ADVANCES IN INORGANIC CHEMISTRY, VOL. 39

TRANSITION METAL AND ORGANIC REDOX-ACTIVE MACROCYCLES DESIGNED TO ELECTROCHEMICALLY RECOGNIZE CHARGED AND NEUTRAL GUEST SPECIES

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I. Introduction

Since the pioneering work of Pedersen (*1*), Lehn (*2*), and Cram (*3*) on synthetic macrocyclic and macropolycyclic host systems such as the crown ethers, cryptands, and spherands, there has been an enormous development of the field of host–guest or supramolecular chemistry. Molecular hosts designed to bind inorganic and organic, charged and neutral guest species via cumulative, noncovalent interactions have all been reported and extensive reviews on this subject have appeared (*4–8*).

Stimulated by nature and in particular by the idea of modeling "coupled reactions," i.e., reactions that mutually influence each other which are known to play a fundamental role in biological processes (*9*) such as ion transport and oxidative phosphorylation, recent attention has focused on a new generation of abiotic host molecules that contain responsive or signaling functions appended to or as an integral part of a host macrocyclic framework. Examples include pH-responsive (*10–13*), photochemical-responsive (*14–19*), and temperature-responsive (*20*) receptors whose binding strength and/or selectivity toward a guest specie can be influenced via the appropriate external physical or chemical trigger. This review is concerned with macrocyclic receptor molecules that contain an *electrochemical* responsive signaling function, i.e., a redox-active center, in close proximity to a host binding site (*21*). Depending on the complementary nature of the host cavity, these systems can in principle be designed to recognize electrochemically the binding of any charged or neutral inorganic or organic guest specie, through either space electrostatic interactions (Fig. 1a) or electrostatic communication via various bond linkages between the receptor site and the redox center (Fig. 1b). Evidently *selective* binding of a particular guest

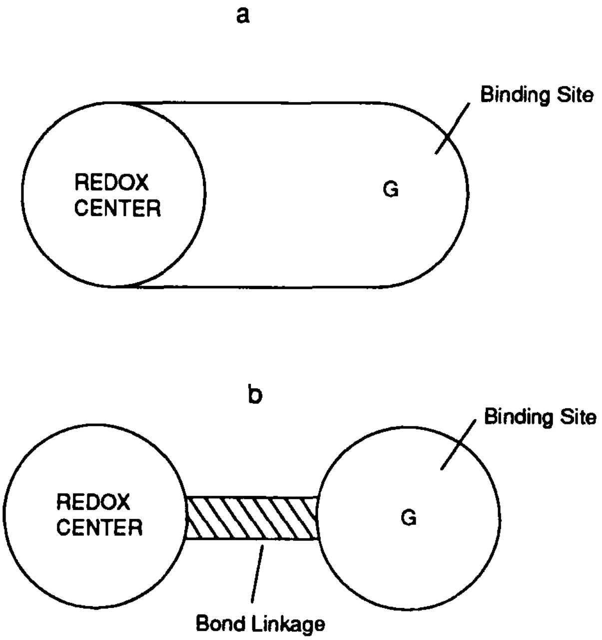


FIG. 1. Depiction of the concept of electrochemical recognition; the binding of a guest (G) in close proximity to a redox-active center electrochemically detectable (a) through space interactions and (b) through various bond linkages.

specie coupled with an electrochemical response is of paramount importance for future potential prototypes of new amperometric molecular sensory devices (*22*). The review of these types of systems is conveniently subdivided according to the nature of the target complexant, i.e., a cation (metal, ammonium), anion (halide, nitrate, sulfate, phosphate, etc.), or neutral (organic or inorganic) guest.

II. Electrochemical Recognition of Cations

A. GROUP IA, IIA METAL CATIONS BY ORGANIC REDOX-ACTIVE MACROCYCLES

Electron-rich cavities such as those possessed by macrocyclic polyethers, the crown ethers (*1*), and the three-dimensional cryptands (*2*) have been combined with a variety of organic and inorganic redox-active centers to produce redox-responsive hosts targeted at Group IA and IIA metal cationic guests. Reducible redox-active quinone-macrocyclic (*23–31*) and nitrobenzene-macrocyclic (*32, 33*) polyether systems (Fig. 2) have been prepared by a number of groups; in particular Gokel and co-workers were arguably the first to demonstrate the electrochemical recognition of a sodium cation by one such system (*32*). Electrochemical reduction of these host molecules produces radical anion species. The binding site, in addition to the cyclic polyether, now contains a negative charge and consequently the metal cation binding strength of the reduced host will be enhanced compared to that of the neutral host. Scheme 1 outlines the respective chemical equilibria involved. Using the simple electrochemical technique of cyclic voltammetry (CV), experimental results have shown that the addition of Group IA metal cations to electrochemical solutions of reducible organic macrocyclic systems leads to the observation of either two distinct CV waves or in some cases a single CV wave that is *anodically* shifted in position relative to the original redox couple. An example of the former situation is shown in Fig. 3: the effect of the addition of sodium cations on the cyclic voltammogram of a nitrobenzene lariat crown ether (**1**). Substoichiometric amounts of the guest metal cation (Figs. 3b, 3c, and 3d) results in two well-resolved redox couples corresponding to the free ligand and the sodium cation complex. The type of electrochemical behavior observed can be rationalized by considering the binding (stability) constant (*K*1) for the neutral macrocycle–metal cation interaction and the binding constant (*K*2) for the radical anionic reduced macrocycle–

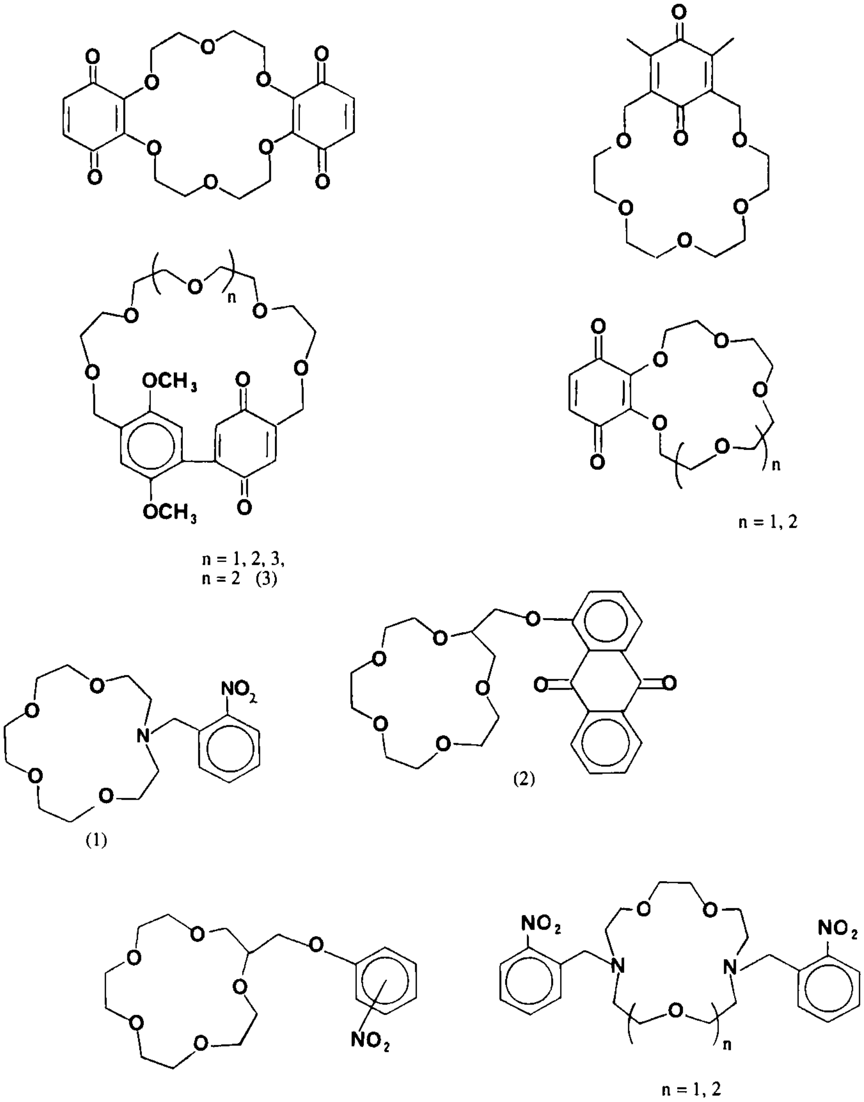
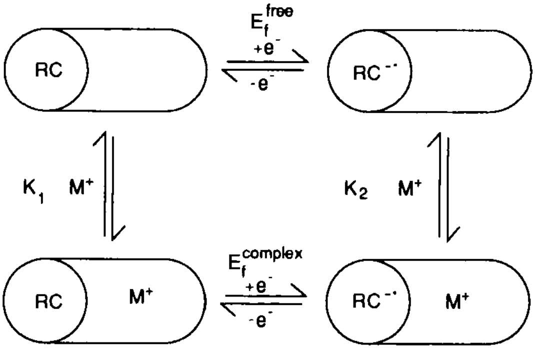


FIG. 2. Reducible redox-active quinone and nitrobenzene macrocyclic polyether ligand systems.

cation interaction (Scheme 1). Kaifer and co-workers (*34*) have devised a cyclic voltammogram computer-based digital simulation scheme that leads to the conclusion that two distinct CV waves will be observed only when the neutral host–metal cation binding constant $K1$ is large,



SCHEME 1. RC, redox center.

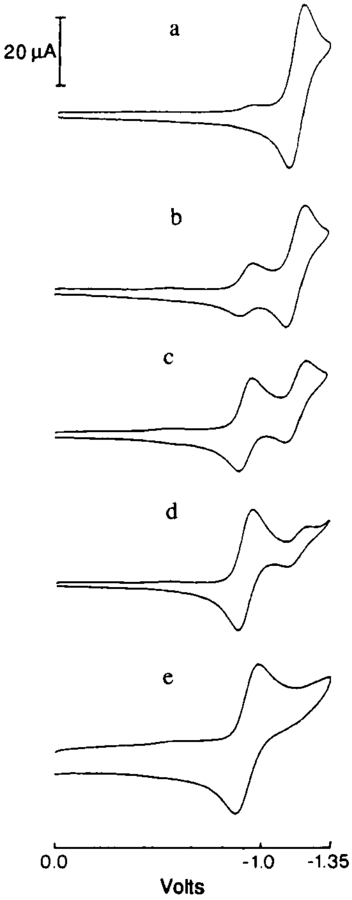


FIG. 3. Experimental cyclic voltammograms of (1) in the presence of varying amounts of $NaClO_4$: (a) 0.0 equivalent; (b) 0.25 equivalent; (c) 0.50 equivalent; (d) 0.75 equivalent; (e) 1.0 equivalent of $NaClO_4$. Scan rate 100 mV s^{-1}, acetonitrile solvent.

and an anodically shifted single CV wave will result from weaker metal cation–host macrocycle interactions. In addition, the authors conclude that quantitative values of electrochemical binding enhancements of Group IA metal cations can be calculated only from the differences of formal redox potentials for the free ligand (E_f^{free}) and the metal complex (E_f^{complex}) using

$$E_f^{\text{complex}} - E_f^{\text{free}} = \frac{-RT}{nF}\left\{\ln\frac{(K1)}{(K2)}\right\} \qquad (1)$$

($K1$ = binding constant for neutral ligand, $K2$ = binding constant for anion radical reduced ligand) in the two CV wave situation (i.e., $K1$ values are $>10^4$). When $K1$ is small ($K1 < 1$), one anodically shifting CV redox couple is observed at all metal cation concentrations; Eq. (1) is not valid as it results in substantially underestimating binding enhancement values. In general 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 I for examples) reflecting the order of decreasing charge–radius ratio of the alkali metal cation guest. This result suggests that the combination of favorable electrostatic ion-pairing between the guest metal cation and the respective reduced anion radical redox center and electrostatic stabilization by a proximal electron-rich macrocyclic

TABLE I

ELECTROCHEMICAL GROUP IA METAL CATION DEPENDENCE OF QUINONE AND NITROAROMATIC CROWN ETHER MACROCYCLES

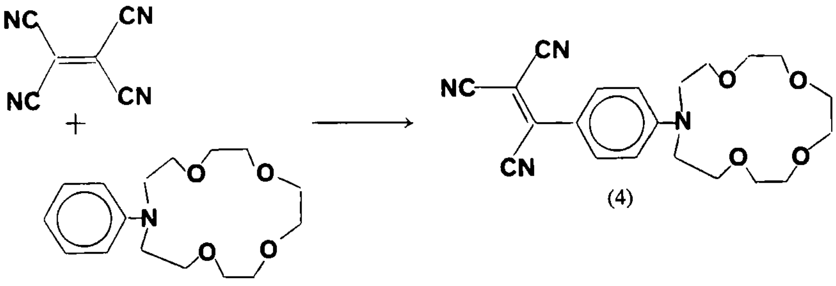
Compound	Group IA metal cation (1 equivalent added)	ΔE (V)[a] ($E_f^{\text{complex}} - E_f^{\text{free}}$)	Binding enhancement (K_2/K_1) calculated from Eq. (1)[b]
(1)	Li^+	200[c]	2.4×10^3
	Na^+	140[c]	2.3×10^2
(2)	Li^+	380[c]	8.2×10^5
	Na^+	280[c]	5.4×10^4
	K^+	200[c]	2.4×10^3
(3)	Li^+	260[d]	—
	Na^+	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. (*34*).

[c] Two-wave situation.

[d] One-wave anodically shifted, 30 equivalents of alkali metal salt added.

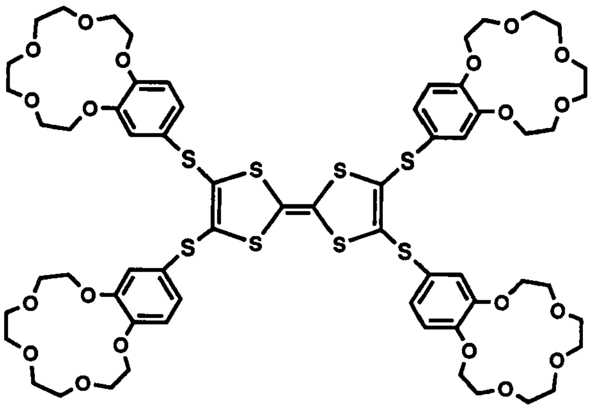


SCHEME 2.

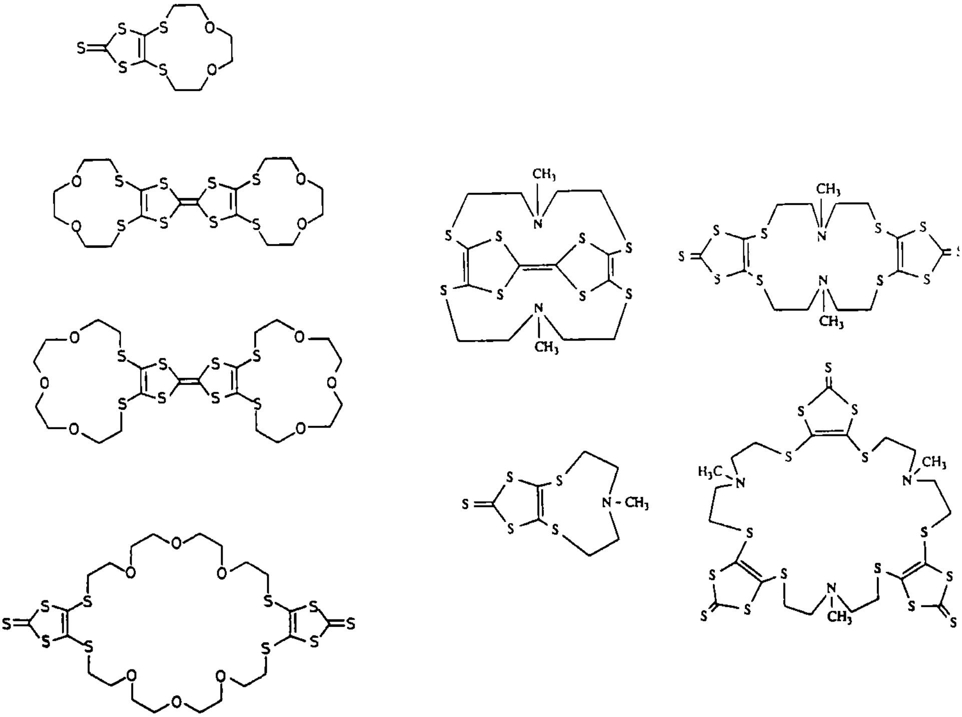
crown ether structural framework are the essential components for electrochemical recognition of Group IA metal cations.

We have recently prepared a new chromophoric and redox-responsive ionophore (**4**) containing a tricyanovinyl redox-active moiety (*35*) (Scheme 2). Electronic absorption spectra of (**4**) exhibit hypochromic shifts on binding Group IA and IIA metal cations and cyclic voltammetric electrochemical investigations reveal that (**4**) electrochemically recognizes Na^+ and K^+ guest cations, resulting in one-wave CV shifts of the tricyanovinyl reduction wave (80 and 20 mV, respectively) to more anodic potentials.

Although Becher, Underhill, and co-workers (*36–48*) have prepared a number of macrocycles containing the tetrathiafulvalene redox center (Scheme 3) primarily designed to coordinate transition metal cations, no electrochemical recognition studies have as yet been reported. A tetrathiafulvalene-tetrasubstituted benzo-15-crown-5 ionophore (**5**) has



(5)



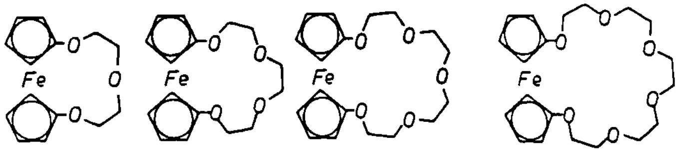
SCHEME 3.

also been synthesized by our group (*39*); however, preliminary CV results suggest that the tetrathiafulvalene redox center is electrochemically insensitive to the binding of Na^+, K^+, or Mg^{2+} cations. Although other organic redox-active moieties such as flavin (*40, 41*) and NADH (*42*) have been incorporated into macrocyclic structures, their electrochemical properties have not been reported.

B. REDOX-ACTIVE MACROCYCLES CONTAINING TRANSITION METAL ORGANOMETALLIC REDOX CENTERS

1. Ferrocene Crown and Bis Crown Ethers Designed to Bind Group IA, IIA Metal Cations

The organometallic ferrocene moiety is an attractive redox center to integrate into macrocyclic polyether ligands because, apart from its established functional group organic chemistry, ferrocene itself is electrochemically well behaved in most common solvents undergoing a reversible one-electron oxidation (*43*).



SCHEME 4.

Although a selection of ferrocene crown ethers (Scheme 4) were initially reported by Biernat and Wilczewski (*44*), Saji (*45*) described the first evidence of anodic shifts in the oxidation potential of pentaoxa[13]-ferrocenophane (**6**) resulting from the addition of alkali metal salts. Two distinct electrochemical CV waves corresponding to complexed and uncomplexed (**6**) were observed for both Na^+ and Li^+ guest cations (Fig. 4). The respective anodic shifts correspond to a decrease of the

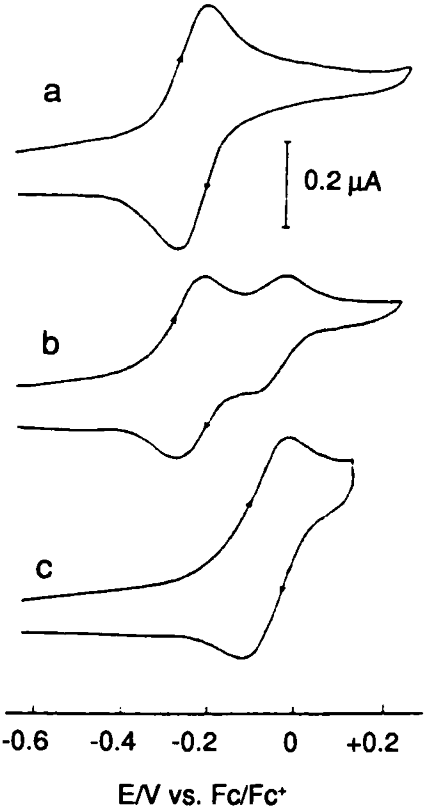
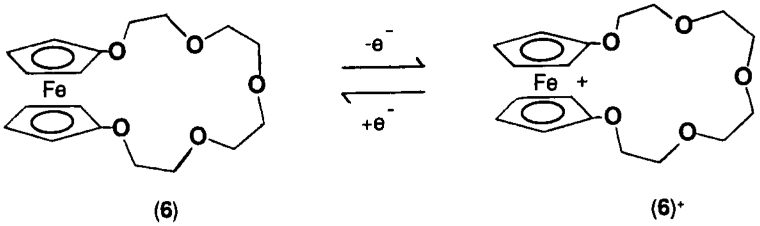
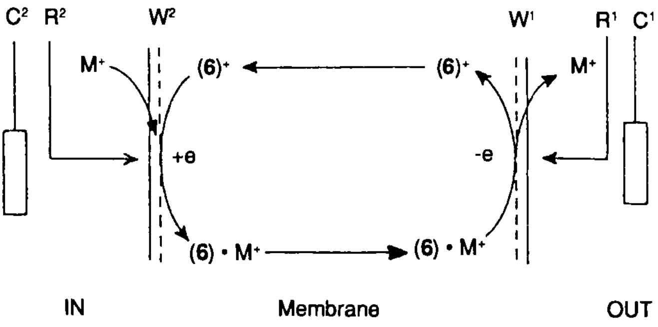


FIG. 4. Experimental cyclic voltammograms of (**6**) in the presence of $NaClO_4$: (a) 0.0 equivalent; (b) 0.5 equivalent; (c) 1.0 equivalent of $NaClO_4$. Dichloromethane solvent.

binding constant of (**6**) compared to that of $(\mathbf{6})^+$ resulting from mutual electrostatic repulsion between the ferricinium positive charge and the guest alkali metal cation. The quantitative magnitudes of this decrease in metal cation binding ability can be calculated using Eq. (1) and are, respectively, 40 and 742 for Na^+ and Li^+. This facility to switch on and switch off cation binding electrochemically has been utilized by Saji and Kinoshita (*46*) to transport alkali metal cations across a liquid membrane containing (**6**) as the carrier. Scheme 5 shows the mechanism of electrochemical redox-driven metal ion transport. Initially at the left aqueous–dichloromethane interface, (**6**) extracts a metal cation to form the complex $(\mathbf{6})M^+$. 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 ferricinium derivative $(\mathbf{6})^+$ then diffuses back to the left interface where it is electrochemically reduced at electrode W^2 back to (**6**). Gokel and co-workers (*47*) have recently demonstrated electrochemical metal cation transport using reducible anthraquinone-derived lariat crown ethers.

