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Letter

Synthesis of a ferrocene-linked biscyclam: a new type of redox active bismacrocyclic ligand

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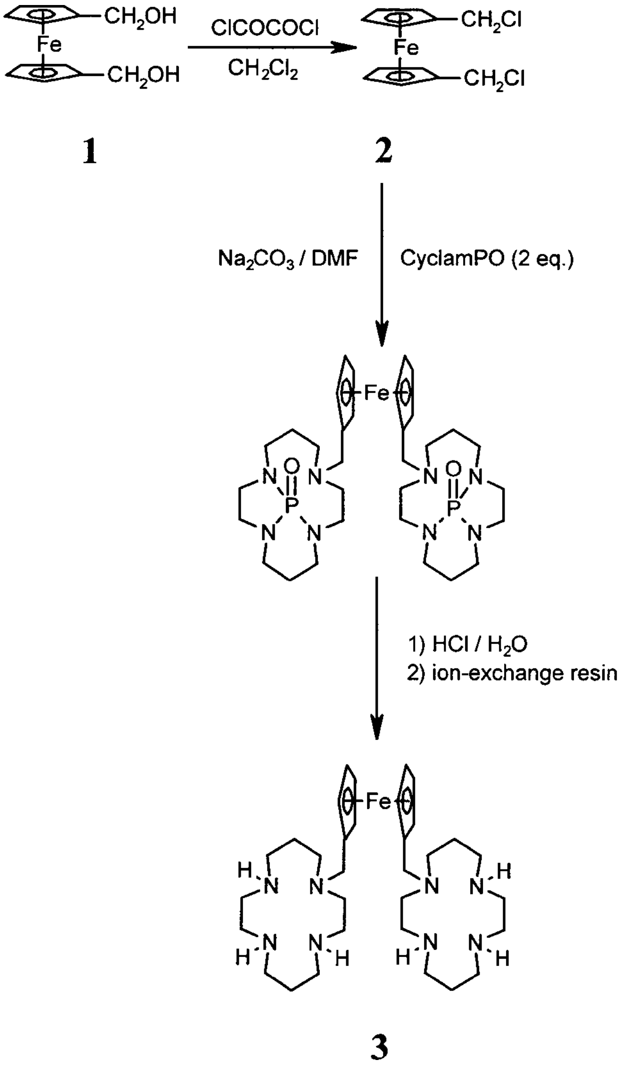
Making use of a selective mono-*N*-alkylation method for tetraazamacrocycles, through the cyclam phosphoryl intermediate, the synthesis of a new redox-active ferrocene-bridged biscyclam is described; strong electrostatic interactions in the binuclear metal complexes (M = Ni, Cu) are electrochemically detected.

Functionalisation of polyazamacrocycles, such as porphyrins and more specifically cyclam (1,4,8,11-tetraazacyclotetradecane), by substituents such as ferrocene has led to a new type of redox active ligands.[1–6] These syntheses have been widely developed for electrochemical recognition and sensing of anionic and cationic substrates.[3] Another source of interest for redox-active ligands stems from the possibility of electrochemical commutation of the properties of their metal complexes, *via* the oxidation state of the ligand. This property can find applications in the area of molecular electronics, multiredox reactivity, catalysis and biomimetic chemistry.[1,2,4,6] We have been interested for a long time by the enhancement of electronic and reactional properties of bimetallic derivatives in which the two sites interact strongly through a face-to-face configuration.[7] This led us to the idea that bismacrocyclic ligands in which the two rings are cofacially linked by an electroactive bridge should result in metal complexes with unusual molecular switchable features of interest in the area of electronic and reactional properties, and small molecule tandem activation. In view of the richness of its coordination chemistry and reactional activity of its metal complexes cyclam appears especially interesting.

We report here the synthesis and characterisation of 1,1′-dimethylferrocenyl bis(1,4,8,11-tetraazacyclotetradecane) and its metal complexes with Ni(II) and Cu(II). In the series of cyclam-appended ferrocenes,[1,3,4,8] this biscyclam ligand is the first in which two cyclams are linked by only one ferrocene bridge. A closely related example was recently reported by Plenio and Aberle, chromatographically isolated as an oligomer from a reaction mixture.[1] In that case the two cyclams were bis-bridged by two ferrocene moieties. The di-*N*-alkylation could hamper their coordinating ability; the characterisation and properties of this ligand and its metal complexes were not described. Some of us have shown that our stoichiometric triprotection method *via* the cyclam phosphoryl derivative is particularly well-suited for the synthesis of bistetraazamacrocycles.[9] The triprotected intermediate, cyclam phosphoryl, is particularly stable under various conditions, and the phosphoryl group is easily removed by acidic hydrolysis at room temperature. These very soft deprotection conditions as compared to detosylation,[10] allow *N*-alkylation by some fragile substituents. Moreover, this method does not necessitate chromatographic separations of mixtures of the mono-, di-, tri- and tetra-substituted derivatives as with other convenient protective groups.[11] Reaction of oxalylchloride on 1,1′-ferrocenedimethanol **1** resulted in the biselectrophile derivative 1,1′-bis(chloromethyl)ferrocene **2**, which reacted with 2 equiv. of cyclam phosphoryl. By acidic treatment the protecting groups were removed; the biscyclam-ferrocene **3** precipitated in ethanol and was isolated as the hydrochloride salt. The free base octaamine was obtained in 47% yield by neutralisation through a strongly basic exchange resin (Scheme 1).



