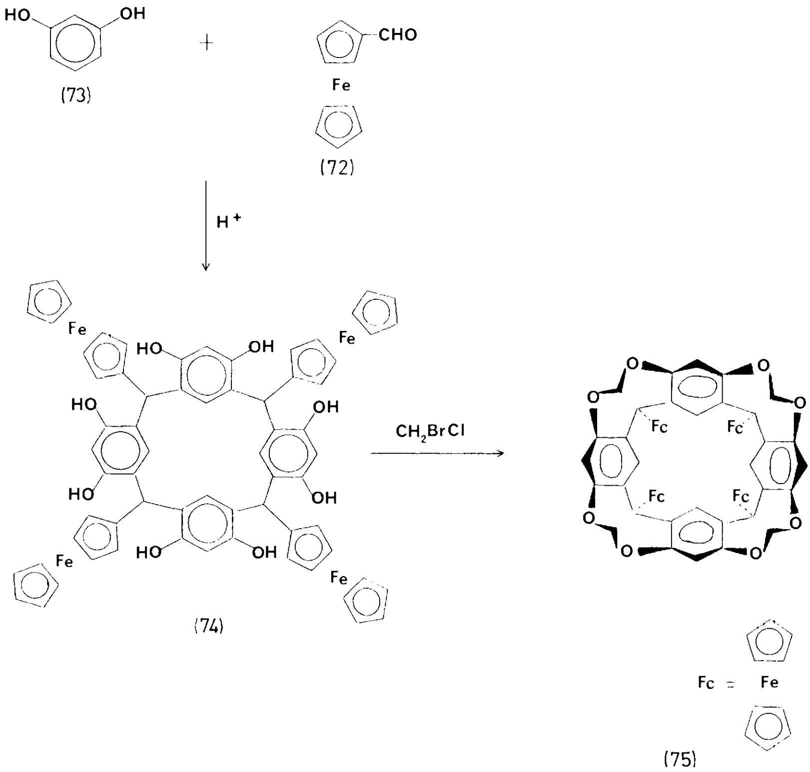
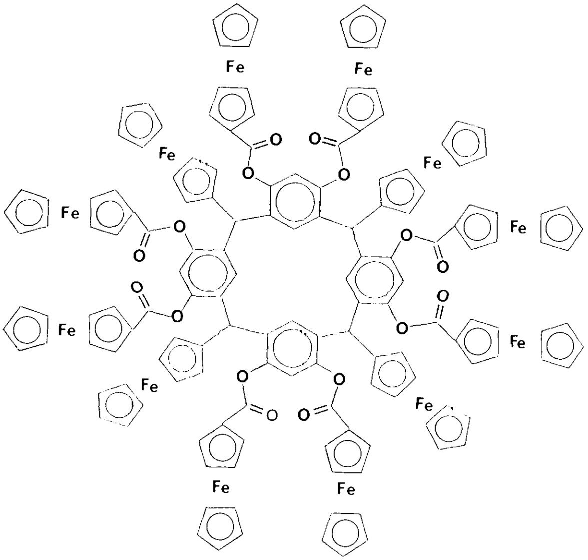


Figure 15 *Depiction of the simple concept of electrochemical recognition: the binding of an organic guest in close proximity to redox-active centres*

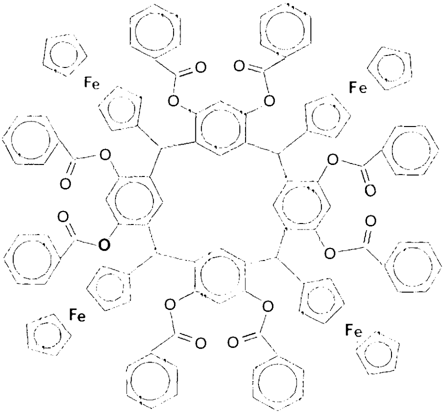


Scheme 13

bromide anion complexation within the macrocyclic cavity of (68) is essential for electrochemical detection. Complexation studies of these and related polycobalticinium receptors with other anions such as phosphate, sulphate, and nitrate are in progress.