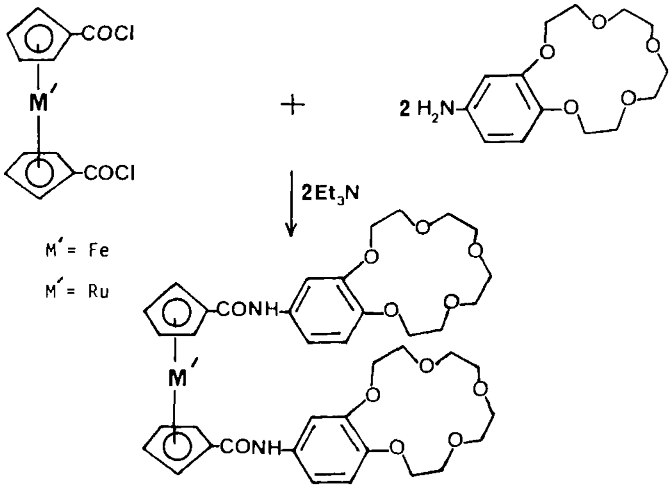
During the last few years we have been preparing a variety of metallocene macrocyclic molecules designed to be not only redox responsive





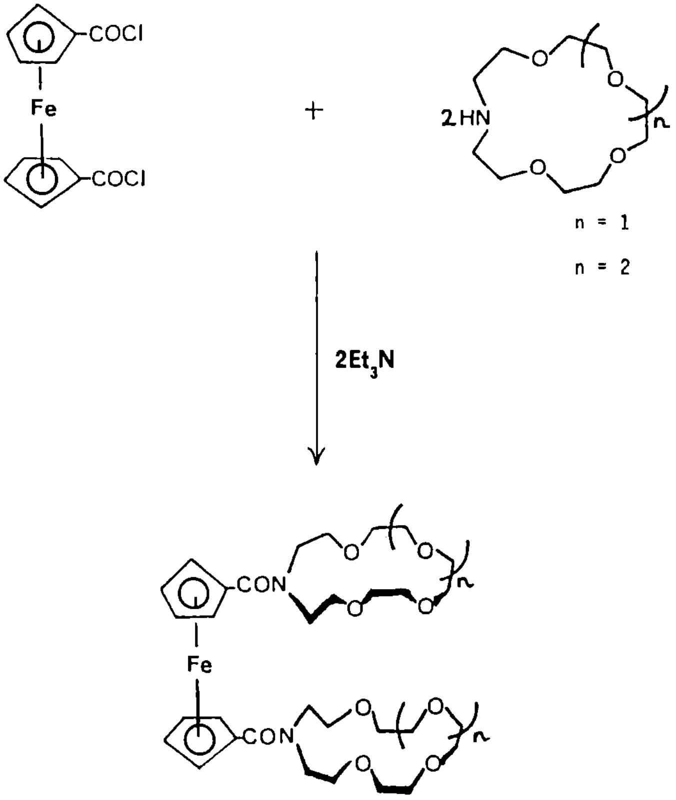
SCHEME 5. Scheme of electrochemical ion transport with redox-active crown ether. W^1, W^2: mini-grid platinum working electrodes. C^1, C^2: platinum plate counter electrodes. R^1, R^2: saturated calomel reference electrodes.

but also selective to the host binding of Group IA metal guest cations. Bis crown ether receptor molecules, which consist of two crown ether subunits linked together by a hydrocarbon chain, are known to exhibit remarkable selectivity for Group IA metal cations through formation of 1 : 1 ligand : M^+ intramolecular sandwich complexes (*48–50*). With this in mind, our initial efforts focused on the syntheses of amido-linked metallocene bis crown ethers (*51–55*) (Scheme 6). Multinuclear NMR titration experiments with (**7**) and (**8**) and Na^+, K^+, and Cs^+ salts gave titration curves suggesting the desired solution 1 : 1 stoichiometric intramolecular sandwich complexes in which the benzo-15-crown-5 ligating units act in a cooperative fashion. Solid-state complexes $[(\mathbf{7})M]PF_6$ (M = Na,K) were also isolated and the single-crystal structure of the potassium complex (*53*) is illustrated in Fig. 5, with the space-filling representation shown in Fig. 6. The potassium guest cation is coordinated to all 10 oxygen atoms of the two benzo crown ether moieties in an irregular pentagonal antiprismatic configuration with K^+–O contact distances ranging from 2.82 to 2.97 Å. The sodium cation was found to form 1 : 2 stoichiometric complexes with the ferrocene bis(aza-crown ethers) (**9**) and (**10**), whereas the larger potassium cation produced a 1 : 1 intramolecular sandwich complex with the former (Fig. 7) and a 1 : 2 complex with the latter (*55*) (Fig. 8).



(7) M′ = Fe (8) M′ = Ru

SCHEME 6.



n = 1, (9)

n = 2, (10)

SCHEME 6 (*Continued*)

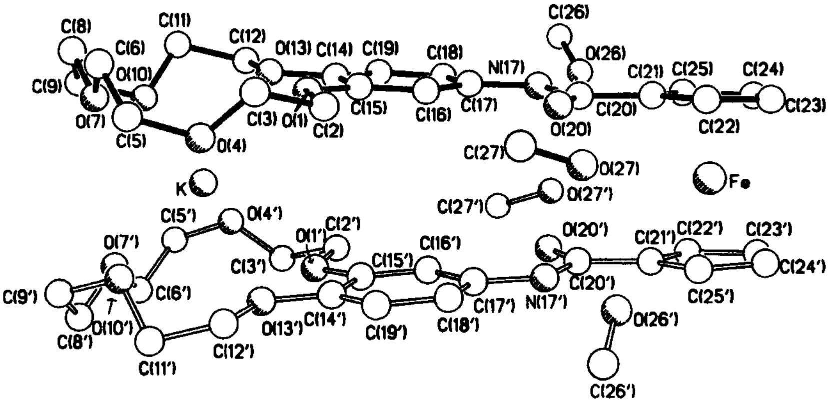


FIG. 5. The skeletal representation of the solid-state structure of [(**7**)K]$PF_6 \cdot 4MeOH$.

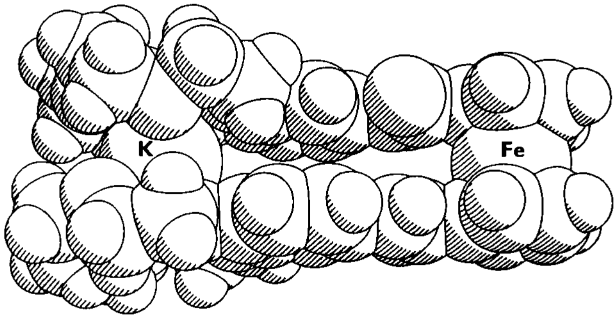


FIG. 6. The space-filling representation of the solid-state structure of the 1 : 1 complex formed between (**7**) and the potassium cation.

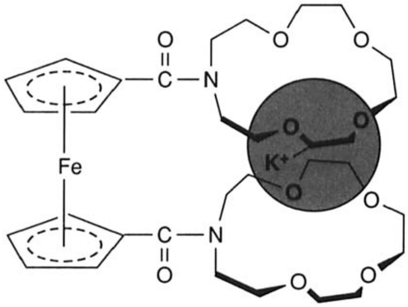


FIG. 7. The 1 : 1 intramolecular sandwich complex of K^+ and (**9**).

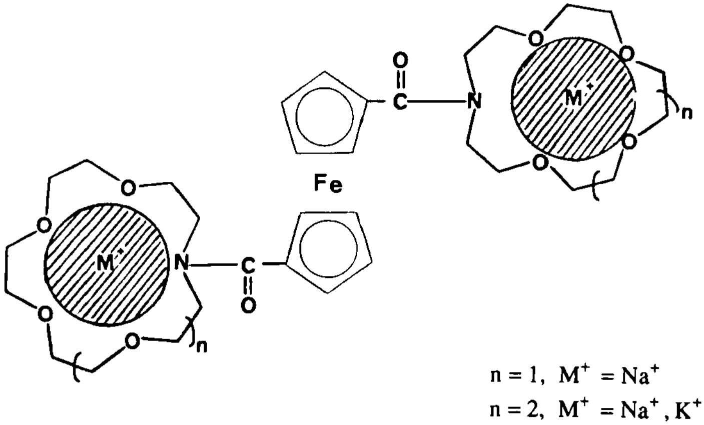


FIG. 8. Ferrocene bis amido aza crown ether 1 : 2 ligand: alkali metal cation complexes. $n = 1$, $M^+ = Na^+$; $n = 2$, $M^+ = Na^+, K^+$.

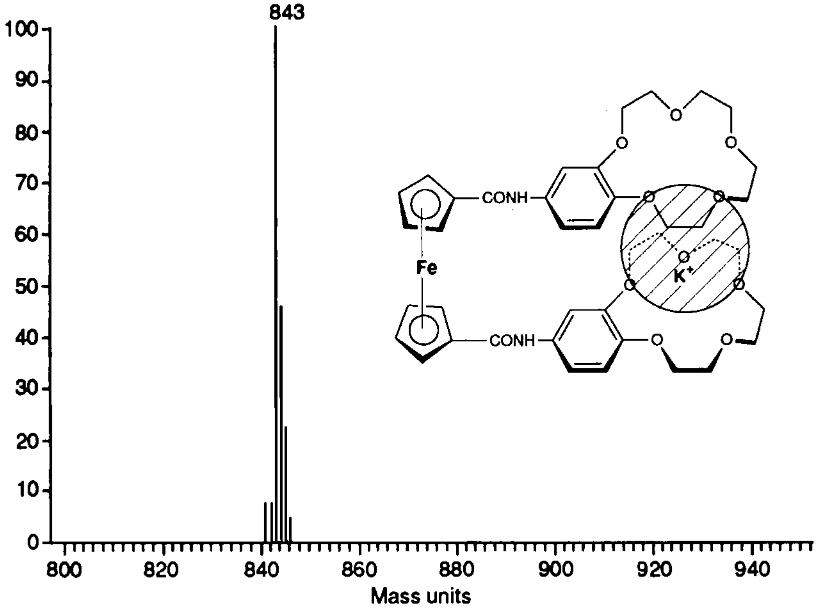
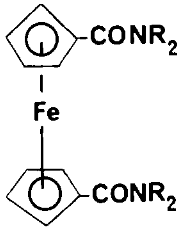


FIG. 9. FAB mass spectrum of [(**7**) + K]$^+$.

Fast atom bombardment mass spectrometry (FABMS) has been used to investigate the selectivity of monocyclic crown ethers for Group IA metal cations in competition experiments (*56*). We applied this semiquantitative technique for the first time to bis crown ethers (*51*, *53*) and observed that (**7**) and (**8**) in competition experiments with Li^+, Na^+, K^+, and Cs^+ exhibited exclusive selectivity for K^+ (Fig. 9). Ligands (**9**) and (**10**) however displayed no preference for any particular alkali metal cation.

Electrochemical complexation studies of (**7**) disappointingly revealed that the reversible ferrocenoyl oxidation wave was not perturbed on addition of either sodium or potassium cations, implying that the complexed alkali metal cation is too far away to influence the electron density at the ferrocene iron atom, via inductive and/or through-space communication effects. Significant one-wave anodic shifts were obtained however with (**9**) and (**10**), and the electrochemical results of Group IA cation binding on these and "model" compounds (**11**)–(**13**) are summarized in Table II. The magnitude of the shift (ΔE) is dependent upon the polarizing power of the metal cation guest; a similar result was observed with the organic redox systems discussed earlier. Interestingly Table II shows that although the model compounds (**11**)–(**13**) are electrochemically insensitive to the presence of Na^+ and K^+, the



(11) R = Me
(12) R = Et
(13) R = (CH_2CH_2)$_2$ O

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 lithium complex (*55, 57*) (Fig. 10). ^{13}C NMR titration experiments with (**11**)–(**13**) suggest that the lithium cation exclusively coordinates to the respective amide carbonyl oxygen donor atoms and not to the respective aza crown ether moieties of (**9**) and (**10**) (*55*).

In order to elucidate primarily the electrostatic "through-bond" mode of electrochemical communication between the ferrocene redox center and the heteroatoms of the crown ionophore, a variety of conjugated

TABLE II

ELECTROCHEMICAL DATA AND GROUP IA METAL CATION DEPENDENCE OF FERROCENE AMIDE AZA CROWN ETHERS AND "MODEL" ANALOGS

Compound:	(**9**)	(**10**)	(**11**)	(**12**)	(**13**)
$E_{1/2}(V)^a$	+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	310	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 compound, and potentials were determined with reference to the saturated calomel electrode (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 $E_{1/2}$ of compound and position of new redox couple associated with a Li^+ complex.

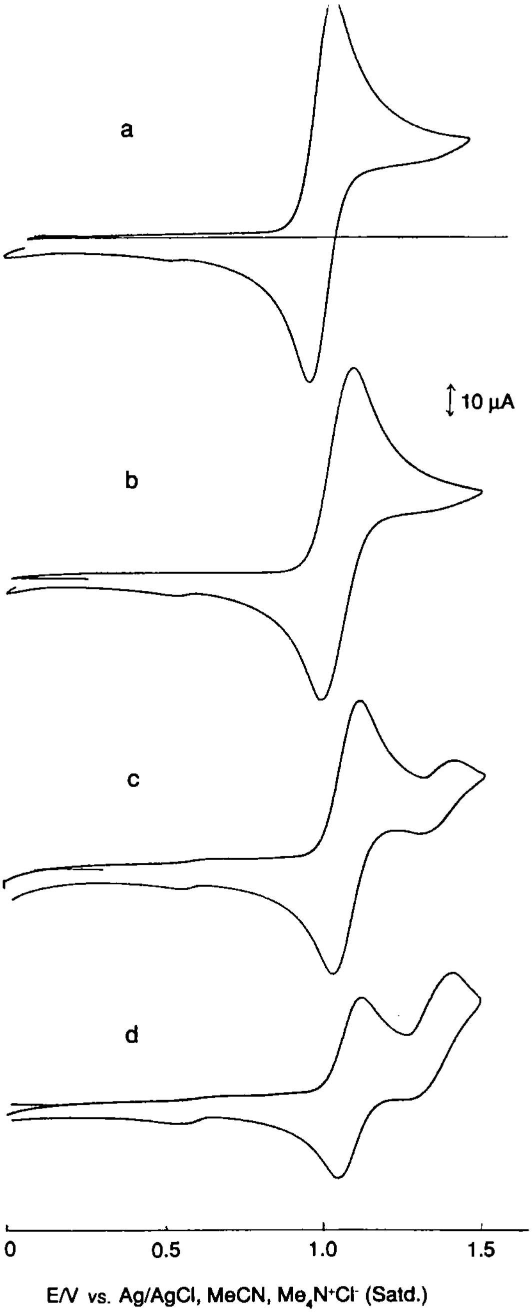


FIG. 10. Cyclic voltammograms in acetonitrile solution of (a) (**11**); (b) (**11**) + 0.5 equivalent of Li$^+$; (c) (**11**) + 2 equivalents of Li$^+$; (d) (**11**) + 4 equivalents of Li$^+$. Sweep rate 50 mV s^{-1}, scanning from 0 to +1.5 V.

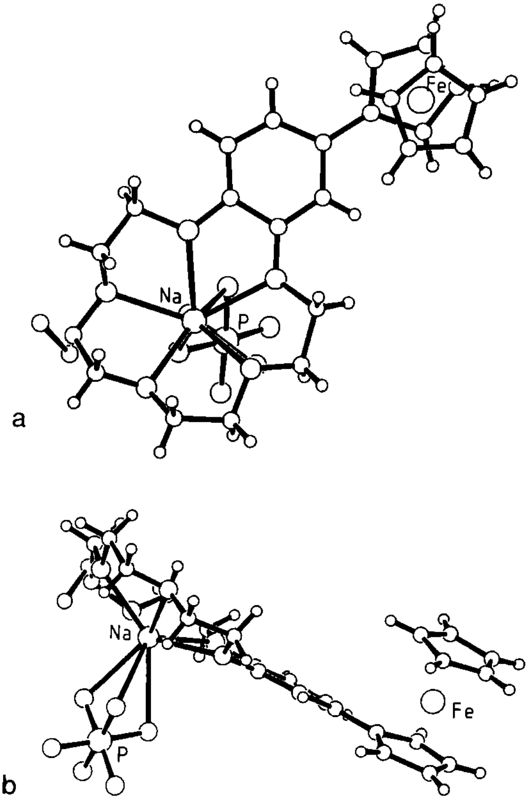
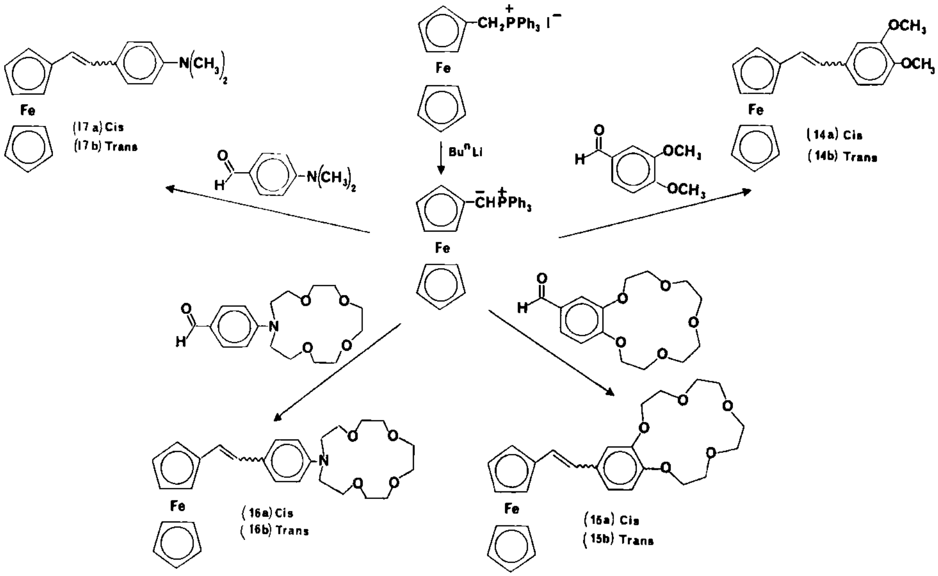


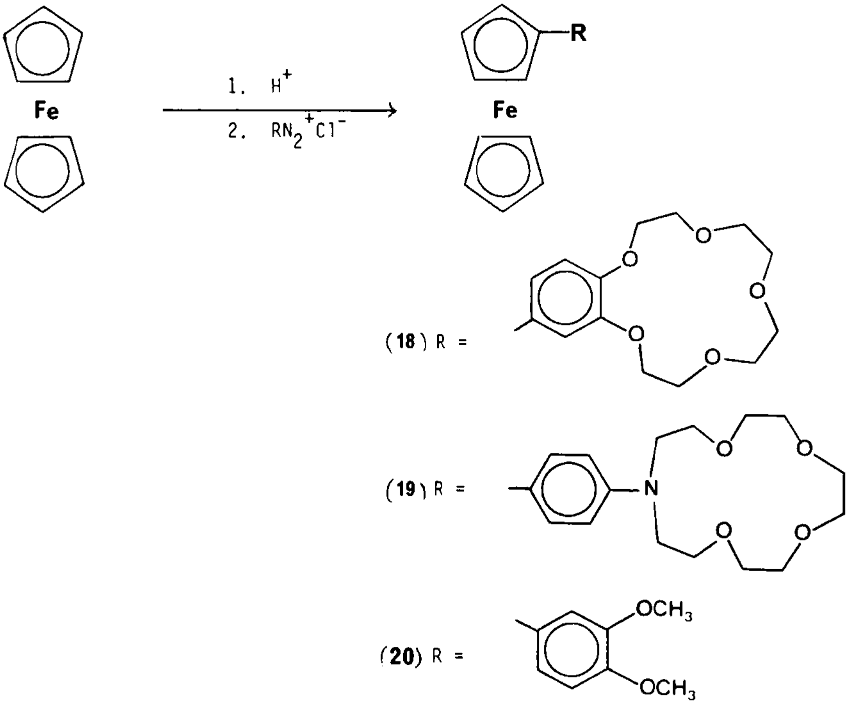
FIG. 11. Crystal structure of $[(18)Na]PF_6$ showing (a) the Na^+ bound to all five oxygens of the benzo crown ether; (b) the Na^+ lying above the 15-crown-5 ligand coordinated to PF_6^-.

(*58, 59*) (**14**)–(**17**), direct (*60, 61*) (**18**)–(**20**), and Schiff base (*62, 63*) (**21**)–(**22**) bond-linked ferrocene benzo crown ether ligand systems have been prepared (Schemes 7–9). The sodium cation forms 1 : 1 stoichiometric complexes with (**15**), (**16**), (**18**), and (**19**); the crystal structure of (**18**) and of its sodium complex (*61*) is shown in Fig. 11. Potassium produces 1 : 2 intermolecular sandwich complexes with the same ferrocenyl ionophores.

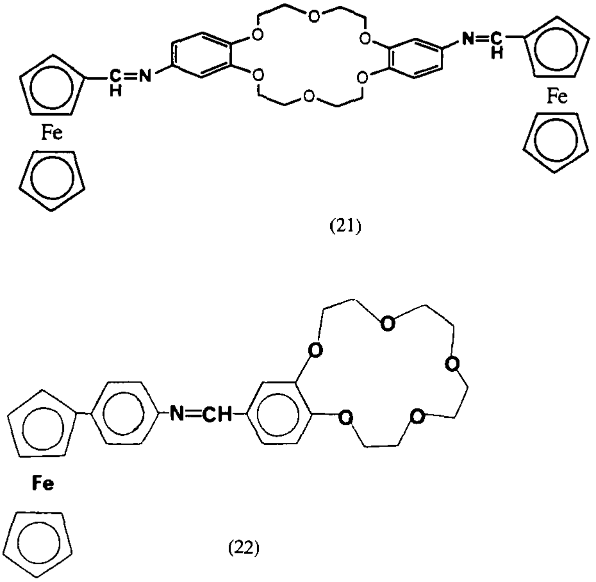
Electrochemical investigations reveal that the addition of Li^+ or Mg^{2+} to acetonitrile solutions of (**16**) leads to the appearance of a new ferrocene redox couple at more anodic potentials (Fig. 12) (Table III) associated with oxidation of a complex $FcIM^{n+}$ (where Fc stands for the



SCHEME 7.



SCHEME 8.



(21)

(22)

SCHEME 9.

TABLE III

ELECTROCHEMICAL DATA AND METAL CATION DEPENDENCE OF FERROCENE OLEFINIC-LINKED CROWN ETHERS AND MODEL ANALOGS

Compound:	(**14a**)	(**14b**)	(**15a**)	(**15b**)	(**16a**)	(**16b**)	(**17a**)	(**17b**)	(**23**)
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	+0.45
ΔE(Na$^+$) (mV)^b	<10	<10	30	30	50	65	<5	<5	—
ΔE(K$^+$) (mV)^b	<10	<10	20	20	20	20	<5	<5	—
ΔE(Mg^{2+}) (mV)^c	<10	<10	70^b	60^b	100	110	120	100	—
ΔE(Li$^+$) (mV)^c	<10	<10	—	—	110	110	110	110	—

[a] Obtained in acetonitrile solution containing 0.2 M [Bu$^n_4$N]BF$_4$ as supporting electrolyte. Solutions were ~2 × 10^{-3} M in complex, and potentials were determined with reference to the 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.

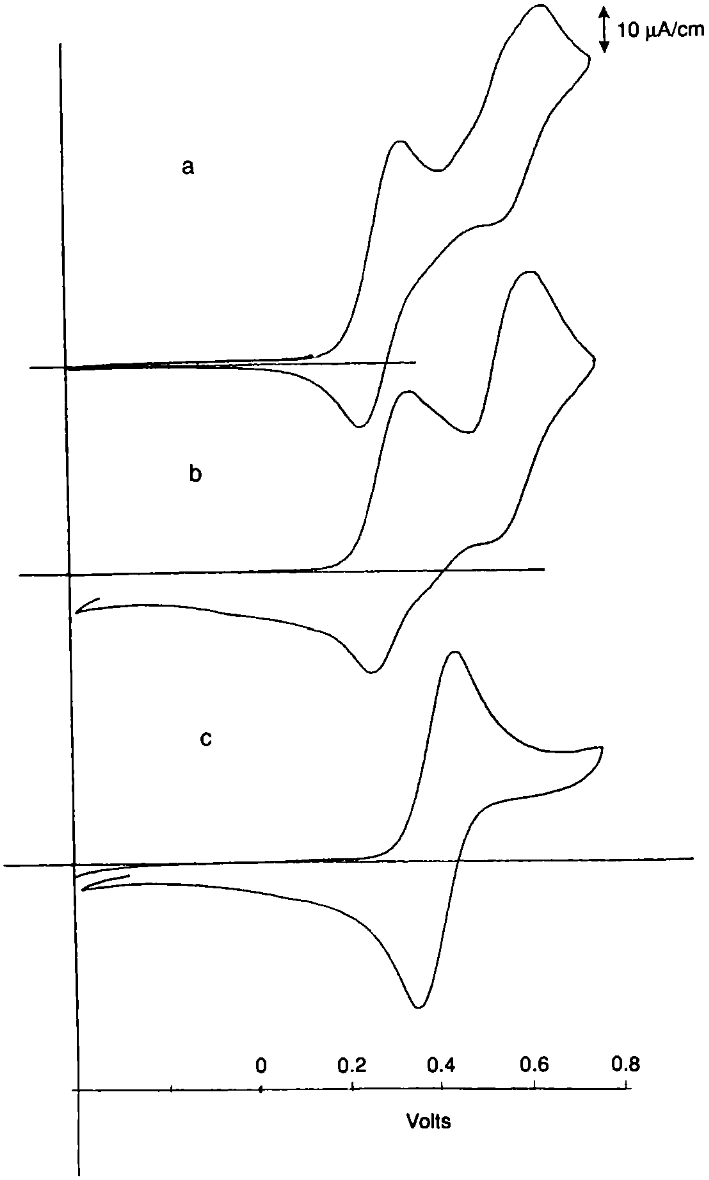
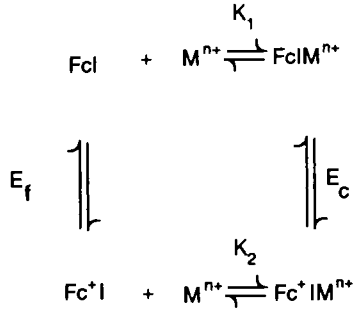


FIG. 12. Cyclic voltammograms of (a) (**16a**); (b) (**16a**) + 0.75 equivalent of Mg^{2+}; and (c) (**16a**) + 1.5 equivalents of Mg^{2+}. Sweep rate 100 mV s^{-1}.



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

ferrocene moiety and I the appended crown ether) (Scheme 10). In contrast to this observation, addition of Na^+ or K^+ gave only one-wave CV shift behavior. With the benzo-15-crown-5 olefinic derivatives (**15a**) and (**15b**), directly linked ionophores (**18**) and (**19**), and Schiff base derivatives (**21**) and (**22**), one-wave anodic shifts of the ferrocene redox couple were observed with the metal cations Na^+, K^+, and Mg^{2+}, with magnitudes of shift increasing with increasing charge (polarizing power) of the guest cation (Tables III and IV). It is noteworthy that the electrochemistry of the model amines (**17a**) and (**17b**) was unaffected by Na^+ or K^+ ions but Li^+ or Mg^{2+} addition led to the evolution of a new ferrocene wave. This observation highlights the importance of the nitrogen atom in the complexation process of these two particular cations. The redox potentials of the ferrocene wave for complexes

TABLE IV

ELECTROCHEMICAL DATA AND METAL CATION DEPENDENCE OF FERROCENE CROWN ETHERS CONTAINING DIRECT AND SCHIFF BASE LINKAGES

Compound:	(**18**)	(**19**)	(**20**)	(**21**)	(**22**)
E_f (V)[a]	+0.54	+0.58	+0.55	+0.44	+0.50
$\Delta E(Na^+)$ (mV)[b]	60	90	<10	30	40
$\Delta E(K^+)$ (mV)[b]	20	40	<10	20	<10
$\Delta E(Mg^{2+})$ (mV)[b]	70	110	<10	70	70

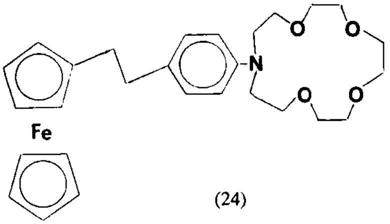
[a] Obtained in acetonitrile solution containing 0.2 M $[Bu^n{}_4N]BF_4$ as supporting electrolyte. Solutions were ca. $2 \times 10^{-3} M$ in compound, and potentials were determined with reference to the SCE.

[b] One-wave shift in oxidation potential produced by presence of metal cation (4 equivalents) added as their perchlorate salts.

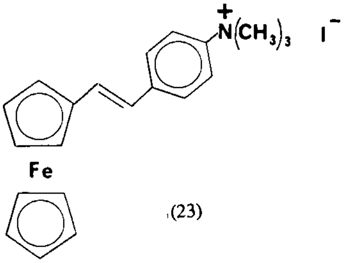
formed between (**16**) or (**17**) and Li^+, Mg^{2+} are close to that observed for the methiodide (**23**), suggesting that metal cations of high charge density induce a positive charge near unity on the nitrogen atom.

Palladium–carbon-catalyzed hydrogenation of (**16**) gave (**24**), and $NaBH_4$ reduction of (**22**) gave (**25**), both receptors now containing a saturated linkage between the aza crown system and the ferrocenyl redox center. This methylene–ferrocene linkage was found to serve as an insulator; both compounds (**24**) and (**25**) are totally electrochemically insensitive to the presence of any alkali metal cation.

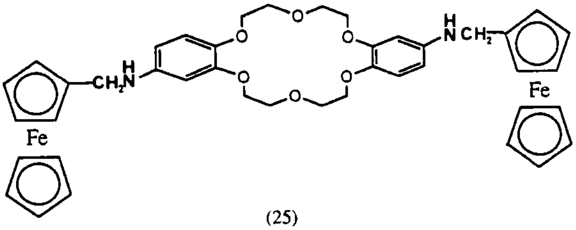
In conclusion, with these types of ligand systems anodic perturbations of the ferrocene oxidation wave are observed if a conjugated π-electron system (—C=C—, —CH=N—) links the heteroatoms of the crown ionophore to the redox center, and the polarizing power of the guest metal cation is of great importance in determining the magnitude



(24)

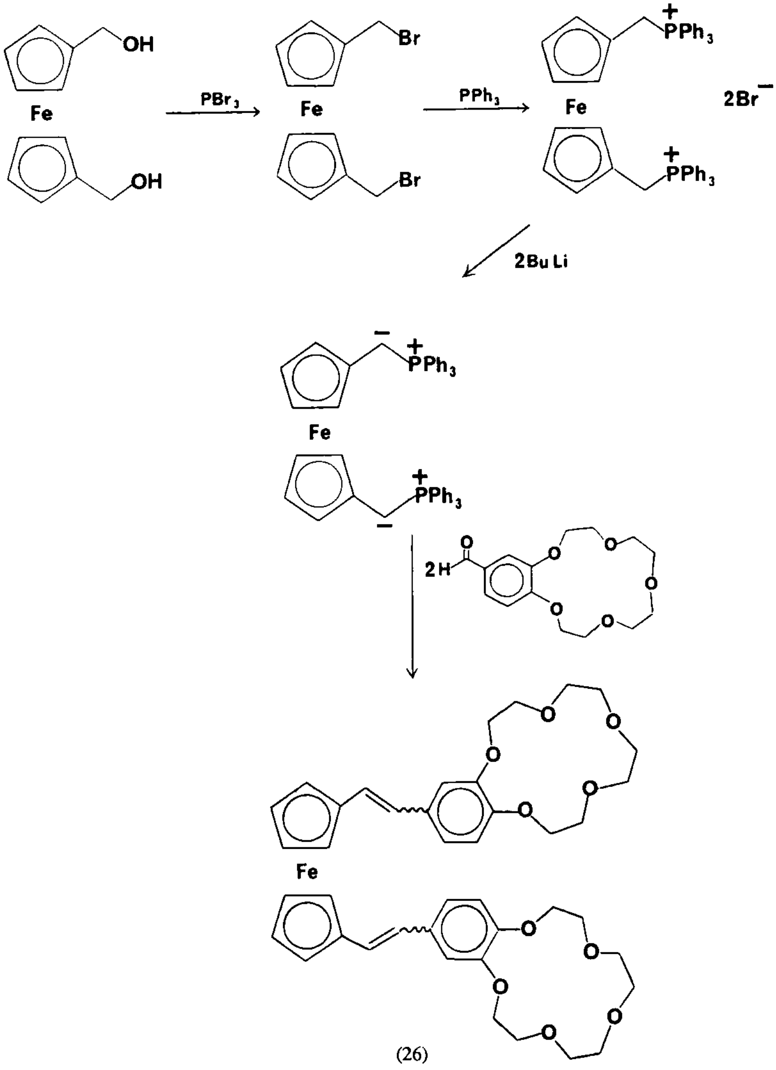


,(23)



(25)

and type (one or two wave) of shift in redox potential of the ferrocenyl redox center. In an attempt to demonstrate for the first time the concept of *selective* electrochemical recognition, we recently prepared the bis-benzo-15-crown-5 ferrocene compound (**26**) containing two vinylic linkages (*64*) (Scheme 11). This compound is a mixture of three isomeric components, the *cis–cis, cis–trans,* and *trans–trans* isomers, which still



(26)

SCHEME 11.

have not yet been successfully separated. However, the precedent of insignificant differences found between the magnitudes of the metal cation-induced anodic shifts in the ferrocenyl redox potentials of the respective separated *cis* (**15a**) and *trans* (**15b**) isomers of (**15**) led us to use the same isomeric mixture of (**26**) throughout the subsequent FABMS and electrochemical experiments.

The FABMS competition experiment of (**26**) with the nitrates of sodium, potassium, rubidium, and cesium gave gas-phase complex ions of $[(\mathbf{26}) + \mathrm{K}]^+$ion (*m/z* 809) and a minor peak $[(\mathbf{26}) + \mathrm{Rb}]^+$ion (*m/z* 855) exclusively. The relative peak intensities suggested a selectivity order of $\mathrm{K}^+ \gg \mathrm{Rb}^+ \gg \mathrm{Na}^+, \mathrm{Cs}^+$, indicative of the "bis crown effect" exhibited by related bis-benzo-15-crown-5 ether ligands (*48–50*).

Cyclic voltammograms of (**26**) were recorded after addition of calculated equivalents of Na^+, K^+, and Mg^{2+}; equimolar mixtures of $\mathrm{Na}^+/\mathrm{K}^+$; and $\mathrm{Na}^+/\mathrm{K}^+/\mathrm{Mg}^{2+}$. The results obtained are presented in Table V. Predictable one-wave metal cation-induced anodic shifts of the ferrocenyl redox couple are observed, and interestingly the magnitudes of these are approximately double those induced by the same metal cations in the redox couple of the mono-substituted vinylic ionophore (**15**) (See Table III).

TABLE V

ELECTROCHEMICAL DATA AND METAL CATION DEPENDENCE OF (**26**)

	(**26**) (mV)
E_f^a	+340
$\Delta E(\mathrm{Na}^+)^b$	55
$\Delta E(\mathrm{K}^+)^b$	35
$\Delta E(\mathrm{Mg}^{2+})^b$	110
$\Delta E(\mathrm{Na}^+/\mathrm{K}^+)^c$	35
$\Delta E(\mathrm{Na}^+/\mathrm{K}^+/\mathrm{Mg}^{2+})^c$	40

[a] Obtained in acetonitrile solution containing 0.2 M $[\mathrm{Bu}^n{}_4\mathrm{N}]\mathrm{BF}_4$ as supporting electrolyte. Solutions were ca. $3 \times 10^{-3}\,M$ in (**26**), and potentials were determined with reference to the SCE; 0.2 V s^{-1} scan rate.

[b] One-wave anodic shifts in oxidation potential produced by presence of metal cation (4 equivalents) added as their perchlorate salts.

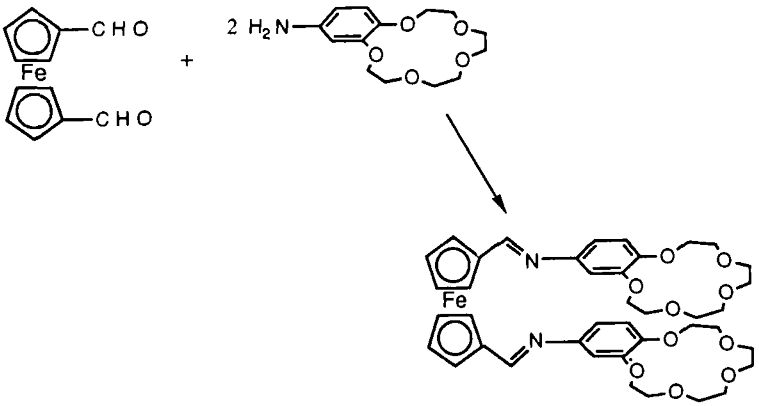
[c] One-wave anodic shift in oxidation potential produced by the presence of an equimolar mixture of cations (4 equivalents).

Of particular relevance to chemical sensor technology are the novel results of the electrochemical competition experiments. When an equimolar mixture of Na^+/K^+ or $Na^+/K^+/Mg^{2+}$ cations is added to electrochemical solutions of (**26**), the ferrocene/ferricinium redox couple shifts anodically by an amount approximately the same as that induced by the K^+ cation alone. This observation, together with the FABMS competition experimental findings, suggests that (**26**) is a first-generation prototype potassium-selective amperometric sensor, capable of detecting the K^+ cation in the presence of Na^+ and Mg^{2+} ions.

We have also prepared the Schiff base and sulfur-linked ferrocene bis-crown ether ligands (*65*) (**27**) and (**28**) (Scheme 12). Preliminary coordination studies have shown both to be K^+ selective; however, (**27**) is not electrochemically well behaved. Unexpectedly, addition of K^+ to electrochemical solutions of (**28**) results in a *cathodic* shift of the ferrocene redox couple, which may be attributable to conformational steric effects involving the sulfur heteroatom lone pairs of electrons.

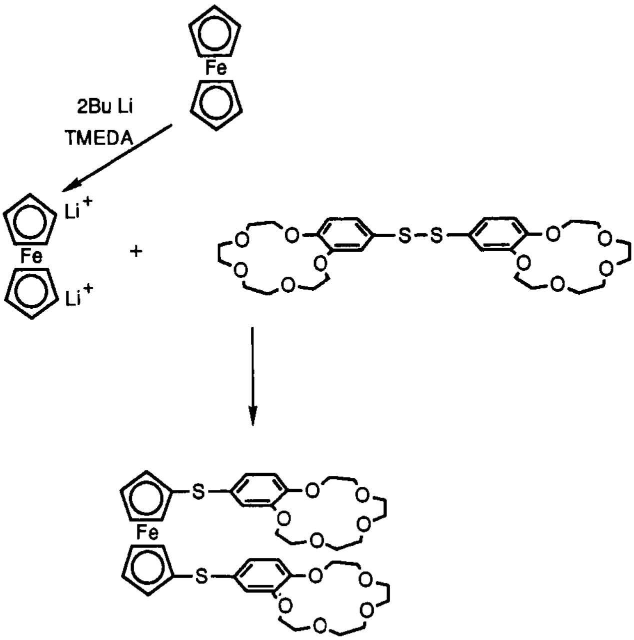
2. *Ferrocene Cryptand Molecules*

A number of ferrocene cryptand molecules (*66–74*) ((**29**)–(**31**)) have been reported in the literature and it is only relatively recently that their electrochemical coordination properties have been disclosed. We have synthesized potassium-selective metallocene cryptands (*72*) (**30**) and (**31**); the electrochemistry of the former in the presence of K^+ guest cations proved disappointingly irreversible (*75*). Hall and co-workers (*76*) have used cyclic voltammetry to investigate the coordination of



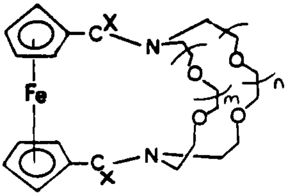
(27)

SCHEME 12.



(28)

SCHEME 12. (*Continued*)



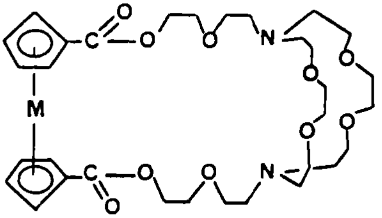
m = 1, 2, 3

n = 1, 2, 3

m = n , m ≠ n

(29) m = 1, n = 1, X = 0

(32) m = 1, n = 1, X = H_2



(30) M = Fe

(31) M = Ru

alkaline earth and lanthanide metal cations by the ferrocene cryptand (**29**). They note that large anodic shifts of the ferrocenoyl redox couple are produced with these metal cations and that there exists a broad correlation between the $\Delta E_{1/2}$ value and the charge/radius ratio of cationic guest (Fig. 13). As with the ferrocene crown ether ionophores discussed previously, as the charge density of the metal guest cation increases so does the observed magnitude of 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 $[(\mathbf{29}^{+})M^{n+}]$ ($M^{n+} = Be^{2+}, Dy^{3+}$) *ejects* the bound metal cation rapidly, presumably as a result of mutual electrostatic repulsion.

Gokel and co-workers (*77*) have very recently managed to reduce the amide carbonyl groups of (**29**) using $LiAlH_4$ to produce the cryptand (**32**). In acetonitile solution, electrochemically this compound exhibits two-wave CV behavior in the presence of substoichiometric amounts of Na^+ similar to the electrochemical results reported by Saji for the ferrocene crown ether ligand (**6**) discussed earlier. This two-wave observation suggests that the neutral cryptand has a relatively large Na^+ binding constant. Similar electrochemical results were found with K^+ and Ca^{2+} with the latter divalent guest cation, as expected from charge/

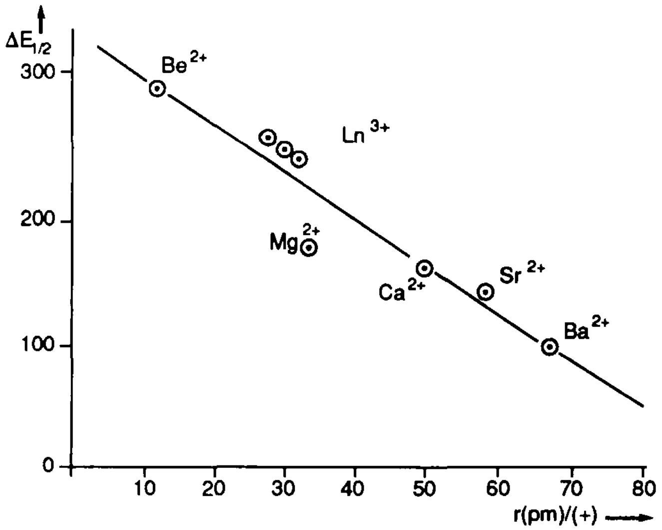
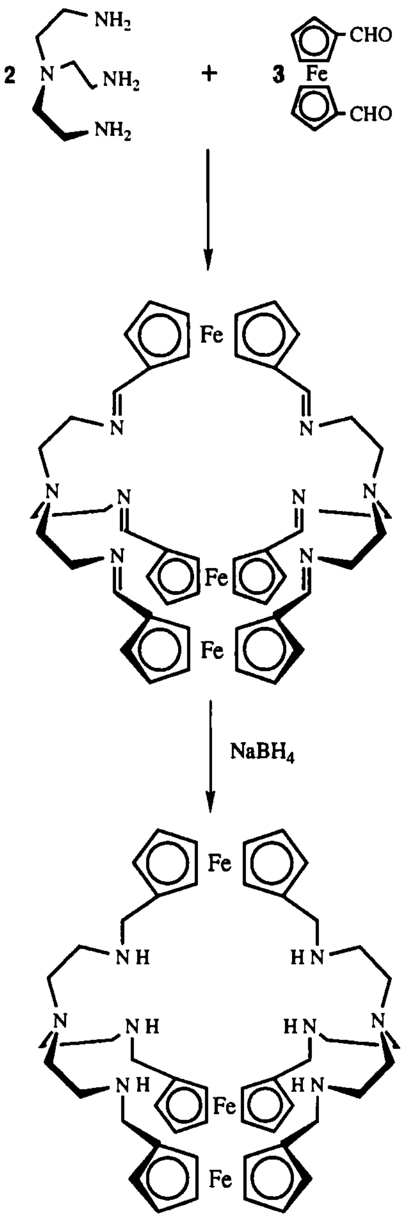


FIG. 13. Plot of $\Delta E_{1/2}$ versus radius, *r* (in pm)/ionic charge, for the complexation of (**29**) with a series of alkaline earth and lanthanide metal cations.



(33)

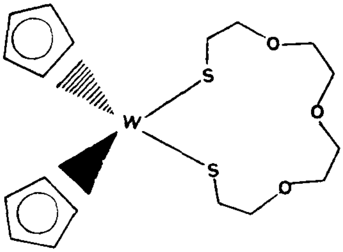
Scheme 13.

radius ratio considerations, producing the largest magnitude of anodic separation between the neutral and the complexed redox couples.

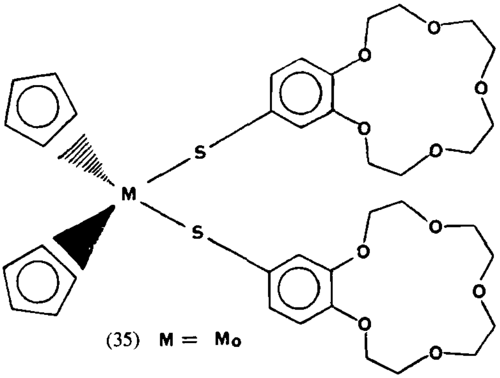
The cryptand (**33**) containing three ferrocene redox centers (*78*) has been prepared by our group via the synthetic pathway shown in Scheme 13. Although electrochemically insensitive to Group IA metal cations, this cryptand does electrochemically recognize Zn^{2+} and forms an isolable $2Zn^{2+}$ (**33**) bimetallic complex.

3. Di-η-Cyclopentadienyl-molybdenum(IV) and -tungsten(IV) Crown Ether Complexes

Green and co-workers (*79, 80*) have prepared ionophoric ligands incorporating the oxidative, redox-active organometallic d^2-di-η-cyclopentadienyl-molybdenum(IV) or -tungsten(IV) fragments into a macrocyclic structural framework. Compounds (**34**)–(**36**) were synthesized via the reaction of $[M(\eta\text{-}C_5H_5)_2Cl_2]$ (M = Mo or W) and the appropriate sodium thiolate, and (**37**)–(**38**) from reaction of the same precursors with 4′-carboxybenzo-15-crown-5.