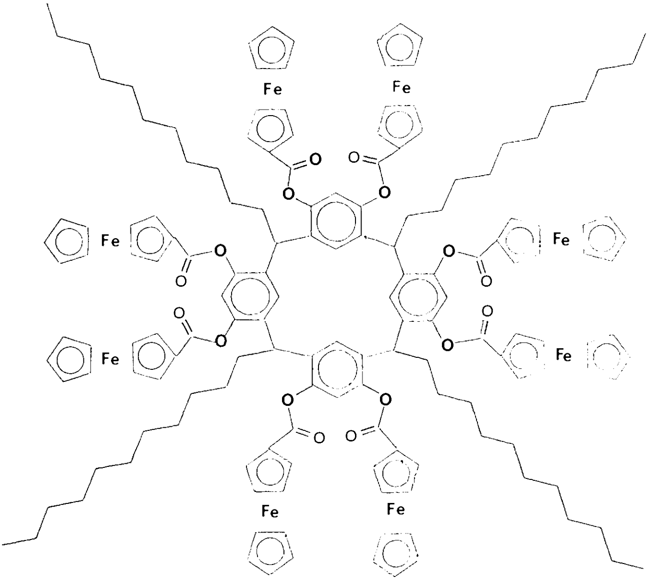


(76)

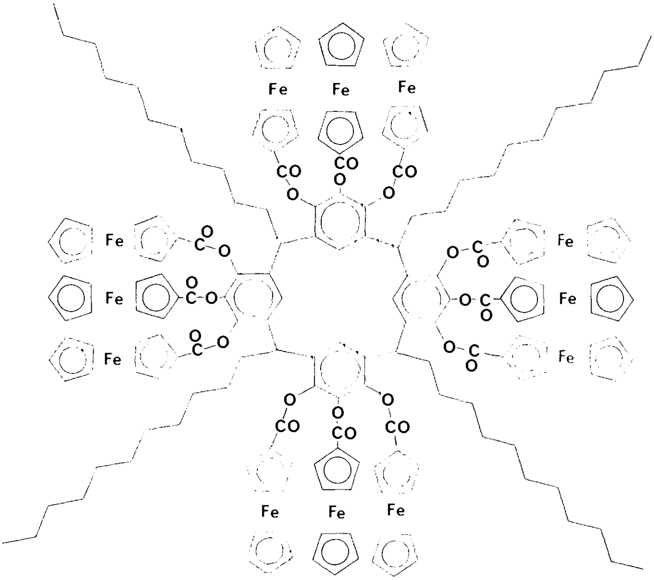


(77)

E. Redox-active Cavitand Host Molecules for Inclusion of Organic Guest Substrates.—The mimicking of enzymes in their capability to bind organic substrates selectively and reversibly and to catalyse chemical reactions upon them has resulted in the synthesis of organic host molecules, known as cavitands, that contain enforced rigid cavities of dimensions large enough to include simple



(78)



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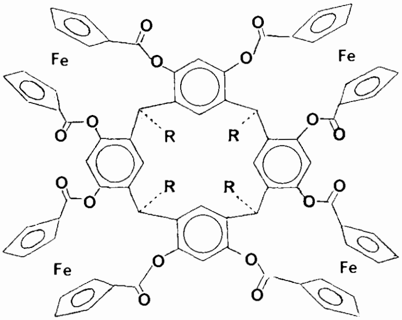
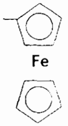


(80) R= CH_3

(81) R=



organic guest species.[98–101] We have modified these abiotic hosts to incorporate redox-responsive functions adjacent to, or as part of, a hydrophobic receptor cavity in an effort to design prototypes of a new generation of molecular sensory devices capable of electrochemically recognizing the inclusion of an *organic* guest in the host cavity[37–42] (Figure 15). Such compounds may also serve as a new class of redox catalyst, promoting redox reactions on an included guest substrate.

The reaction of ferrocenecarbaldehyde (72) and resorcinol (73) under acidic conditions gave the phenolic macrocycle (74), which on addition of $BrCH_2Cl$ produced the first redox-active cavitand (75)[41] (Scheme 13). Similar synthetic procedures have been used to prepare (76)—(81), some of which [(80) and (81)] contain ferrocene moieties lining the wall of the cavitand cavity. Crystals of (75) suitable for *X*-ray structural investigation were obtained from a dichloromethane–diethyl ether solvent mixture, and the structure (Figure 16) reveals the inclusion of a dichloromethane guest molecule within the cavitand host cavity.[41]

Related rigid macrocyclic hydrophobic calix[4]arene metallocene hosts[38,39] have also been prepared by our laboratory (Scheme 14), and the crystal structure of one (82) is shown in Figure 17.[38] Although all of these hosts undergo reversible redox oxidation processes, preliminary *solution* electrochemical and ^1H n.m.r. complexation studies in solvents such as CD_3CN, $CDCl_3$, and CD_2Cl_2 showed none to respond electrochemically or form solution host–guest complexes with simple organic substrates such as aliphatic or aromatic amine or halogenated

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[98] D. J. Cram, *Science*, 1983, **219**, 1177.