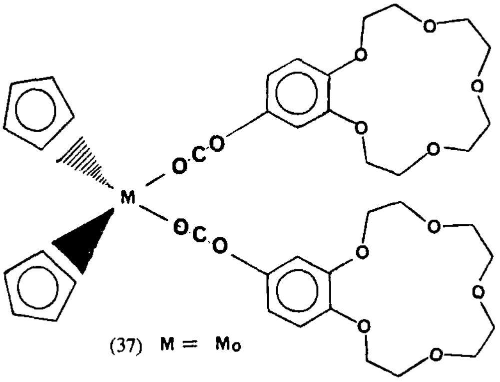


(34)



(35) M = Mo

(36) M = W



(37) M = Mo

(38) M = W

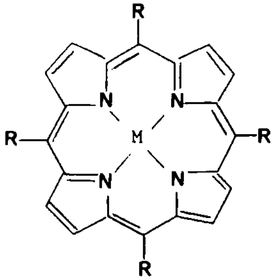
Despite the fact that the respective reversible one-electron oxidation couples of (**34**), (**37**), and (**38**) proved insensitive to the presence of alkali metal cations, replacing the Et_4NPF_6-supporting electrolyte with $NaPF_6$, KPF_6, or $LiClO_4$ resulted in significant one-wave anodic shifts with compounds (**35**) and (**36**), of up to 110 mV with Na^+ and (**36**).

C. COORDINATED TRANSITION METAL REDOX-ACTIVE MACROCYCLES

So far in this review we have seen examples of how organic and organometallic redox-active moieties can be fabricated into crown ether- and cryptand-type structures. Another synthetic strategy concerns the design of multisite ligand systems that contain recognition coordinating sites for, in principle, any redox-active transition metal in close proximity to a Group IA, IIA coordinating crown ether moiety. This section reviews these types of reported systems.

1. *Metalloporphyrin Crown Ether Compounds*

Kobayashi (*81*) first reported the iron(II) tetrakis-(benzo-15-crown-5) porphyrin (**39**) in 1981 and Krishnan (*82*) has isolated the corresponding divalent cobalt, nickel, copper, zinc, manganese, and magnesium complexes along with the vanadium(IV) oxide compound. Electrochemical investigations of these metalloporphyrins revealed that in the absence of alkali metal cations each complex exhibited a reversible oxidation. Addition of potassium chloride led to the formation of dimeric species displaying two reversible oxidation processes; the first oxidation was at lower potential and the second oxidation at higher potential than that of the corresponding monomer. No dimeric species were formed on addition of sodium ions to the zinc-complexed porphyrin; however, a



(39) M = Fe (II)

R = Benzo-15-crown-5

M = Fe(II), Ni(II), Co(II),
Cu(II), V(IV)O.

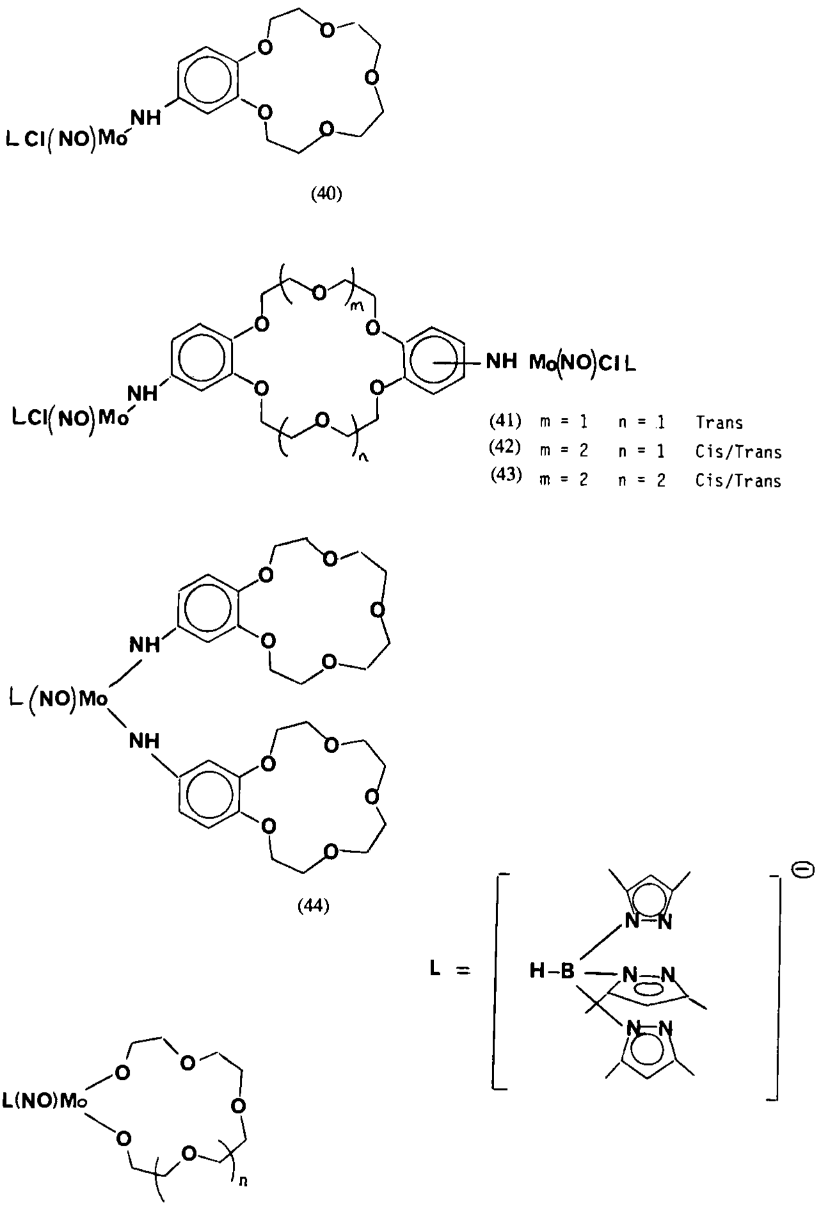
relatively small anodic shift of 40 mV was observed in the oxidation potential, suggesting some electrostatic communication between the crown ether bound cation and the π-electron system of the porphyrin macrocycle.

Related copper(II) phthalocyanines substituted with crown ether groups have been reported (*83, 84*) and shown to form discotic mesophases and ion channels for alkali metal cations (*85*). Although polymetallic Group IA salts have been isolated, no electrochemical studies on these systems were described.

2. *Molybdenum Coordinated Crown Ether Systems*

A series of polyether macrocycles (**40**)–(**47**) that contain a coordinated reducible transition metal redox-active 16-electron molybdenum nitrosyl $\{Mo(NO)\}^{3+}$ group have been prepared by us in collaboration with McCleverty and Jones (*86, 87*) (Scheme 14). Compounds (**40**)–(**44**) were synthesized 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. Compounds (**45**)–(**47**) were prepared from reactions between $[Mo(NO)LI_2]$ and tetra-, penta-, or hexaethylene glycol, respectively, in the presence of triethylamine. A crystal structure determination of (**45**) (*88*) is shown in Fig. 14.

The electrochemical properties of (**40**)–(**47**) in the presence and absence of stoichiometric amounts of Na^+ and K^+ guest cations were investigated in acetonitile solution by cyclic voltammetry. Table VI 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 center. Comparing (**45**)–(**47**) with the organic redox-active quinone systems described earlier (see Table I), in the case of Na^+ guest cation these ΔE



(40)

(41) m = 1 n = 1 Trans
(42) m = 2 n = 1 Cis/Trans
(43) m = 2 n = 2 Cis/Trans

(44)

(45) n = 1
(46) n = 2
(47) n = 3

SCHEME 14.

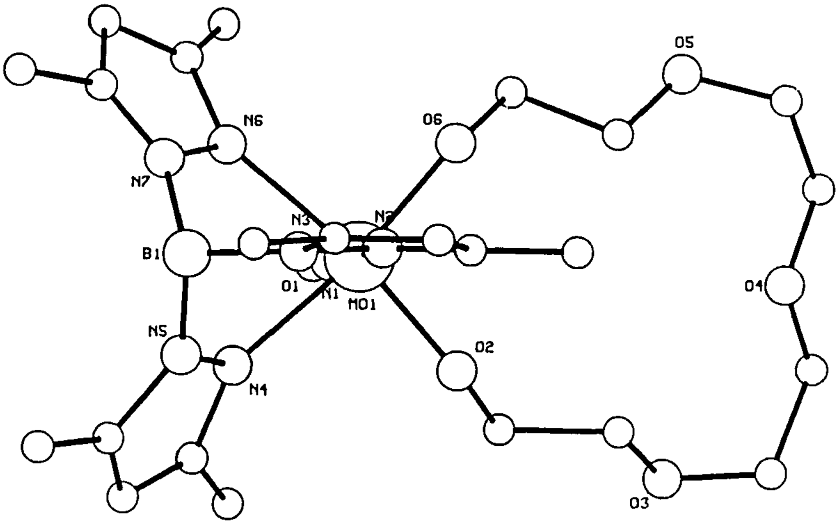


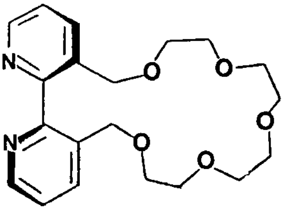
FIG. 14. Crystal structure of (**45**).

values are generally much larger in magnitude, suggesting that the transition metal molybdenum redox center is more electrochemically sensitive to the presence of a closely bound metal cation than the quinone redox-active moiety.

Once again from Table VI it can be concluded that the polarizing power of the metal cation guest is of great importance in determining the magnitude of the anodic shift; the larger K^+ cation having the smaller charge/radius ratio produces approximately half the shift of the Na^+ guest cation.

3. *Crown Ether and Bis Crown Ether Ligands Containing Bipyridyl Transition Metal Recognition Sites*

Rebek (*89, 90*) and co-workers have synthesized the 2-2′-bipyridyl crown ether ligand (**48**) and elegantly shown that this system exhibits



(48)

TABLE VI

ELECTROCHEMICAL DATA AND CATION DEPENDENCE OF REDUCIBLE MOLYBDENUM MACROCYCLES

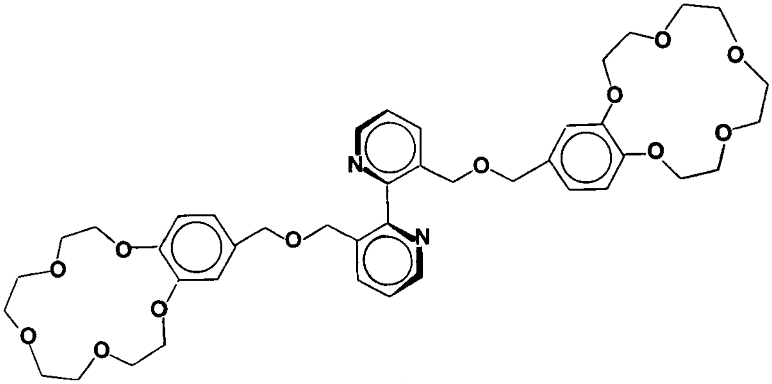
Compound	$E_f^{\mathrm{free}\ a}$ (V)	$E_f^{\mathrm{complex}\ a}$ (V)	ΔE^b ($E_f^{\mathrm{complex}} - E_f^{\mathrm{free}}$) (mV)
(**40**)	−0.95		
(**40**) + Na^+		−0.89	60
(**41**)	−0.96		
(**41**) + Na^+		−0.89	70
(**41**) + K^+		−0.92	40
(**42**)	−0.94		
(**42**) + Na^+		0.855	85
(**42**) + K^+		−0.90	40
(**43**)	−0.92		
(**43**) + Na^+		−0.835	85
(**43**) + K^+		−0.88	40
(**44**)	−1.36		
(**44**) + Na^+		−1.25	90
(**44**) + K^+		−1.32	40
(**45**)	−1.32		
(**45**) + Na^+		−1.00	320
(**46**)	−1.28		
(**46**) + Na^+		−1.00	280
(**47**)	−1.24		
(**47**) + 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.

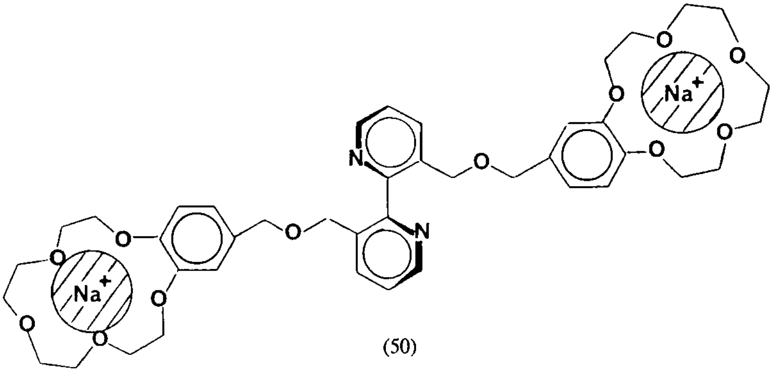
[b] Shift in reduction potential produced by the presence of Na^+ or K^+ added as their BPh_4 salts, in solution, and in aliquots to provide up to 2 *M* equivalents with less than 5% volume change in the solution. Broadening of the cyclic voltammogram trace was observed when between 0.2 and 1.0 equivalents 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 equivalent to give a cation/complex molar ratio of 2. The 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 $[Mo(NO)L\text{-}\{NHC_6H_4\text{-}3,4\text{-}(OMe)_2\}_2]$ for which shifts in reduction potential of less than 10 mV were found under similar conditions.

allosteric behavior; i.e., 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 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. Ruthenium(II) complexes of related ester-linked bipyridyl crown ether ligands have very recently been reported by Durr and co-workers (*91*), although no electrochemical binding studies are described.

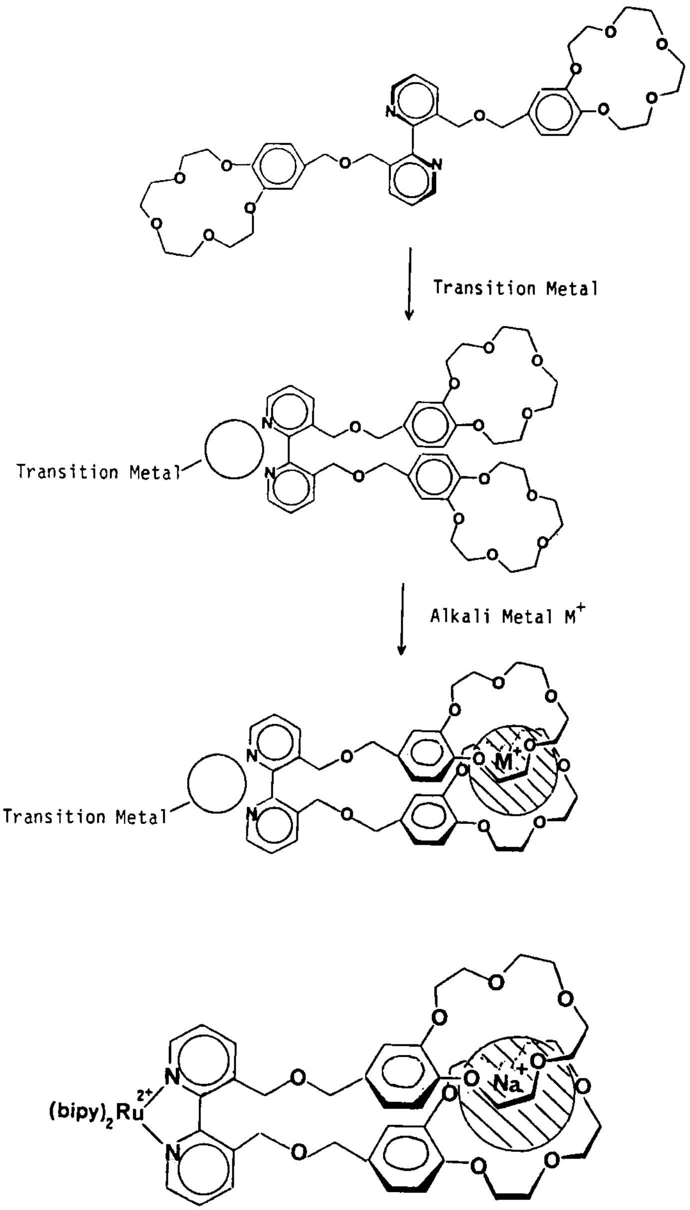
We have prepared the bis crown ether ligand (**49**) consisting of the 3,3′-disubstituted-2,2′-bipyridyl fragment and two benzo-15-crown-5 moieties (*92, 93*). In the absence of a transition metal the ligand forms a $2Na^+$: (**49**) complex with sodium cations, in which each benzo crown ether coordinates one sodium cation (**50**). Interestingly, the reaction of (**49**) initially with $(bipy)_2RuCl_2{\cdot}H_2O$ gave the ruthenium(II) complex, which on addition of an excess of $NaPF_6$ produced $[(bipy)_2Ru($**51**$)Na]^{3+}(PF_6)_3$ (**52**) (Scheme 15). This observed change of stoichiometry of Na^+ binding suggests that the initial allosteric effect of



(49)



(50)

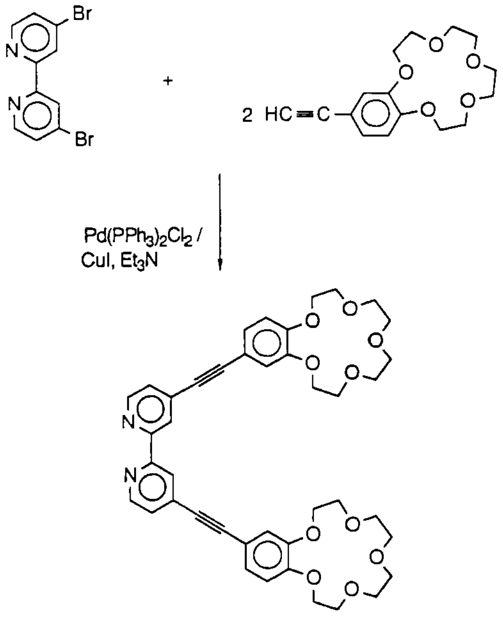

Transition Metal
Transition Metal
Alkali Metal M+
Transition Metal
M+
(bipy)2Ru2+
Na+
N
O

(51)

SCHEME 15.

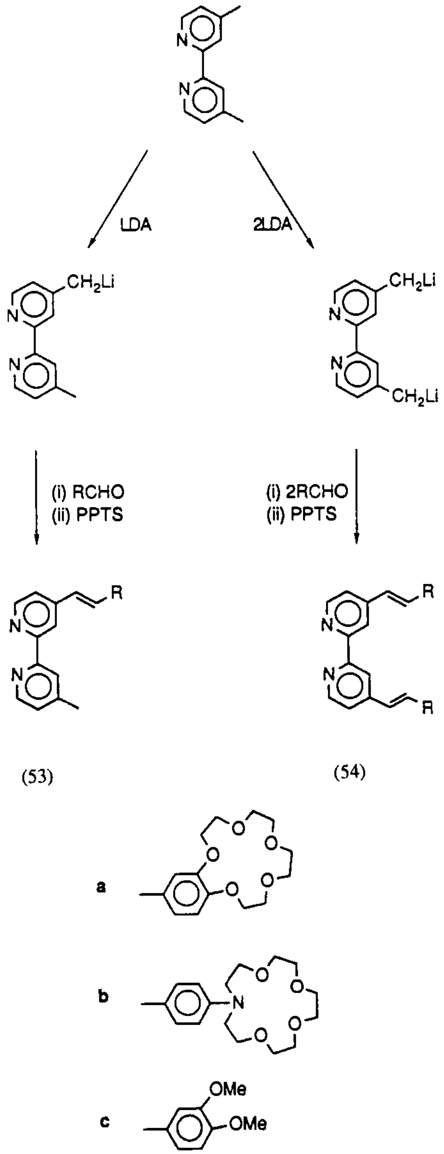
ruthenium(II) chelation at the bipyridyl coordinating function restricts the conformational freedom of the two benzo crown ether groups in such a way as to favor the formation of an intramolecular sandwich complex with the alkali metal cation. Because of the saturated ether linkage between the bipyridyl unit and the benzo crown ether moiety of (**49**), it was not surprising that the ruthenium(II/III) redox couple was not perturbed in the presence of an excess amount of sodium cations (*93*). We have since modified this type of ligand system to produce new alkynyl- and vinyl-linked benzo crown ether and aza crown ether bipyridyl compounds (*94–96*) (Schemes 16, 17). Monoligand ruthenium(II) complexes $[RuL(bipy)_2][PF_6]_2$ and the corresponding tris(ligand) ruthenium(II) complexes $[RuL_3][PF_6]_2$ (L = (**52**)–(**54**)) were prepared together with heteropolymetallic ruthenium(II)–sodium complexes such as (**55**) and (**56**).

Although the results of electrochemical recognition studies with Na^+, K^+, Mg^{2+} were disappointing—very small ΔE values (<10 mV) were observed—spectrochemical recognition investigations proved fruitful (*96*). The metal-to-ligand charge transfer (MLCT) emission maxima for the ruthenium(II) complexes are shifted to significantly

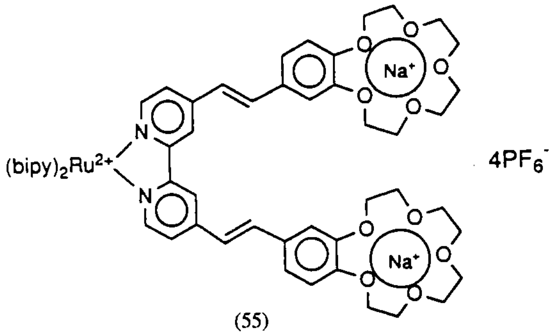


(52)

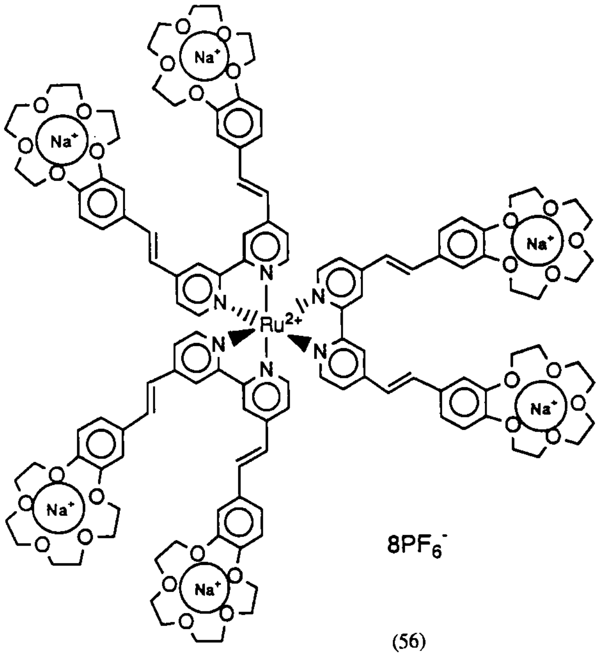
Scheme 16.


LDA
2LDA
CH$_2$Li
CH$_2$Li
CH$_2$Li
(i) RCHO
(ii) PPTS
(i) 2RCHO
(ii) PPTS
R
R
R
(53)
(54)
a
b
c
OMe
OMe
N
O

SCHEME 17.



(55)



(56)

lower wavelengths and increase in intensity in the presence of Li^+, Na^+, or Mg^{2+}. For example, with [Ru(**53**)(bipy)$_2$][PF$_6$]$_2$ addition of an excess amount of sodium ions gave a 16-nm blue shift from 686 to 670 nm in acetonitrile solution (Fig. 15). No corresponding shift was observed for complex [Ru(**54c**)][PF$_6$]$_2$ or [Ru(bipy)$_3$][PF$_6$]$_2$, suggesting that alkali or alkaline earth metal cation coordination at the crown

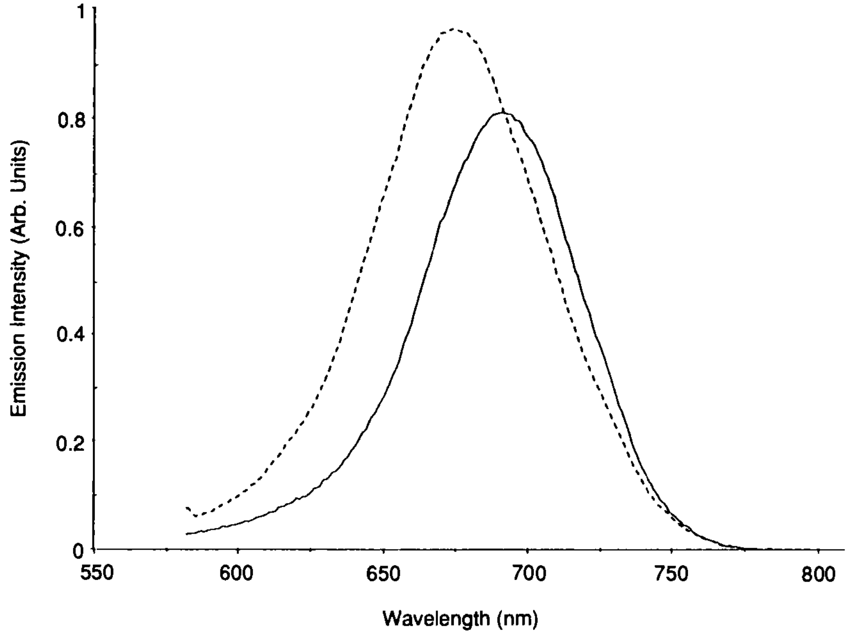
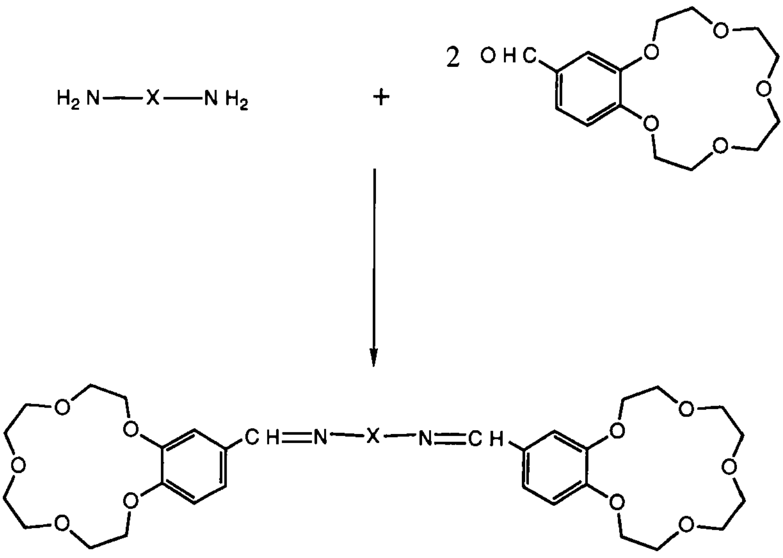


FIG. 15. Emission spectrum (solid line) of 1 × 10^{-4} [Ru(**53**)(bipy)$_2$][PF$_6$]$_2$ in deoxygenated CH_3CN solution at 25°C. Dashed line shows emission spectrum after addition of excess Na^+ (as $NaClO_4/CH_3CN$ solution). Excitation wavelength = 550 nm.

ether recognition site is responsible for this effect. Valeur and co-workers (*97*) have recently reported similar Group IA, IIA metal cation-induced blue shifts in the emission spectra of fluorophores linked to crown ethers. In addition cathodic electropolymerization of these ruthenium(II) complexes onto platinum and optically transparent conducting glass electrodes produced novel polymer films also capable of spectrochemically recognizing alkali and alkaline earth metal guest cations (*96*).

4. *Schiff Base Crown Ether Ligands*

We have prepared a variety of new Schiff base bis crown ether ligands (*98–100*) that contain alkali and transition metal coordinating sites via the condensation of two or three equivalents of 4-formyl-benzo-15-crown-5 with an appropriate di- or triamine (Scheme 18). Homometallic copper(I), silver(I), and heteropolymetallic copper(I)–sodium, silver(I)–sodium, and potassium complexes have been isolated. The single-crystal X-ray structure of the [Cu(**57**)K](PF$_6$)$_2$ complex (*100*) is shown



$X = CH_2CH_2SCH_2CH_2$

$X = CH_2CH_2SCH_2CH_2SCH_2CH_2$ (57)

$X = CH_2CH_2SCH_2CH_2CH_2SCH_2CH_2$

$X = CH_2CH_2CH_2SCH_2CH_2SCH_2CH_2CH_2$

$X = CH_2CH_2NHCH_2CH_2$

SCHEME 18.

in Fig. 16. Interestingly the stoichiometry of ligand (**57**) to K^+ guest cations is dependent upon the stereochemical requirements of cobound transition metal guests. For example, ligand (**57**) forms a 1 : 1 intramolecular sandwich with K^+; however, with tetrahedrally coordinated Ag^+ the subsequent formation of the intramolecular sandwich complex with K^+ is prevented and the polymetallic complex (**58**) results. With the square planar or tetragonally bound copper(II) complex, however, the stereochemical requirements of this transition metal allow the formation of the preferred 1 : 1 sandwich complex with K^+ (**59**). A

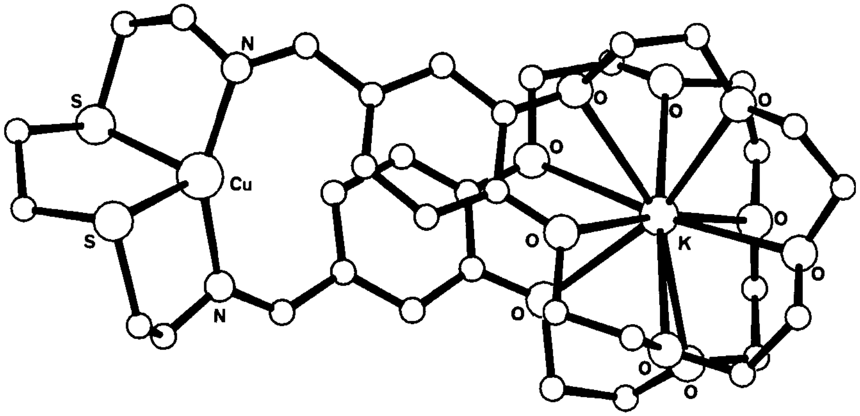
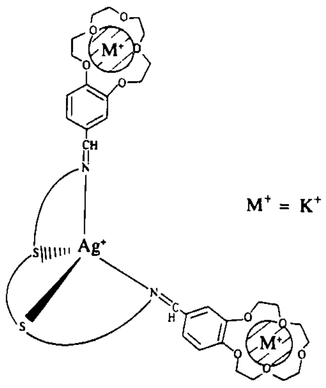
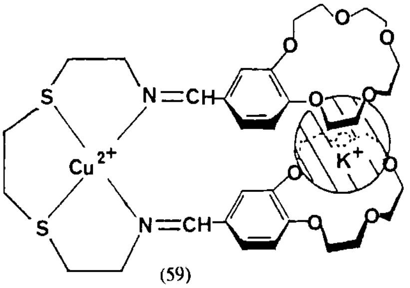


FIG. 16. Crystal structure of [Cu(**57**)K][PF$_6$]$_2$.

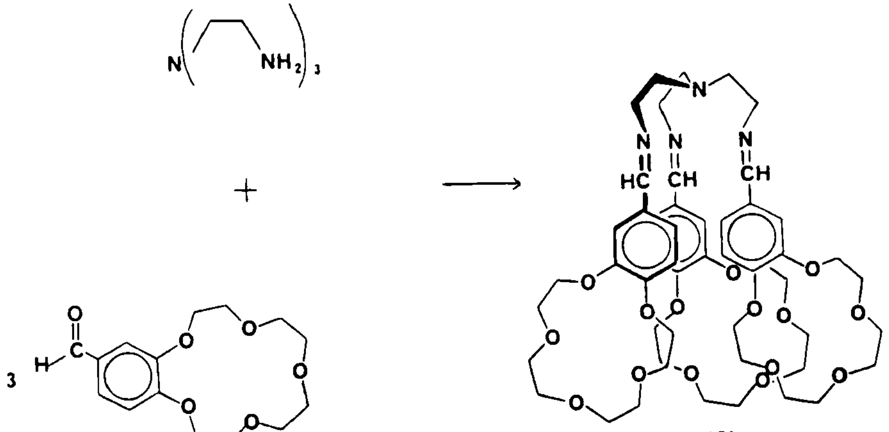


(58)

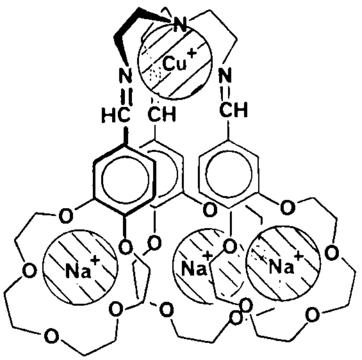


(59)

heteropolymetallic [Cu(**60**)Na_3]$(PF_6)_4$ complex (**61**) has also been isolated (*99*). Electrochemical investigations on the homometallic copper complexes of ligands (**57**) and (**60**) revealed that both exhibit irreversible copper(II)/copper(I) redox couples in acetonitrile- and dimethylformamide solvents.

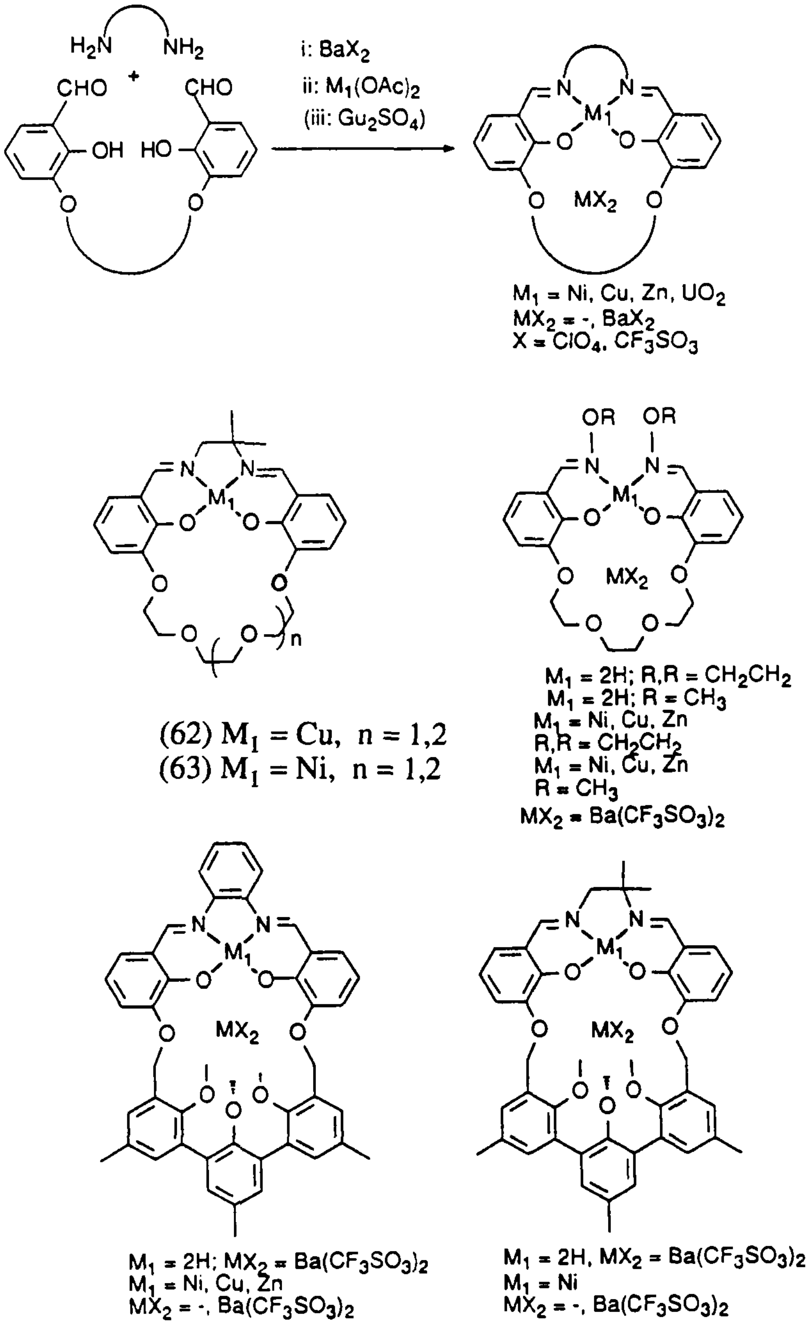


(60)



(61)

Reinhoudt and co-workers (*101–105*) have reported a series of Schiff base macrocyclic polyether ligand complexes prepared via barium cation-templated Schiff base condensation of the appropriate polyether dialdehyde with a diamine, in the presence of a transition metal or uranyl acetate, followed by removal of the Ba^{2+} template cation on subsequent addition of guanidinium sulfate (Scheme 19). The copper(II) and nickel(II) complexes (**62**) and (**63**) exhibit reversible redox couples

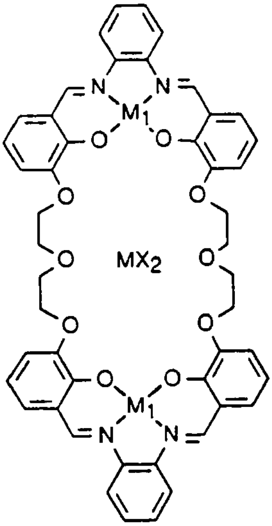


(62) $M_1 = \mathrm{Cu}$, $n = 1,2$
(63) $M_1 = \mathrm{Ni}$, $n = 1,2$

SCHEME 19.

which are anodically shifted by modest magnitudes on addition of Group IA metal cations, for example, $\Delta E_{1/2} \sim 9$ mV for K^+. However, addition of the more polarizing Ba^{2+} cation resulted in larger anodic shifts of up to 213 mV for the copper(II) complex (**62**). Recently uranyl complexes of related ligands have been shown to bind polar neutral molecules such as urea and DMSO (*106*).

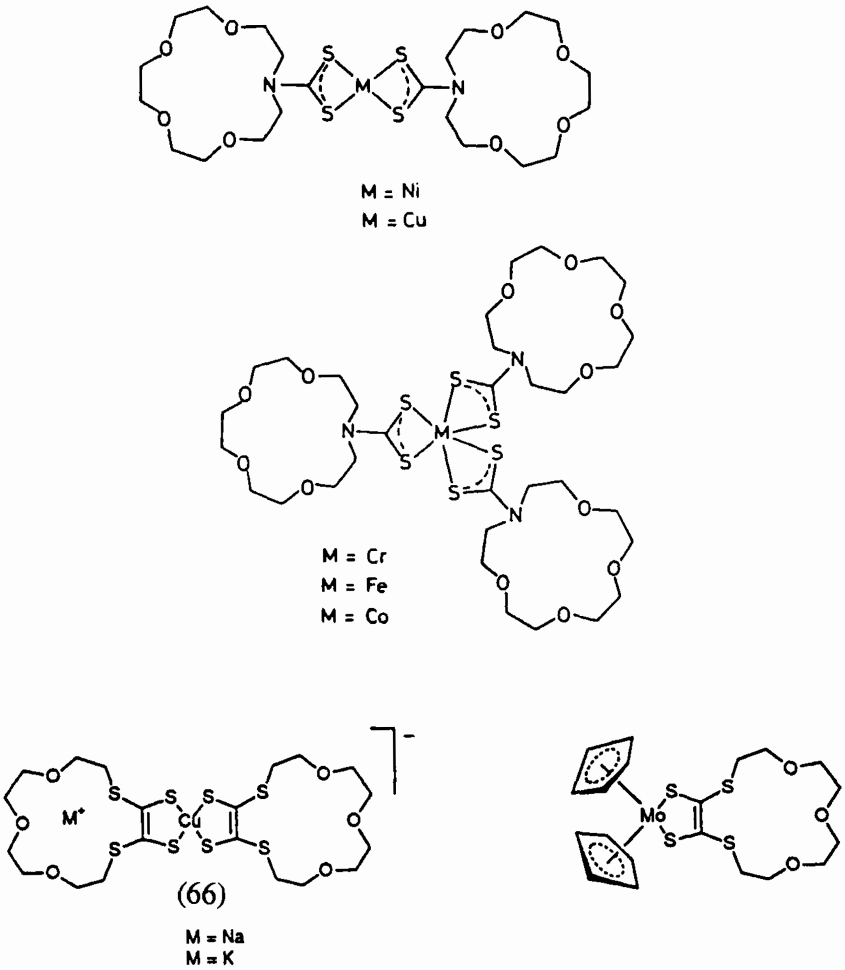
Novel heterotrinuclear complexes ((**64**), (**65**)) have also been described by the same group (*107*), although no electrochemical recognition studies of Group IA, IIA guest cations are reported.



(64) $M_1 = Ni$
(65) $M_1 = Cu$
$MX_2 = Ba\,(CF_3SO_3)_2$

5. *Crown Ether Dithiocarbamate and Dithiolene Complexes*

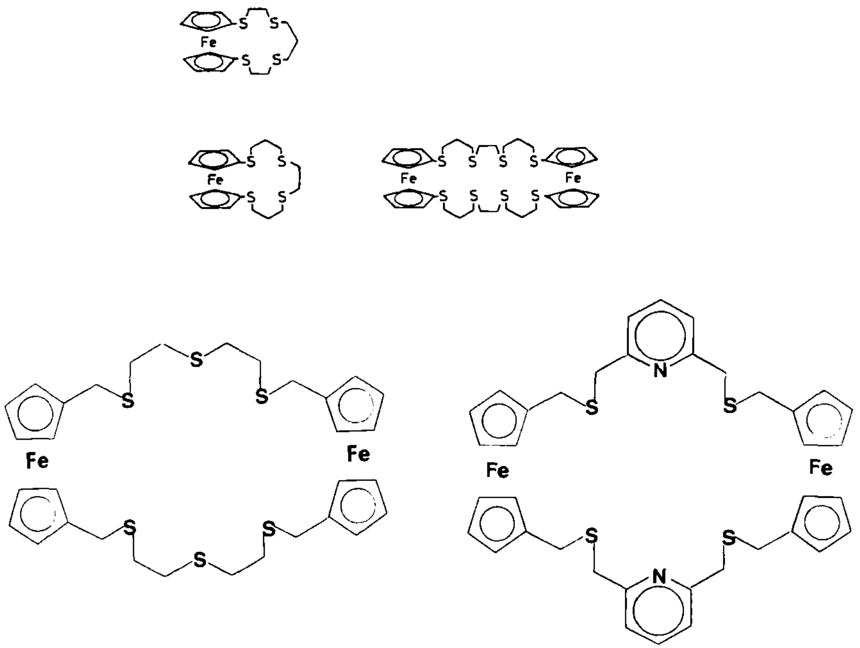
The syntheses of a variety of crown ether dithiocarbamate and dithiolene complexes have been reported by Green *et al.* (*108, 109*) (Scheme 20). Cyclic voltammetric experiments with Group IA metal cations displayed modest anodic shifts of the respective transition metal redox couples of the dithiocarbamate complexes. The copper dithiolene complex (**66**), however, exhibited much larger shifts of up to 175 mV with an excess amount of Na^+. The authors suggest the extensive π-delocalization of charge in the dithiolene complexes is responsible for bound Group IA metal cations producing greater magnitudes of electrochemical interactions compared to the dithiocarbamate complexes where there is localization of electron density.



SCHEME 20.

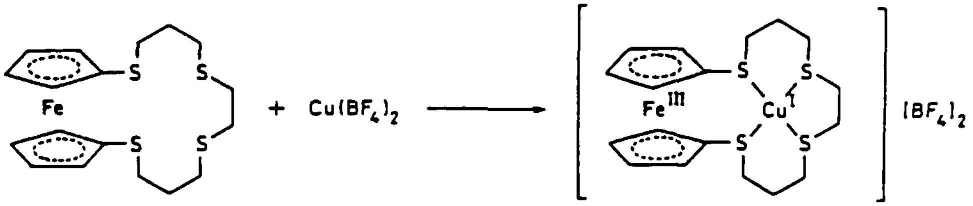
D. ELECTROCHEMICAL RECOGNITION OF TRANSITION METAL GUEST CATIONS BY FERROCENE AZA-, THIA-DONOR MACROCYCLIC LIGANDS

Besides the ferrocene crown ether ligands described earlier, a variety of related macrocyclic ferrocenophanes containing various sulfur, oxygen, and nitrogen heteroatoms have been reported by a number of groups (*110–115*) (Scheme 21). These ligands complex transition metal guest cations such as Ag(I), Cu(I), and Pd(II) (*116, 117*). Of particular

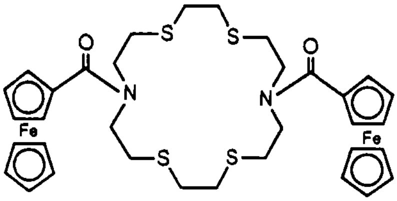


SCHEME 21.

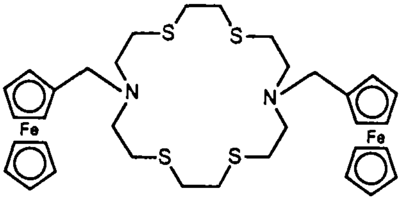
note is recent work by Sato and co-workers (*118*) describing the spontaneous reduction of initially coordinated copper(II) to copper(I) and concomitant oxidation of ferrocene to ferrocenium on addition of $Cu(BF_4)_2$ to polythia[*n*]ferrocenophanes (Scheme 22). To our knowledge no electrochemical transition metal coordination studies of these ligands have been described. We have prepared bis(ferrocenecarbonyl)- and bis(ferrocenyl)-diazatetrathia mixed-donor macrocyclic ligands (**67**) and (**68**) (*119*). The single-crystal X-ray structures of (**68**) and of its copper(I)



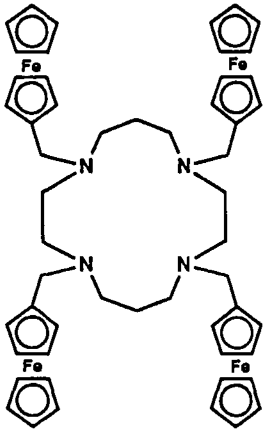
SCHEME 22.