[99] D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1039.

[100] F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 362.

[101] J. Franke and F. Vogtle, *Top. Curr. Chem.*, 1986, **132**, 135.

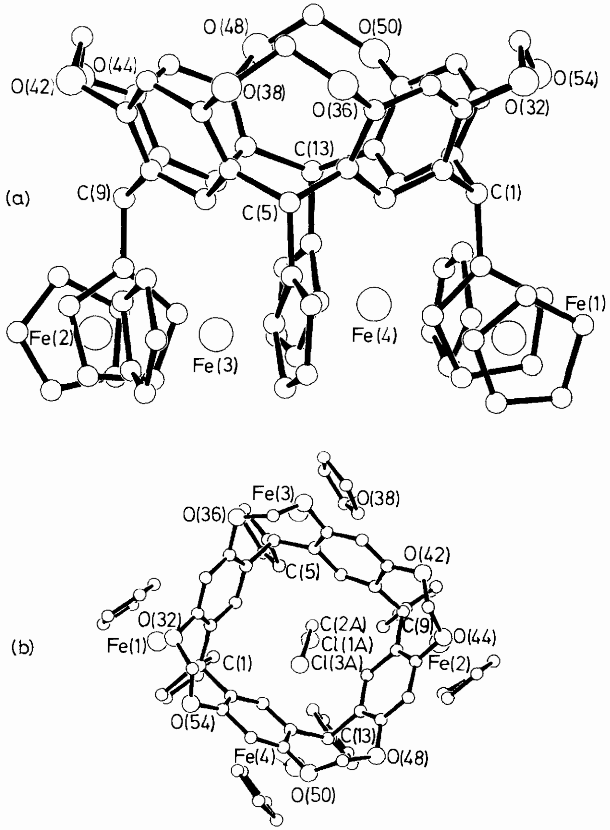

Figure 16 *The crystal structure of* (75) *showing;* (*a*) *the regular cone shape, and* (*b*) *the inclusion of a dichloromethane guest molecule*

molecules. Future work is being directed at synthesizing water-soluble analogues in an effort to utilize the 'hydrophobic effect'[102] as the driving force for inclusion of organic guest species.

7 Conclusions

It has been demonstrated by ourselves and others that reducible or oxidizable redox-active macrocyclic receptor molecules can electrochemically recognize cationic (metal, ammonium) and anionic (bromide) guests, by 'through-space' electrostatic perturbation and/or *via* various conjugated bond linkages connecting the heteroatoms of the ionophore to the redox centre. The magnitude and type (one or two wave) of the shift in the respective redox couple of these host systems produced by charged guest binding is dependent upon a combination of many

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[102] A. Ben-Naim, 'Hydrophobic Interactions,' Plenum Press, New York, 1980.