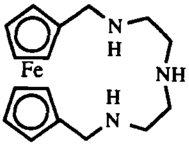
(67)



(68)



(69)



(70)

complex are shown in Figs. 17 and 18. Electrochemical investigations reveal that the respective ferrocene redox couples of (**67**) and (**68**) are perturbed to more positive potentials, by 60 and 40 mV on coordination of the copper(II) ion. The ferrocene-appended cyclam ligand (**69**) and aza macrocycle (**70**) both electrochemically recognize Ni^{2+} and Zn^{2+} guest cations (*120*).

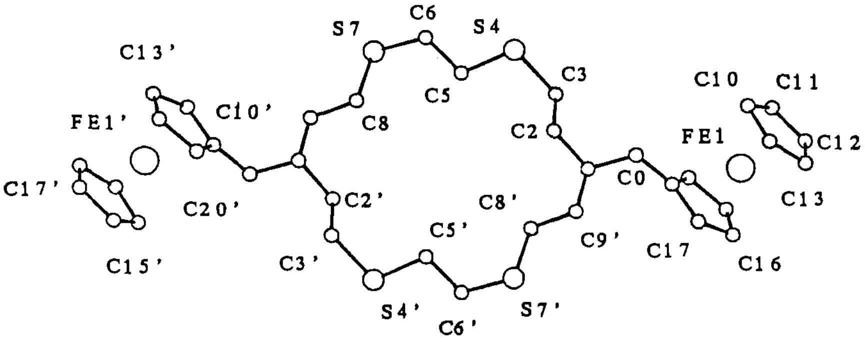
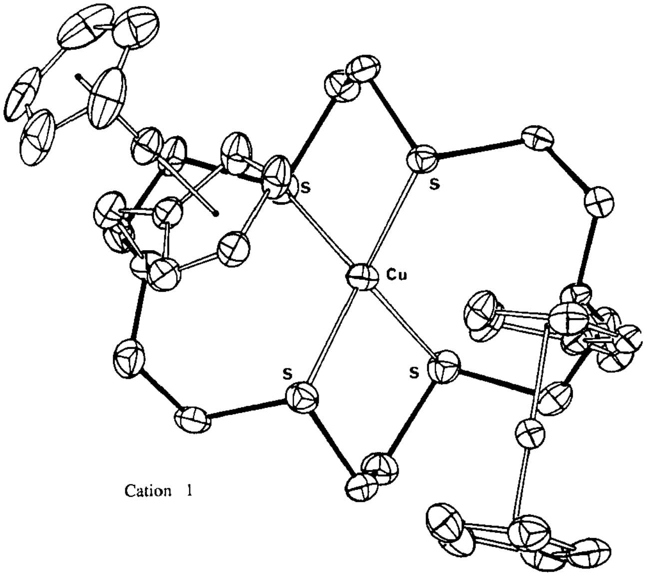
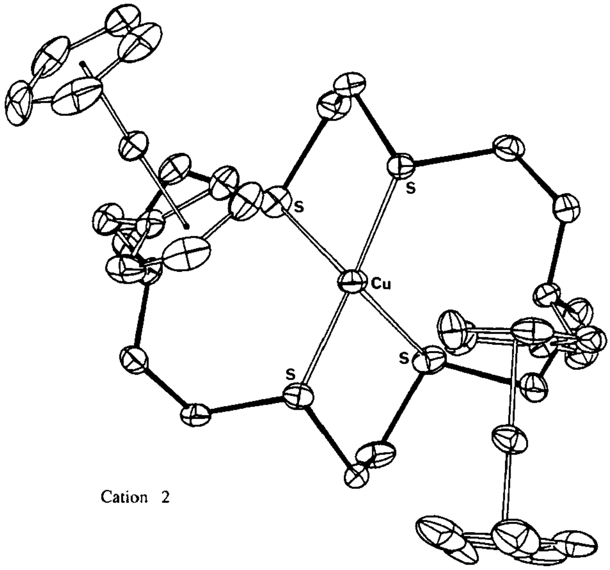


FIG. 17. Crystal structure of (**68**).



Cation 1



Cation 2

FIG. 18. Structure of [Cu(**68**)]PF_6. The three cations projected down their S(**7**)–Cu–S(**7′**) bisector; 20% thermal ellipsoids are shown for the nonhydrogen atoms, together with key atom labeling.

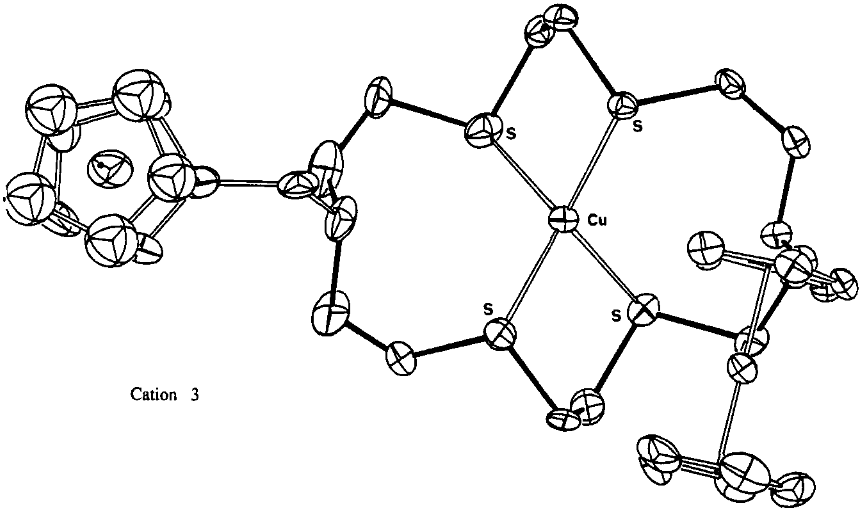
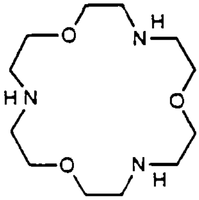


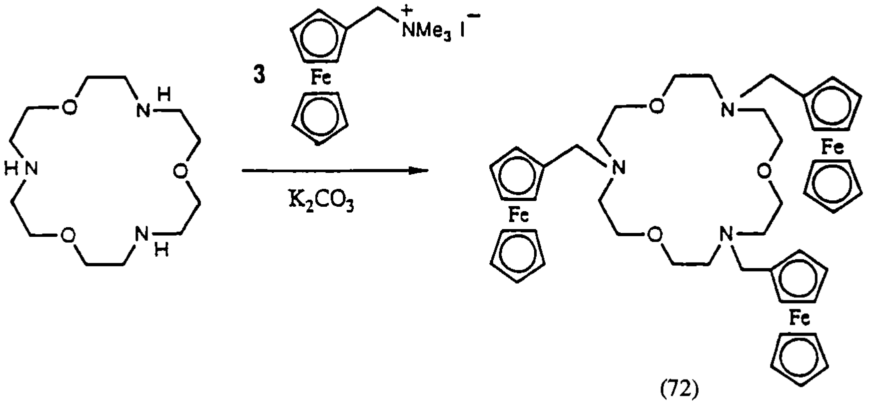
FIG. 18. (*Continued*)

E. AMMONIUM CATION ELECTROCHEMICAL RECOGNITION

In contrast to the alkali and alkaline earth metal coordination investigations of organic and inorganic redox-active macrocycles discussed in the previous sections of this review, the design and syntheses of prototype amperometric ammonium cation sensor systems have yet to be exploited. Graf and Lehn (*121, 122*) first described the synthesis of 4,10,16-triaza-18-crown-6 (**71**) and showed that this macrocycle forms very stable ammonium and primary ammonium complexes by the formation of three complementary $^+NH \cdots N$ hydrogen bonds between host and guest. With this precedent in mind, we have incorporated ferrocene (*123*) and quinone (*124*) redox-active centers into this type of macrocyclic system by preparing (**72**)–(**78**) via synthetic routes shown in Schemes 23–27.



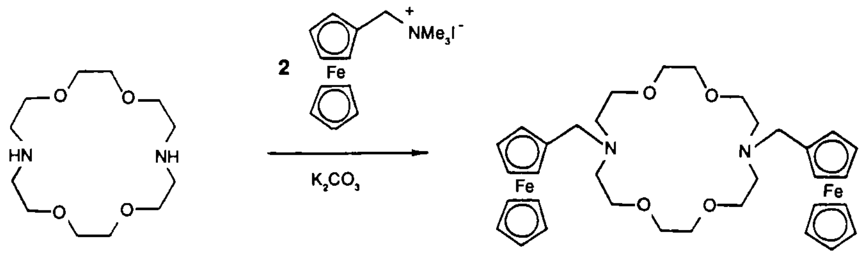
(71)



(72)

SCHEME 23.

Significant one-wave anodic shifts of the ferrocene redox couple were produced on addition of NH_4^+ to electrochemical solutions of (**72**)–(**75**) and (**78**) (Table VII). No response was observed with (**79**) or (**80**), suggesting that the crown ether structural framework containing tertiary amine nitrogen donor atoms is an essential component for successful NH_4^+ binding. Disappointingly the quinone redox couple of ligand systems (**76**) and (**77**) proved electrochemically insensitive to the presence of the NH_4^+ guest, a result which may be attributable to steric effects. The largest magnitude of anodic shift was 220 mV with ligand (**74**). The nature of the communication between NH_4^+ and the ferrocene redox centers of host (**74**) probably results from a combination of through-space electrostatic effects and through-bond $N^+—H\cdots O{=}C—$ferrocene lariat-type perturbation (Fig. 19) similar to those reported by



(73)

SCHEME 24.

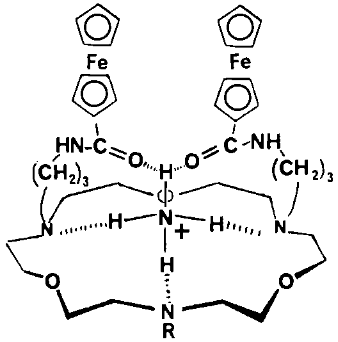
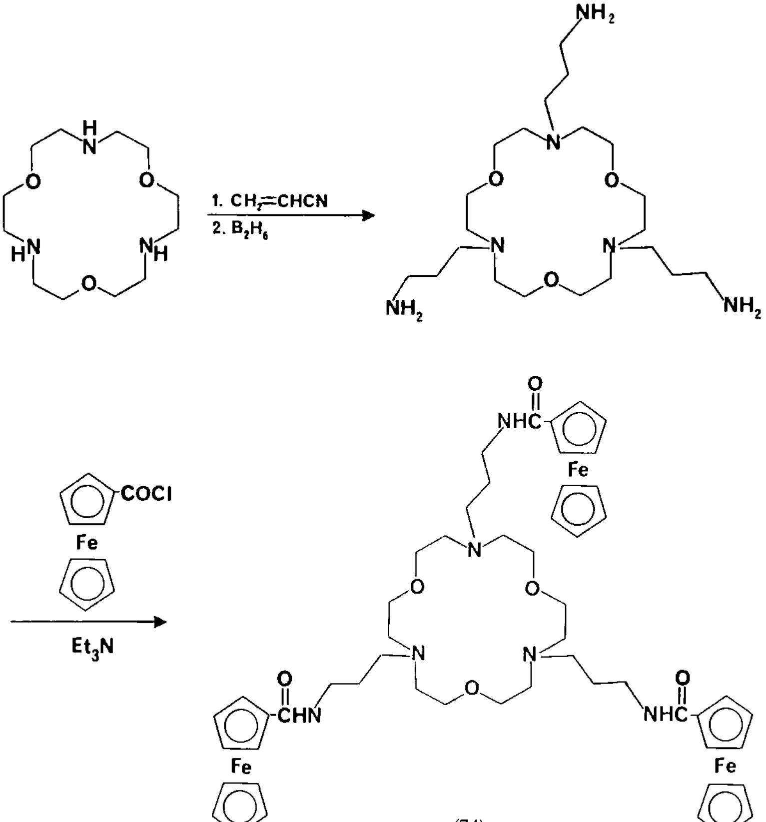
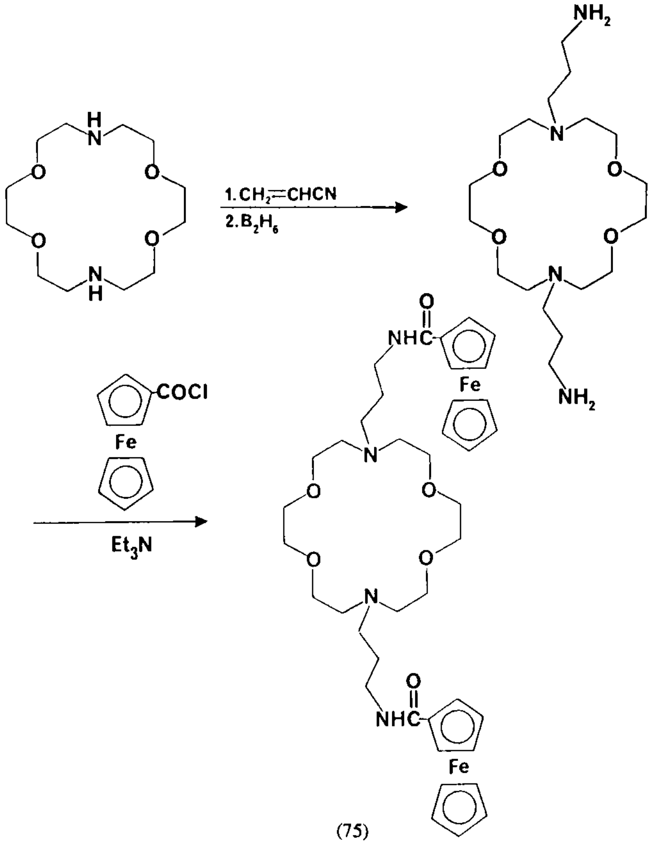


FIG. 19. Lariat-type electrostatic perturbation of (**74**) and NH_4^+.



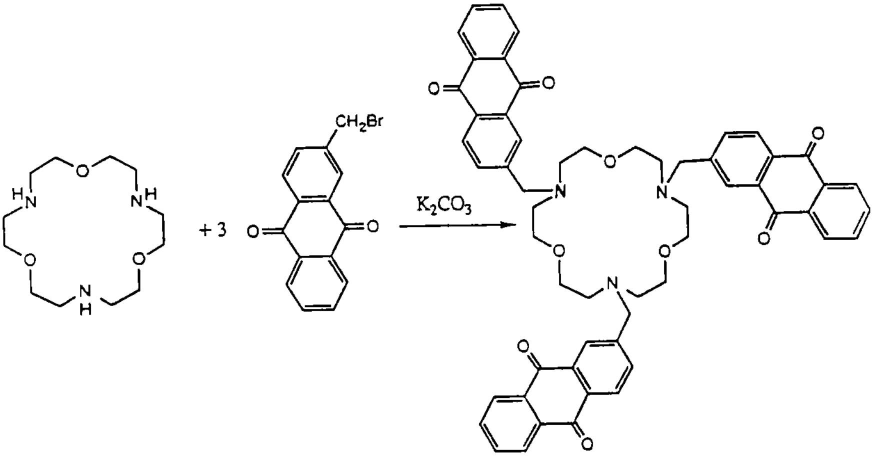
(74)

SCHEME 25.



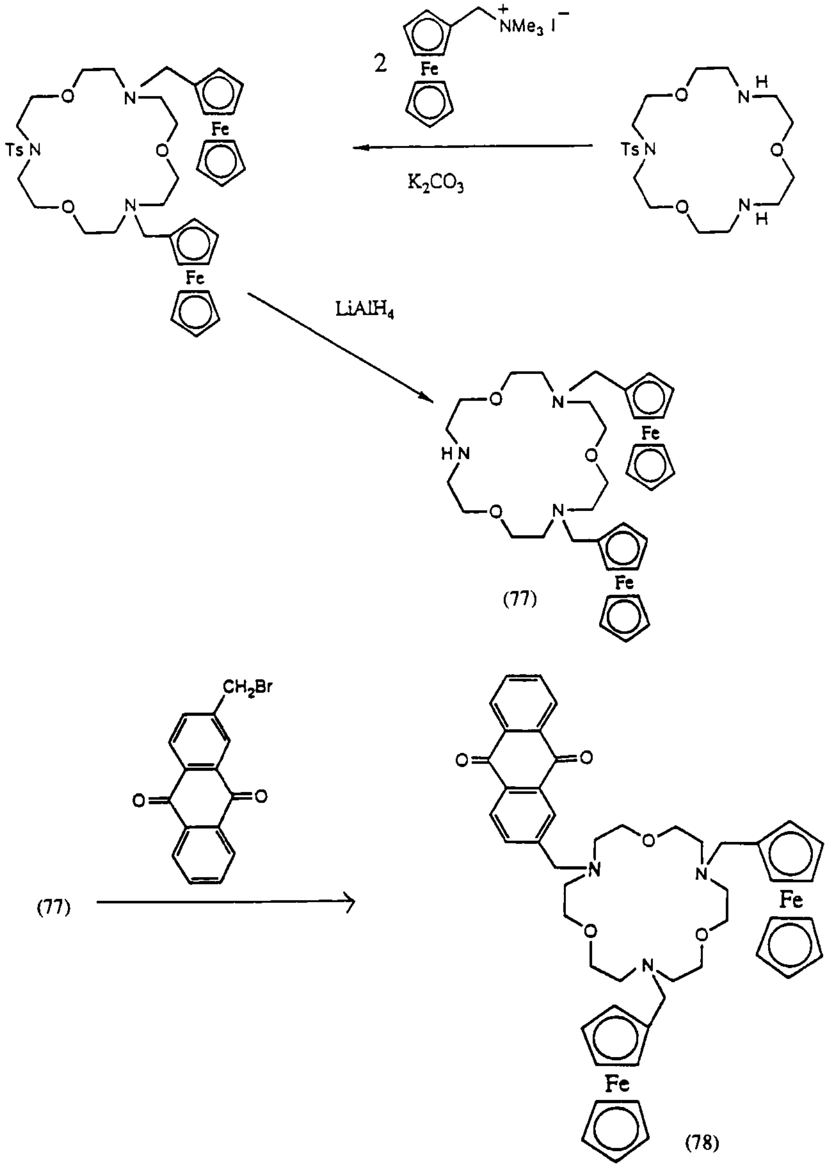
(75)

SCHEME 25. (*Continued*)



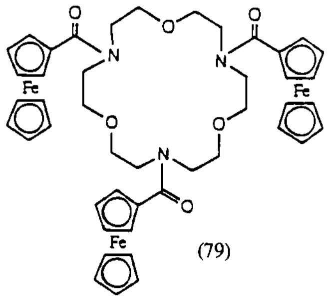
(76)

SCHEME 26.

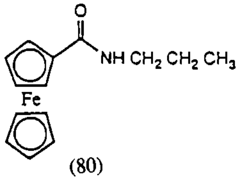


SCHEME 27.

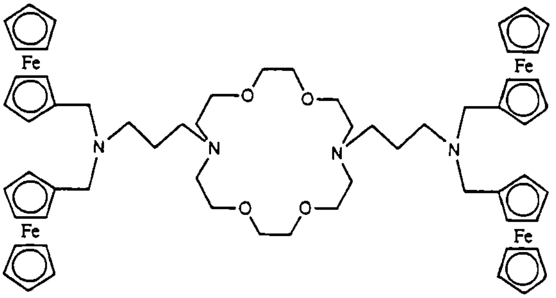
Gokel for reducible quinone (*25, 26*) and nitroaromatic (*32, 33*) lariat crown ethers with alkali metal guest cations discussed earlier. Support for the latter effect comes from the related ligand system (**81**), containing no amide carbonyl groups, and electrochemical results revealing



(79)



(80)



(81)

(**81**) to be nonresponsive to NH_4^+. Also of note is the observation that alkyl- and phenyl-ammonium cations, though forming solution complexes with (**72**)–(**78**), are not electrochemically recognized by these ligand systems (*125*) (Table VII).

TABLE VII

ELECTROCHEMICAL DATA AND AMMONIUM CATION DEPENDENCE

Compound:	(**72**)	(**73**)	(**74**)	(**75**)	(**78**)	(**79**)	(**80**)
E_f(V)[a]	+0.43[b]	+0.41[c]	+0.62[b]	+0.54[c]	+0.44[c]	+0.67[b]	+0.59
ΔE_p (mV)[d]	90	90	100	100	90	80	80
$\Delta E(NH_4^+)$ (mV)[e]	30	50	220	170	50	<10	<10
$\Delta E(K^+)$ (mV)[e]	20	40	50	85	40	<10	<10
$\Delta E(CH_3NH_3^+)$ (mV)[e]	—	—	<10	<10	—	<10	<10
$\Delta E(C_6H_5CH_2NH_3^+)$ (mV)[e]	—	—	<10	<10	—	<10	<10

[a] Solutions were ca. 2 × 10^{-3} *M* in compound, and potentials were determined with reference to the SCE.

[b] Three-electron reversible oxidation process.

[c] Two-electron reversible oxidation process.

[d] Separation between anodic and cathodic peak potentials; values for ferrocene under identical conditions ranged from 80 to 90 mV.

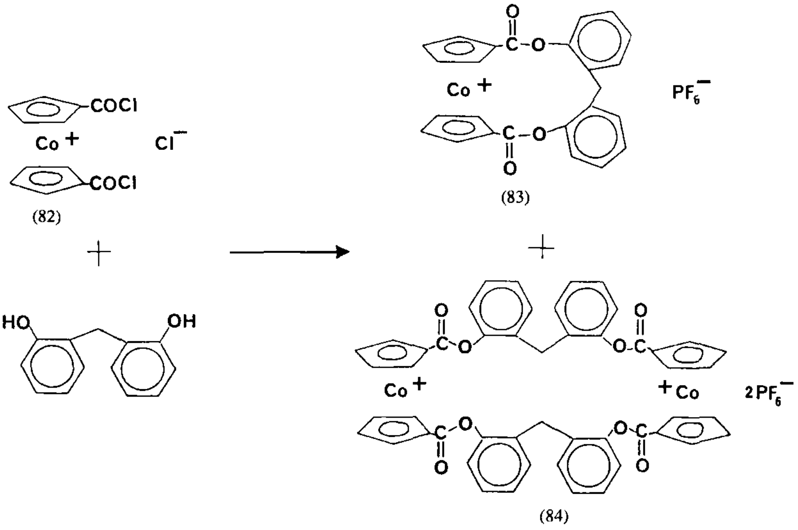
[e] Shift in respective ferrocenyl oxidation potential produced by presence of guest cation (2 equivalents) added as their thiocyanate salts for potassium and ammonium, and their picrate salts for methylammonium and phenethylammonium.