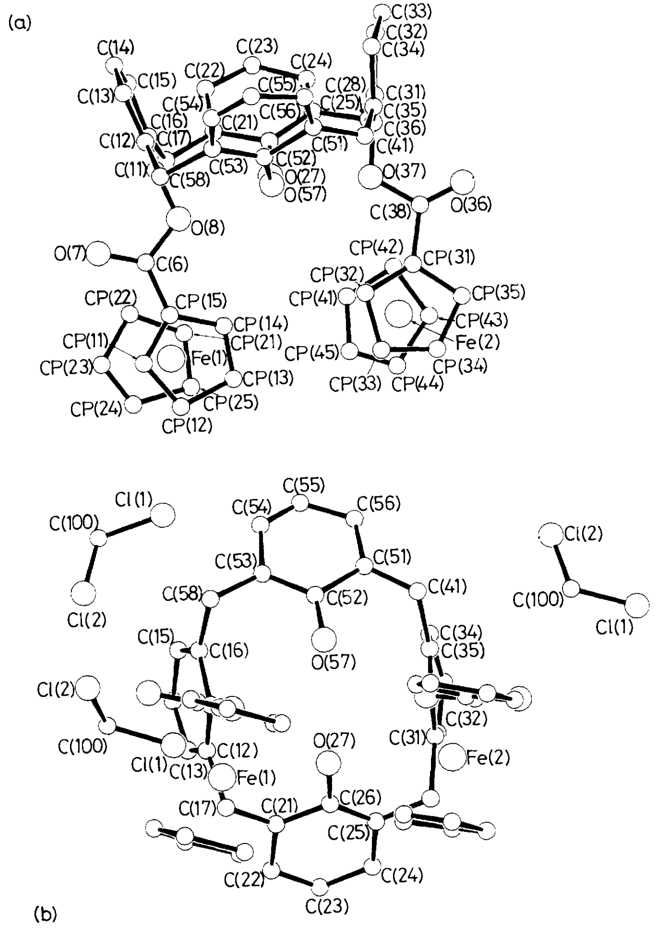
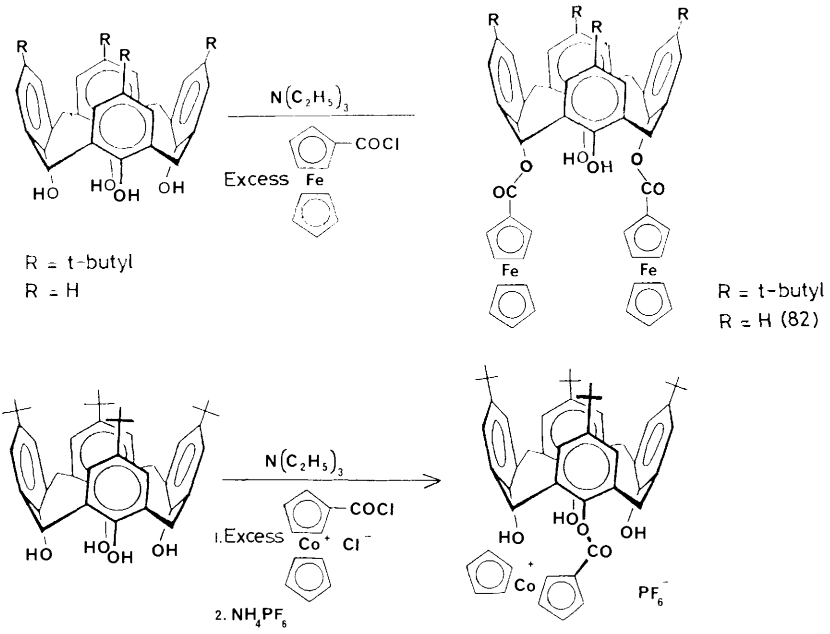


Figure 17 *Crystal structure of* (82): (*a*) *in absence of dichloromethane,* (*b*) *in presence of dichloromethane*

factors including: (i) redox-active host–guest complementarity, *i.e.* thermodynamics and kinetics of redox-active host–guest binding; (ii) the charge/radius ratio or polarizing power of the guest (for example, for metal cations the general order of decreasing magnitude of shift is lanthanides > Group IIA > Group 1A for a ferrocene cryptand host (52); (iii) proximity of host binding site to redox centre; (iv) nature of bond linkage from host binding site to redox centre; (v) nature of redox centre. Other experimental considerations such as solvent, temperature, and instrumentation also contribute to the process of electrochemical recognition. Apart from the obvious future commercial applications of these systems to a new generation of amperometric molecular sensing devices, they also promise to exhibit exciting new redox catalytic properties—promoting redox reactions on an



Scheme 14

included guest substrate—and novel solid state anisotropic electronic and non-linear optical behaviour such as second harmonic generation.[103]

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Note added in proof. We have recently discovered that the novel ferrocenyl ionophore (44) selectively complexes, electrochemically recognizes, and responds to the potassium guest ion in the *presence* of equimolar amounts of sodium and magnesium ions (reference 104).

[103] Simple ferrocene derivatives have recently been shown to exhibit non-linear optical behaviour, see for example: M. L. H. Green, S. R. Marder, M. E. Thompson, J. A. Bandy, D. Bloor, P. V. Kolinsky, and R. J. Jones, *Nature*, 1987, **330**, 360; M. L. H. Green, J. Qin, D. O'Hare, H. E. Bunting, M. E. Thompson, S. R. Marder and K. Chatakondu, *Pure Appl. Chem.*, 1989, **61**, 817.

[104] P. D. Beer, H. Sikanyika, C. Blackburn, and J. F. McAleer, *J. Chem. Soc., Chem. Commun.*, 1989, in press.