III. Electrochemical Recognition of Anions

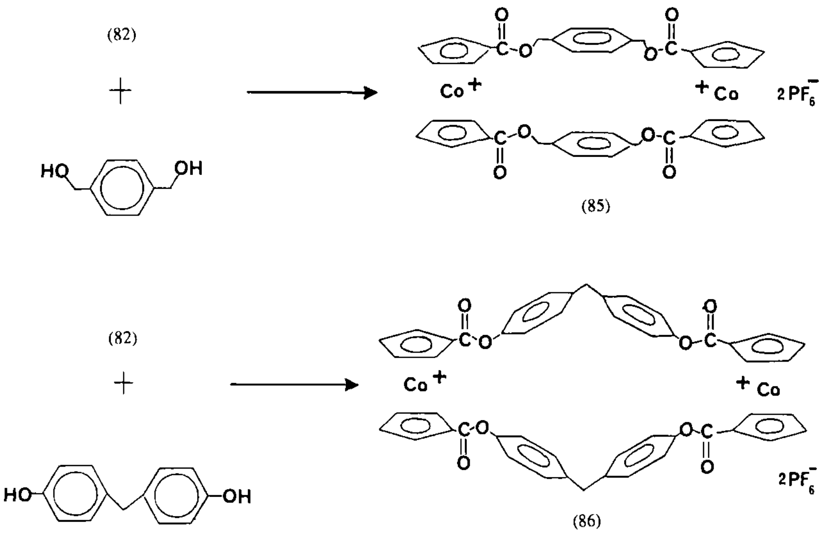
MACROCYCLIC AND ACYCLIC POLYCOBALTICINIUM LIGAND SYSTEMS

The molecular recognition of anionic guest species by positively charged or electron-deficient neutral abiotic organic receptor molecules is a relatively new area of chemical investigation (*126*). This is somewhat surprising in view of the ubiquitous role anionic substrates play in chemical and biochemical processes. Only a few classes of anion receptors have been reported; these include Lewis acid-containing ligands (*127*), ammonium quaternary salts (*128*), protonated polyamines (*129*), and guanidines (*130*). The latter, positively charged pH-dependent hosts, form strong and sometimes selective complexes with a variety of anions, including the binding of linear dicarboxylates with chain-length selectivity (*129*). We have reported the synthesis and electrochemistry of the *first* redox-responsive class of anion receptor based on the positively charged, pH-independent, air stable, 18-electron, redox-active, cobalticinium moiety (*131, 132*).

The condensation of 1,1′-bis(chlorocarbonyl)-cobalticinium chloride (**82**) with various phenols and alcohols followed by chromatographic purification and excess ammonium hexafluorophosphate gave the ester-linked polycobalticinium macrocycles (**83**)–(**86**) (Scheme 28). The first

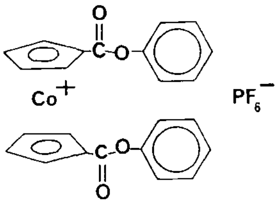


SCHEME 28.



SCHEME 28. *(Continued)*

evidence indicating that these receptors would complex anionic guests came from FABMS and Fourier transform infrared investigations. For example, the hexafluorophosphate salt of (**84**) exhibits an ester carbonyl stretch at 1747 cm^{-1}. Interestingly, this effect was not observed with the hexafluorophosphate and chloride salts of the acyclic model (**87**), suggesting the presence of a macrocyclic effect in these ester systems.

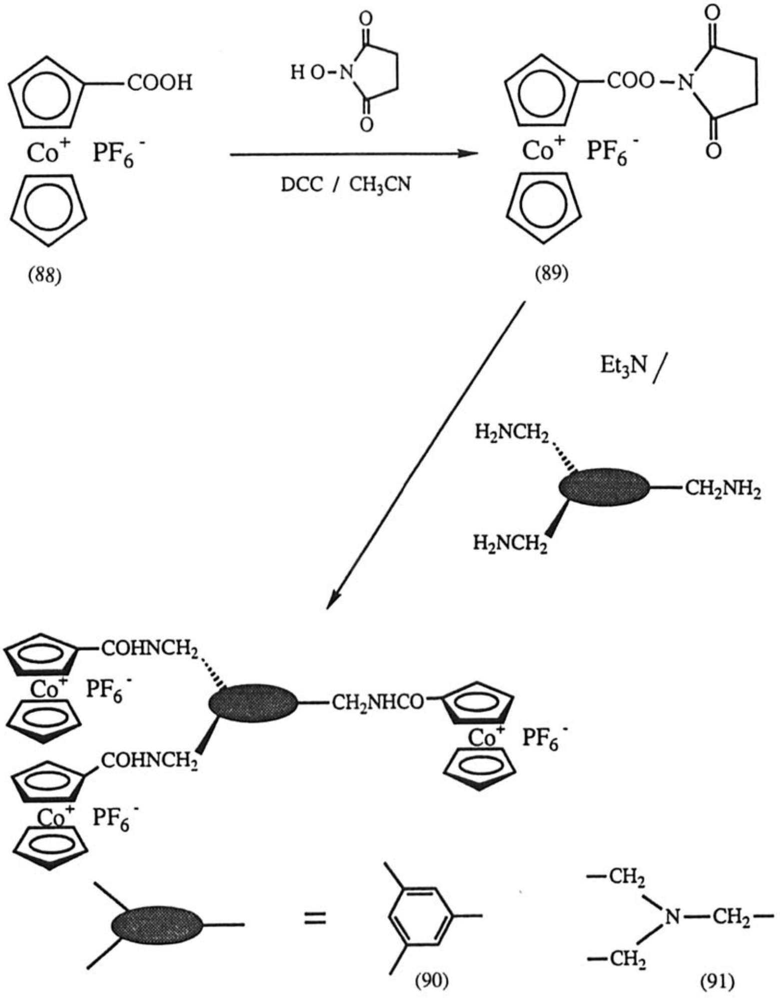


(87)

The addition of stoichiometric amounts of tetrabutylammonium bromide to electrochemical solutions of (**84**) led to gradual *cathodic* shifts in the reversible reduction wave of the host. A maximum shift of 45 mV was observed after 4 equivalents had been added. No cathodic shifts were observed with (**87**), which implies that bromide anion complexation within the macrocyclic cavity of (**84**) is essential for electrochemical detection.

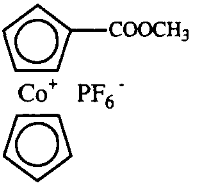
The general poor solubility of these macrocyclic polycobalticinium systems coupled with their lability to ester hydrolysis has very recently led us to a new synthetic strategy which utilizes the stable amide linkage to construct novel acyclic cobalticinium anion receptors (*132*).

The reaction of carboxycobalticinium hexafluorophosphate (**88**) with *N*-hydroxysuccinimide gave the activated ester (**89**) in excellent yield. Condensation of 3 mol of (**89**) with 1,3,5-triaminomethylbenzene and tris(2-aminoethyl)amine in the presence of triethylamine gave, respectively, the new acyclic tripodal receptors (**90**) and (**91**) in 65 and 60% yields (Scheme 29).

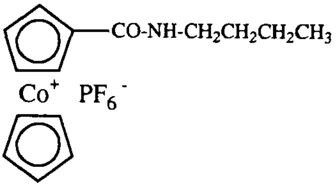


SCHEME 29.

The addition of tetrabutylammonium chloride to deuteriated acetonetrile ^1H NMR solutions of (**90**) and (**91**) resulted in remarkable shifts of the respective protons of both receptors. Of particular note were the substantial downfield shifts of the amide protons ($\Delta\delta$ = 1.28 ppm for (**90**); 1.52 ppm for (**91**)) on addition of one equivalent of chloride. These results suggest that a significant $-CO-NH\cdots Cl^-$ hydrogen bonding interaction is contributing to the overall anion complexation process. Subsequent ^1H NMR titration studies in CD_3CN and d_6-DMSO with Cl^-, Br^-, and NO_3^- produced titration curves suggesting 1 : 1 ligand (**90**), (**91**) anion stoichiometry in all cases (Fig. 20). Negligible shifts were observed under identical experimental conditions with cobalticinium hexafluorophosphate itself or the ester derivative (**92**). However, the simple monoamide-substituted cobalticinium compound (**93**) did exhibit some significant solution interactions with halide anions. These results imply it is the unique combination of the positively charged cobalticinium moiety *and* the appending amide N–H unit, which can form a favorable hydrogen bond with a coordinated anion guest, that are the essential components for successful anion complexation.



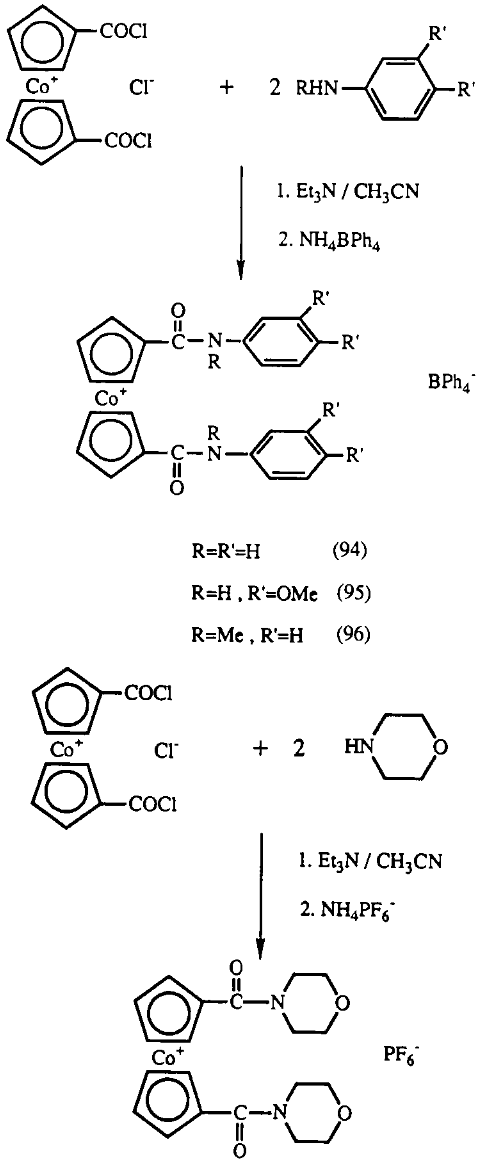
(92)



(93)

To test this hypothesis further, a series of simple acyclic cobalticinium-amide containing derivatives (**94**)–(**97**) were prepared (Scheme 30) and solution ^1H NMR complexation studies with Cl^- and Br^- anions investigated. Remarkable shifts of the amide N–H and respective host protons were again observed. Figure 21, for example, shows the titration curve of (**95**) with Br^-, which implies that a 1 : 1 complex is formed in solution. Interestingly, introducing a 20-fold excess of NH_4BPh_4 and repeating this ^1H NMR titration experiment gave the same result, negating the possibility for a simple anion-exchange process. In addition, it is also noteworthy that if the amide proton is replaced by a methyl or methylene group as in the case of compounds (**96**) and (**97**), no solution shifts of the host are observed under analogous experimental conditions.

The electrochemical properties of compounds (**90**)–(**97**) were investigated in acetonitrile using cyclic voltammetry with $[Bu^n{}_4N]BF_4$ as the supporting electrolyte. Each compound exhibited a reversible redox



R=R'=H (94)

R=H , R'=OMe (95)

R=Me , R'=H (96)

(97)

SCHEME 30.

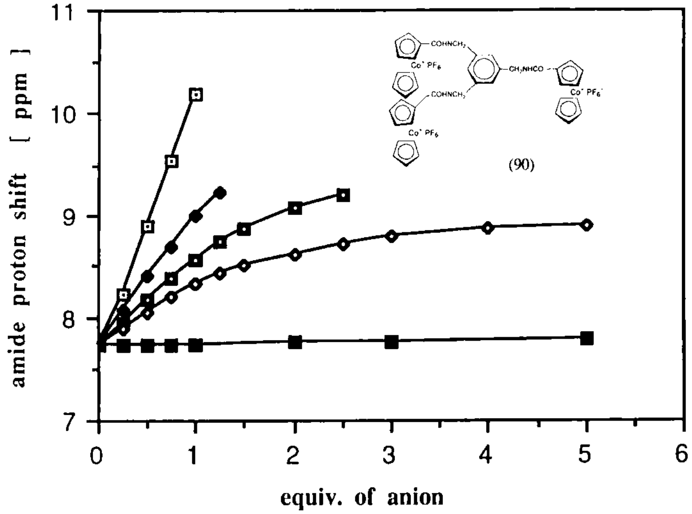


FIG. 20. ^{1}H NMR titration curves of (**90**) and various anionic guest species. (□) F^-; (◆) Cl^-; (▣) Br^-; (◈) NO_3^-; (■) BF_4^-.

reduction wave in the −0.5- to −0.7-V region (Table VIII). Cyclic voltammograms were also recorded after progressive addition of stoichiometric equivalents of anion guests to the electrochemical solutions, and the results are summarized in Table VIII.

Only in the case where the cobalticinium receptor contains at least one amide N–H linkage are significant one-wave cathodic shifts pro-

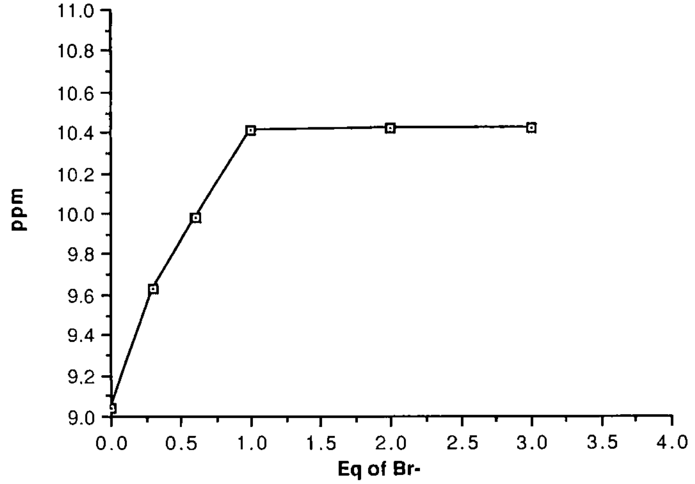


FIG. 21. ^{1}H NMR titration curve of (**95**) and Br^- in $CDCl_3$ solution.

TABLE VIII

ELECTROCHEMICAL DATA AND HALIDE ANION DEPENDENCE

Compound:	**(90)**	**(91)**	**(92)**	**(93)**	**(94)**	**(95)**	**(96)**	**(97)**
$E_{1/2}$ (V)[a]	-0.74[b]	-0.75[b]	-0.45	-0.74	-0.55	-0.52	-0.50	-0.60
$\Delta E(F^-)$ (mV)[c]	55[d]	60[d]	<5	—	—	—	<5	<5
$\Delta E(Cl^-)$ (mV)[c]	30	30	<5	30	35	30	<5	<5
$\Delta E(Br^-)$ (mV)[c]	—	—	<5	45	60	55	<5	<5

[a] Obtained in MeCN solution containing 0.2 mol dm^{-3} $[Bu^n_4N]BF_4$ as supporting electrolyte. Solutions were ca. 2×10^{-3} mol dm^{-3} in ligand, and potentials were determined with reference to the SCE.

[b] Three-electron reduction process as determined by coulometric experiments.

[c] Cathodic shift in reduction potential produced by the presence of anions (4 equivalents) added as their ammonium or tetrabutylammonium salts.

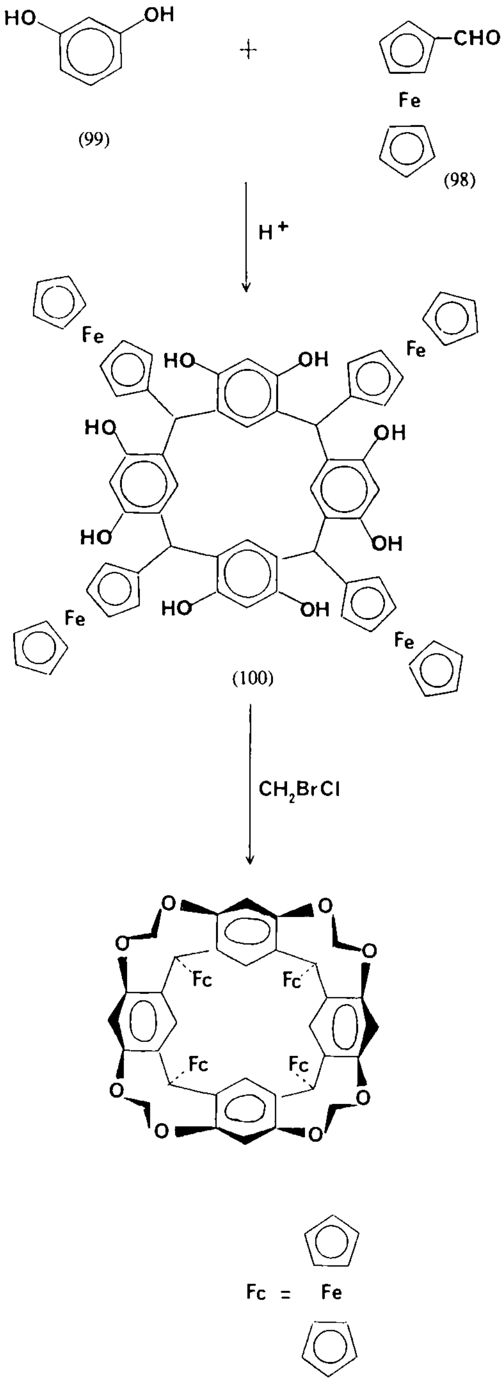
[d] Values obtained in DMSO solution.

duced with the anionic guest species, in agreement with the results obtained from ^1H NMR anion complexation experiments. Thus, these preliminary anion coordination studies have revealed that relatively simple, easily prepared, acyclic cobalticinium derivatives containing amide N–H groups can coordinate and electrochemically recognize anionic guest species via the cooperative binding forces of mutual electrostatic attraction between the positively charged host and the anionic guest and favorable amide N–H···anion hydrogen bonding interactions.

IV. Electrochemical Recognition of Neutral Guest Species

REDOX-ACTIVE CAVITAND HOST MOLECULES

Inspired by how nature's catalysts, the enzymes, selectively bind and catalyze chemical reactions upon organic guest substrates, a number of research groups (*133–135*) have designed and synthesized a variety of macrocyclic cyclophane organic host molecules. The cavitands (*133, 136*) are one such class of host that contain enforced *rigid* hydrophobic cavities of dimensions large enough to include simple neutral organic guest species. 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 a neutral organic guest in the host cavity (*137–142*) (Fig. 22). Such compounds may also serve as a new class of redox catalyst, promoting redox reactions on an included guest substrate.



(101)

SCHEME 31.

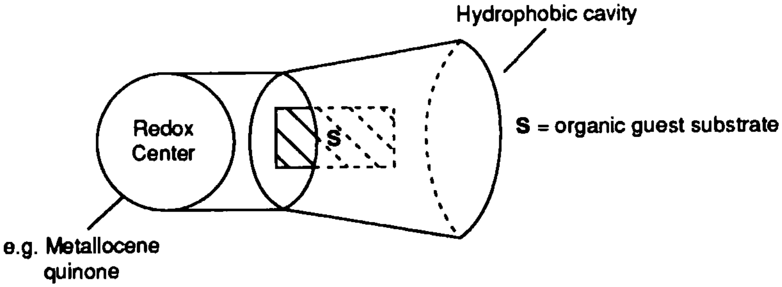
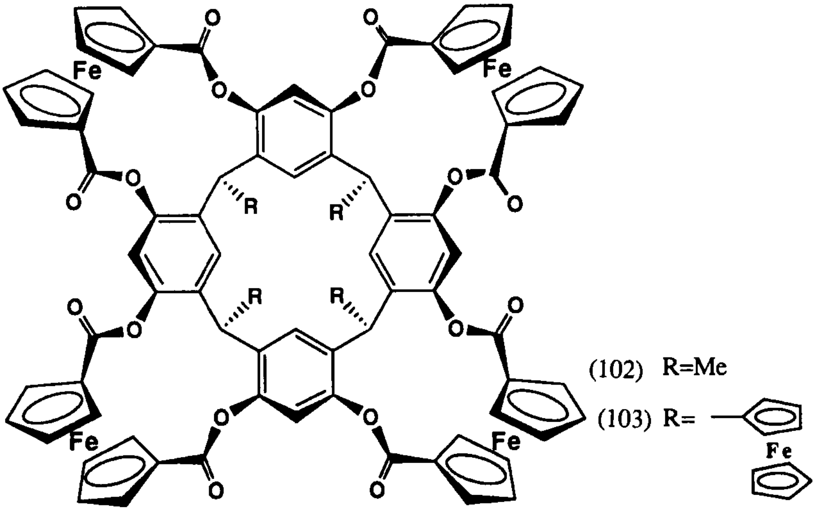


FIG. 22. The binding of an organic guest substrate S in close proximity to a redox-active center.

The reaction of ferrocenecarbaldehyde (**98**) and resorcinol (**99**) under acidic conditions gave the phenolic macrocycle (**100**), which on addition of chlorobromomethane in the presence of a base produced the first redox-active cavitand (*141, 142*) (**101**) (Scheme 31). An X-ray structural investigation on crystals of (**101**), obtained from a dichloromethane–diethyl ether solvent mixture, revealed the inclusion of a dichloromethane guest molecule within the cavitand host cavity (Fig. 23). Related redox-active cavitand host molecules ((**102**) and (**103**)) containing ferrocene moieties lining the wall of the cavitand cavity have also been prepared by our group (*141, 142*).



Molecular mechanics calculations (*142*) performed on neutral inclusion complexes of cavitand (**101**) suggested that the cavitand cavity would allow inclusion of small organic guest species such as carbon

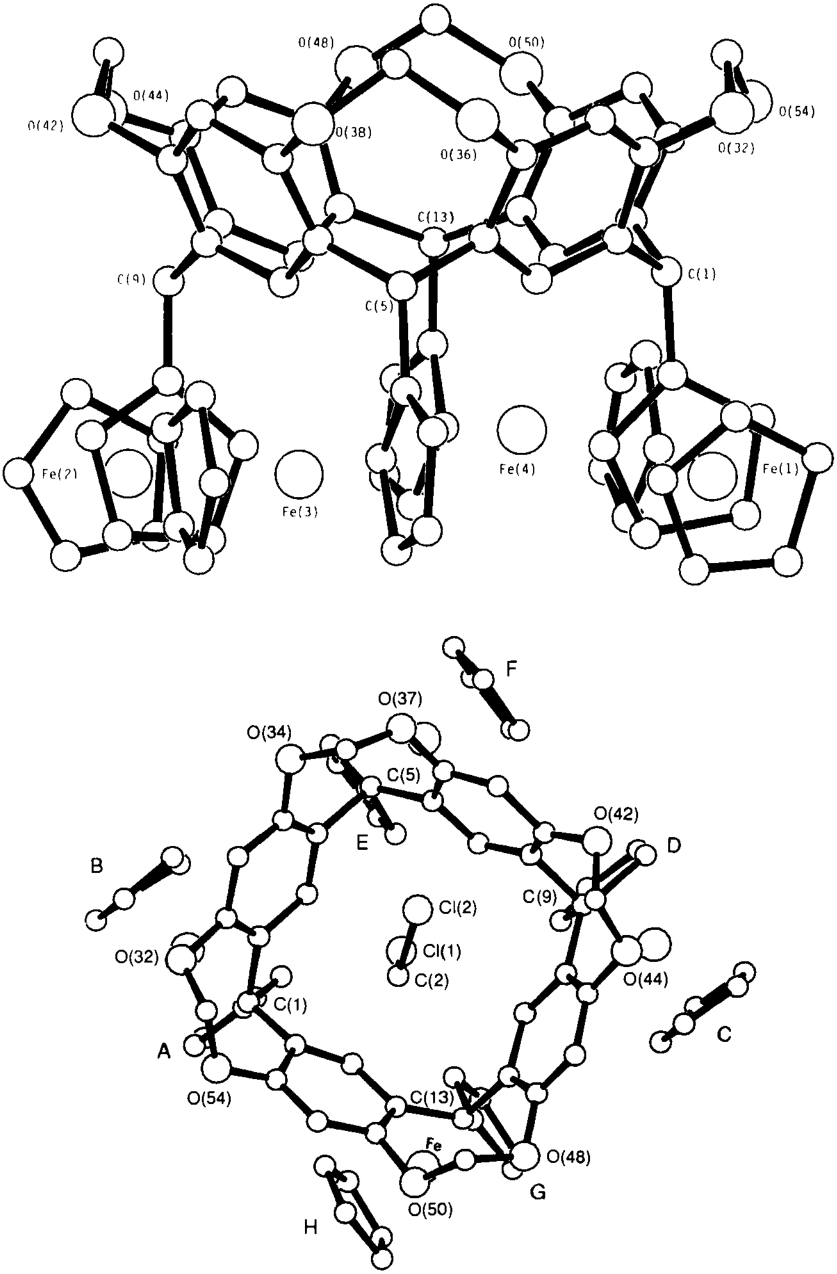
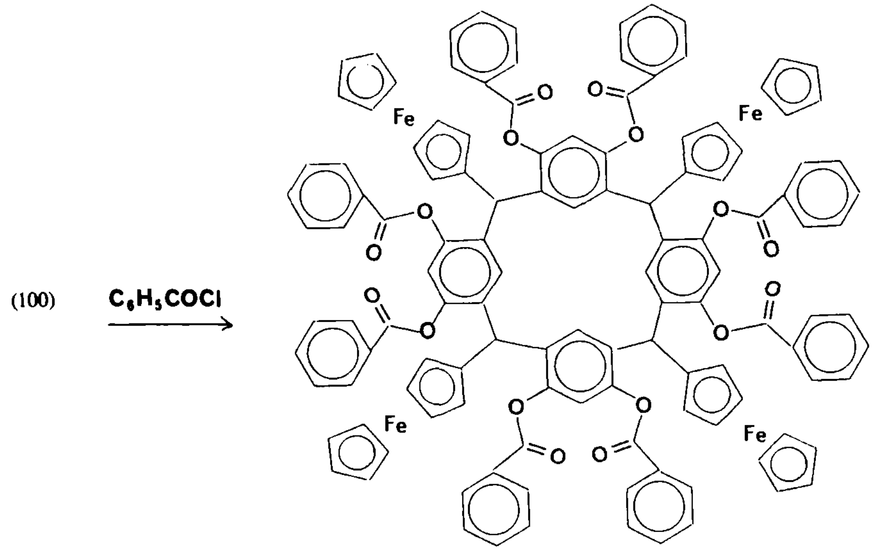


FIG. 23. The crystal structure of (**101**) showing (a) the regular cone shape and (b) the inclusion of a dichloromethane guest molecule.

dioxide and dichloromethane. However, electrochemical investigations revealed that the addition of dichloromethane to or bubbling of carbon dioxide through electrochemical dimethylformamide solutions of (**101**) or (**102**) produced no significant changes in the respective cyclic voltammograms of both hosts.

A variety of associated multi-redox-active macrocyclic host molecules containing multiple ferrocene and benzo crown ether moieties have also been recently described by our group (*143, 144*) (Schemes 32–34). The crystal structure of (**104**) (*145*) is shown in Fig. 24. The four ferrocenyl redox centers present in (**104**) undergo two one-electron oxidations at +0.58 and +0.67 V in dichloromethane, whereas (**105**), containing eight ferrocenoyl moieties, exhibited independent reversible one-electron oxidations in the same solvent. Even though solution complexation studies with neutral organic guests have proved fruitless, hosts (**106**)–(**107**) do complex bipyridinium guest species, exclusively at the host's benzo crown ether binding site (*143, 144*).

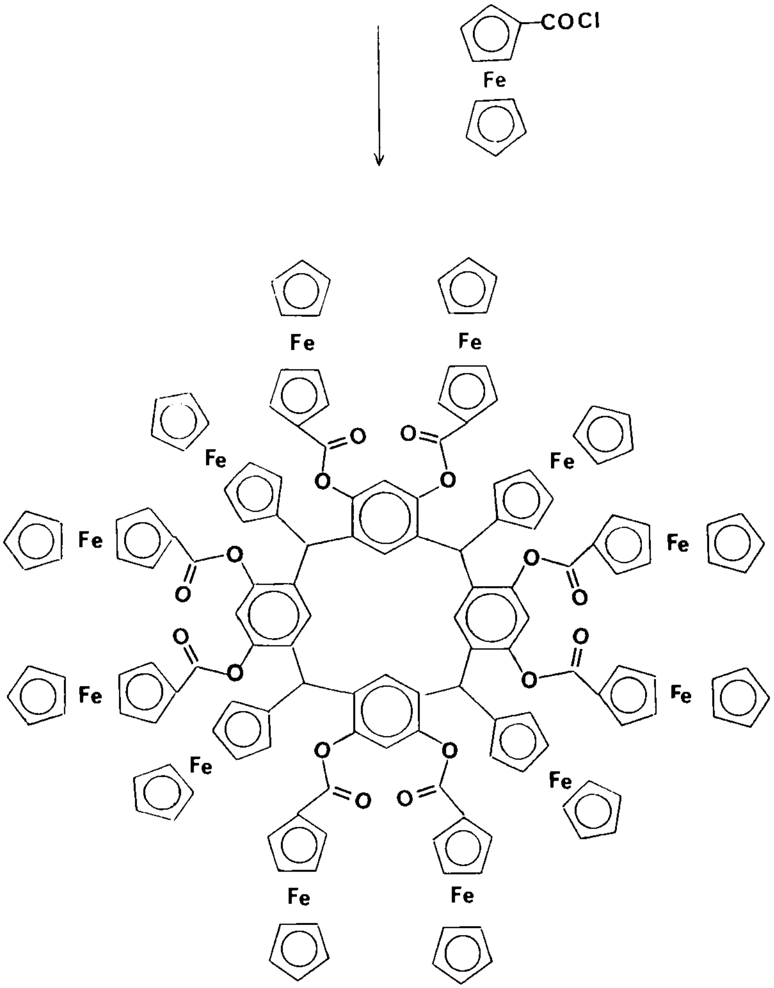
Macrocyclic calix[4]arene metallocene hosts have been prepared by our laboratory (*138, 146*) (Schemes 35, 36) and the crystal structures of (**109**) and the dimeric host (**110**) are shown in Figs. 25 and 26. Preliminary solution ^{1}H NMR and electrochemical inclusion studies in solvents such as acetonitrile, chloroform, and dichloromethane showed



(104)

SCHEME 32.

(100)

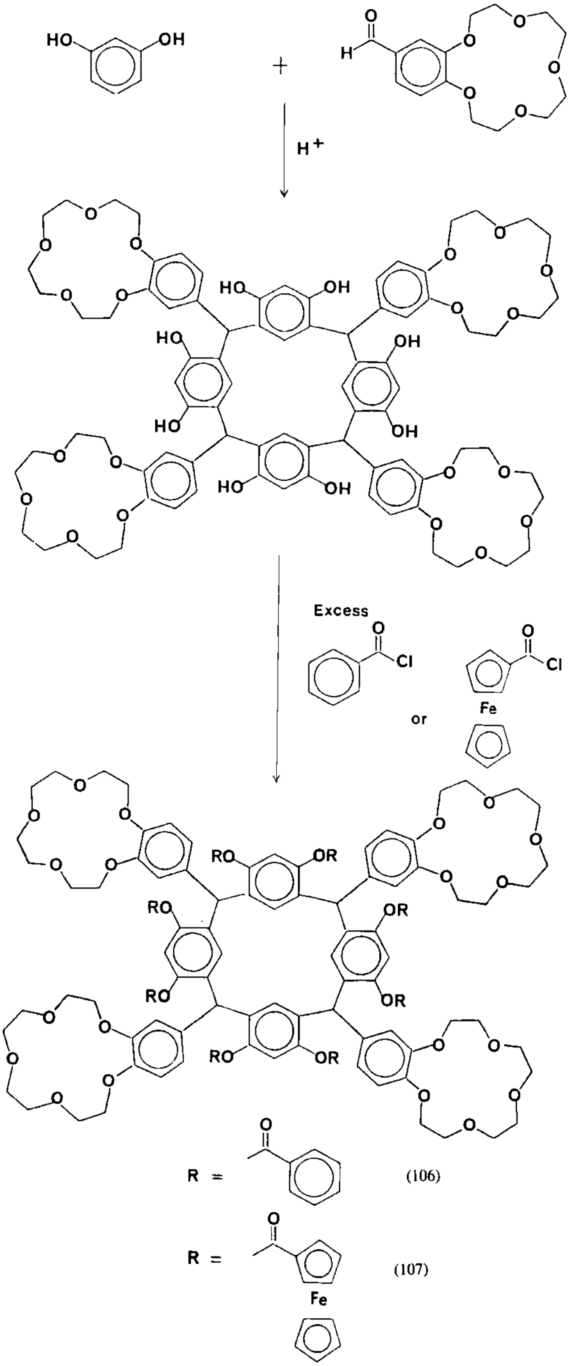


(105)

SCHEME 33.

none to form solution host–guest complexes with various aliphatic or aromatic amines.

Future work is focused at preparing water-soluble analogs in an effort to utilize the "hydrophobic effect" (*147*) as the driving force for inclusion of neutral organic guest species.



SCHEME 34.

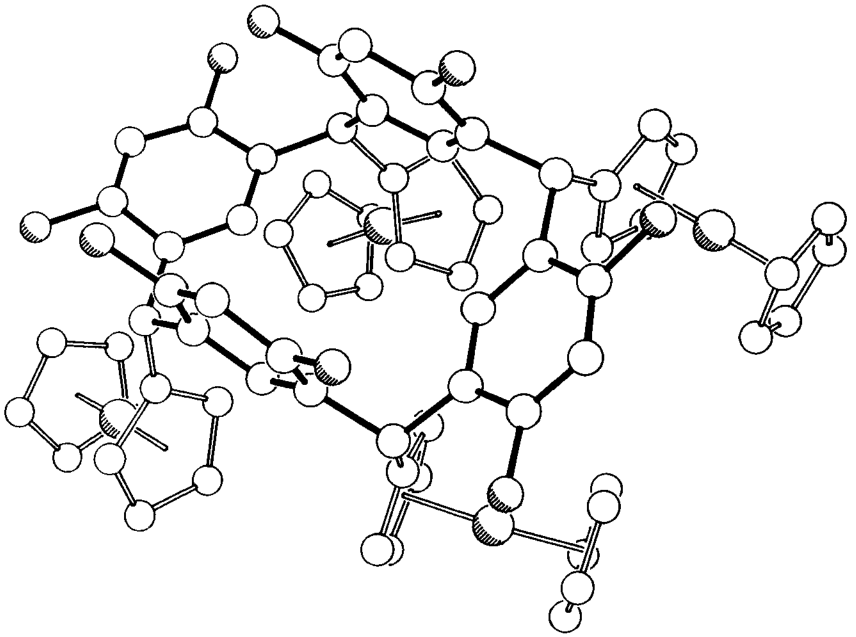
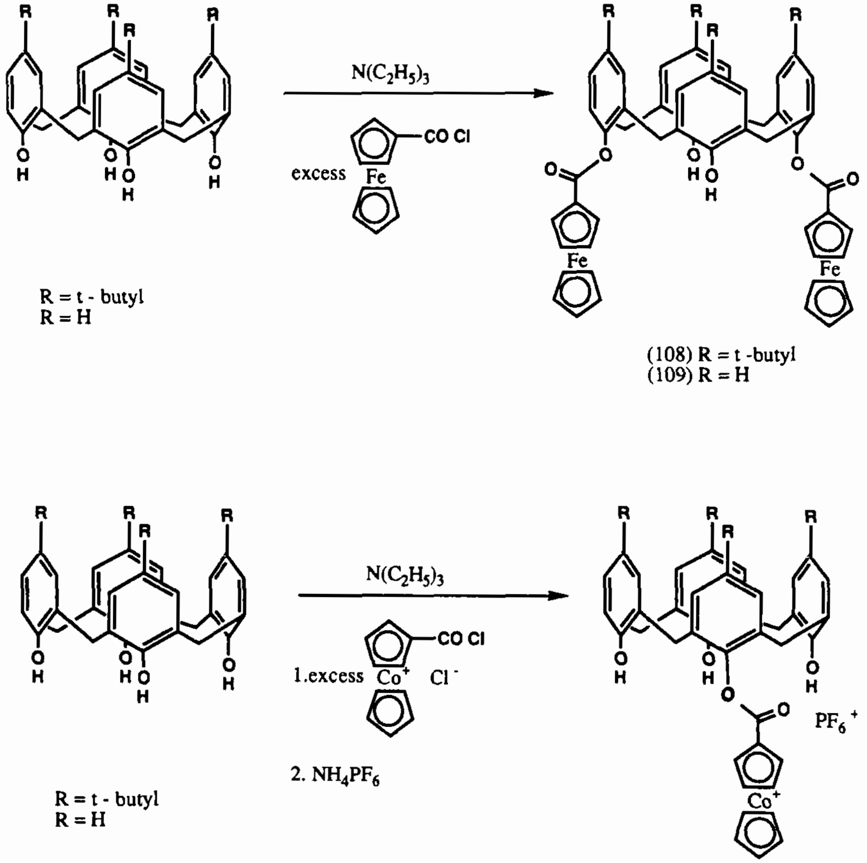


FIG. 24. Crystal structure of (**104**), benzoyl groups omitted.

V. Conclusions

This review has been concerned with illustrating the concept of electrochemical recognition of a guest specie by a redox-active host system. We have seen how various transition metal and organic redox-active macrocyclic receptor molecules can initially bind and subsequently redox-respond to cationic (metal, ammonium) and anionic (halide, nitrate) guests by through-space electrostatic perturbation and/or via various conjugated bond linkages connecting the redox center to the cation/anion ligand binding unit. The magnitude and type (one- or two-wave cyclic voltammogram) of ΔE shift in the respective redox couple of these host systems produced by charged guest binding are dependent upon the following factors: (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

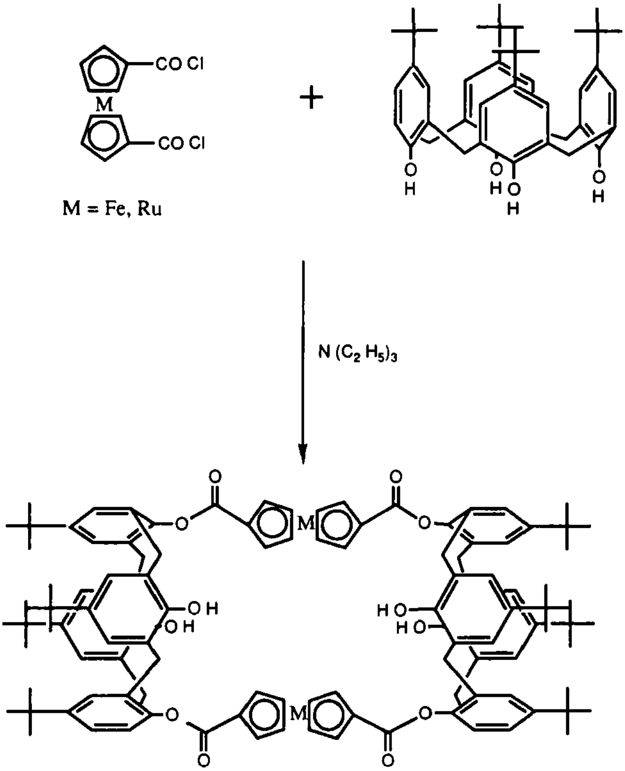


(108) R = t -butyl
(109) R = H

SCHEME 35.

of anodic shift is lanthanides > Group IIA > Group IA for the ferrocene cryptand (**29**)); (iii) proximity of host binding site to redox center; (iv) nature of bond linkage from host binding site to redox center; (v) nature of redox center.

The latter three factors are of special importance when considering the design of future generation redox-responsive systems. In particular for a given target guest cation or anion, larger magnitudes of electrostatic perturbation (ΔE) may result when the redox center's HOMO, in the case of an oxidation process, or LUMO, in the case of a reduction process, is designed to be predominantly ligand based. For example, there is no doubt that the ΔE values exhibited by the ferrocene vinylic-linked benzo crown ether ligand systems (**15**) and (**16**) on metal cation



M = Fe (110)

SCHEME 36.

binding would be much greater if the ferrocene–ferrocenium redox couple's HOMO was not mainly metal based (*148*). In addition, a highly delocalized conjugated π system that links the cation or anion coordinating site to the redox-active center can act as an efficient through-bond electrostatic transmission unit compared to saturated alkyl alternatives.

The nature of the solvent can also have a profound effect on the electrochemical recognition process. All of the redox-responsive ligand systems cited in this review give examples of guest cation/anion redox couple perturbations in organic solvents such as dichloromethane and acetonitile. The next challenge will be to demonstrate analogous redox-responsive behavior in the aqueous environment.

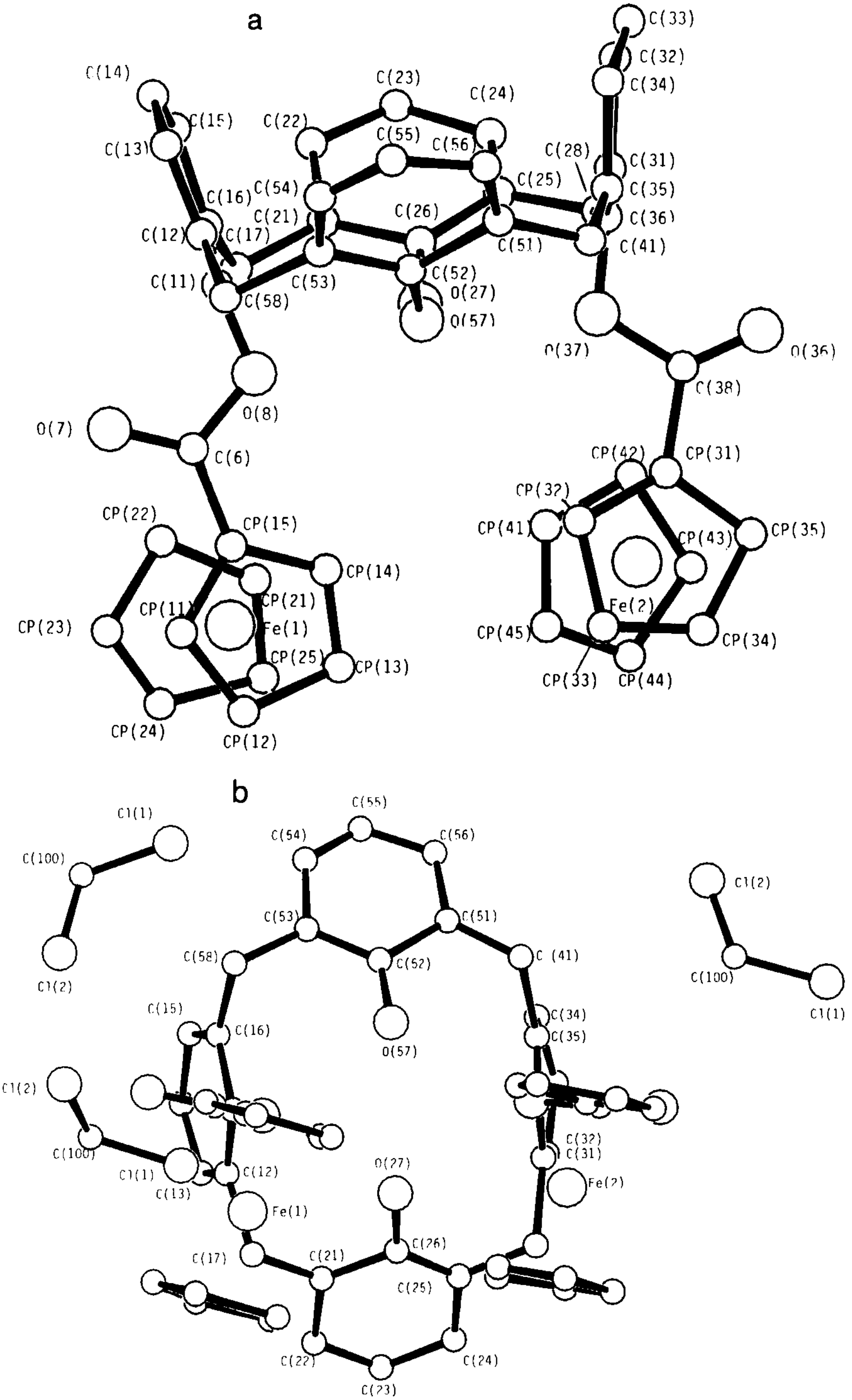


FIG. 25. Crystal structure of (**109**) (a) in the absence of dichloromethane and (b) in the presence of dichloromethane.

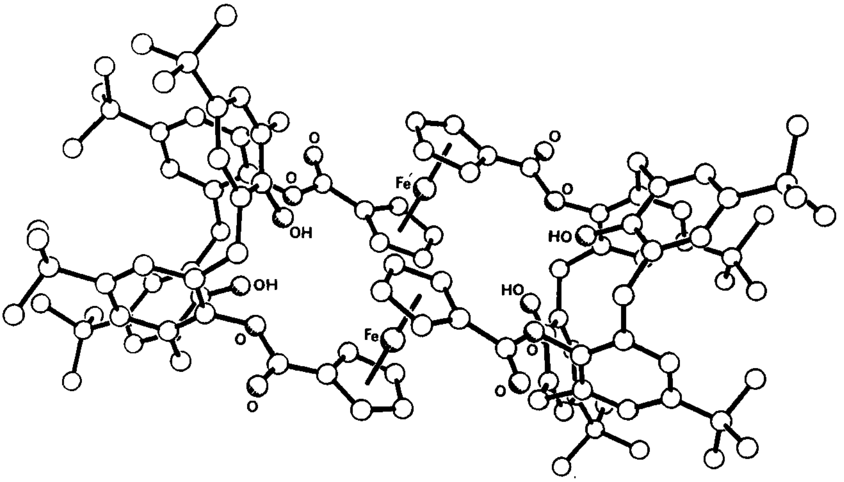


FIG. 26. Crystal structure of (**110**).

Finally, apart from the obvious future commercial applications of redox-active ligand systems to a new class of amperometric molecular sensing devices, they also promise to exhibit exciting new redox catalytic properties by promoting redox reactions on an included guest substrate, and novel solid-state anisotropic electronic, magnetic, and optical (*49*) behavior.

ACKNOWLEDGMENTS

I thank my postgraduate and postdoctoral co-workers for undaunting motivation and determination to succeed in this multidisciplinary research field; their names appear in the references. Special thanks go to Dr. M. G. B. Drew for his many structure determinations and molecular mechanics calculations. I gratefully acknowledge the financial support of the SERC, ICI Specialties, ICI Pharmaceuticals, ICI Chemicals and Polymers, BP (Sunbury), MediSense, Ministry of Defence, Kodak, Serpentix, Unilever, The Royal Society, NATO, Research Corporation Trust, and L. and D. Blond.

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