Scheme 1

Table 1 Electrochemical data for **3** and its dinickel and dicopper complexes[a]

	E'° (ΔE_p)	
	Fc^+/Fc	M^{III}/M^{II}
3	0.00(100)	—
[Ni cyclam]$(BF_4)_2$	—	0.63(80)
[Ni_2(**3**)]$(BF_4)_4$	0.23(100)	0.88(160)
[Cu cyclam]$(BF_4)_2$	—	1.03(100)
[Cu_2(**3**)]$(BF_4)_4$	0.24(140)	$E_{p_{ox}} = 1.57$

[a] Data determined by cyclic voltammetry in CH_3CN using Bu_4NPF_6 as supporting electrolyte. (Pt electrode, 0.1 V s^{-1}). E'° (V) = $0.5(E_{p_a} + E_{p_c})$, $\Delta E_p = E_{p_a} - E_{p_c}$ (mV), $E_{p_{ox}}$ (V) is the oxidation peak potential for an irreversible system; potentials *vs.* Fc^+/Fc.

We have prepared binuclear transition metal complexes of **3**. These complexes were obtained through a classical metallation procedure by reaction of **3** with 2 equiv. of $Ni(BF_4)_2$ or $Cu(BF_4)_2$.

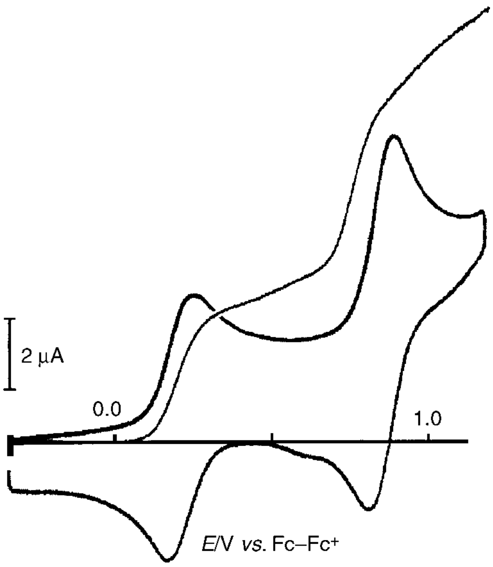


Fig. 1 Cyclic and rotating disk voltammograms of a 1×10^{-3} mol dm^{-3} solution of [Ni_2(**3**)]$(BF_4)_4$ in MeCN containing Bu_4NPF_6 (0.2 mol dm^{-3}) on a platinum electrode [sweep rate = 0.1 V s^{-1} (CV) and 0.01 V s^{-1} (RDV)]. Potentials *vs.* ferrocene.

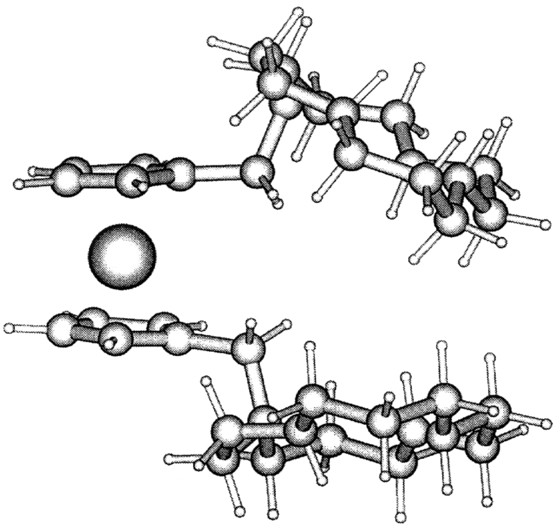


Fig. 2 Molecular modelisation of **3**. Stable cofacial geometry (dihedral angle between the CH_2 axes and the two cis macrocyclic planes = 12.5°).

Such complexes bear two types of electroactive entities, the ferrocene-bridging moiety and the two equivalent [M(II)cyclam] complexes [M = Ni(II) or Cu(II)]. Electrochemical data obtained by cyclic voltammetry in acetonitrile are listed in Table 1. For the uncomplexed ligand **3** it is shown that substitution of two cyclam units on the ferrocene does not affect the redox potential of the Fc^+/Fc system. In the case of the metal complexes, two systems in oxidation can be seen: the first corresponds to the Fc^+/Fc exchange and the second to the M(III)/M(II) redox process. For M = Ni, both systems are fully reversible. As could be expected, by cyclic voltammetry, the current of the second peak is almost twice as intense as the first one, as shown in Fig. 1. This result is corroborated by the heights of the rotating disk voltammetry also shown in this figure. In the case of [Cu_2(**3**)]$(BF_4)_4$, the Cu(III)/Cu(II) redox system is irreversible. This irreversibility could be explained by the high reactivity of Cu(III) species, as well as by modification of the coordination.[8,12] In any case, the two [M(II)cyclam] moieties are oxidised at the same potentials, this is perfectly clear in the case of Ni (Fig. 1). This indicates no mixed valence behaviour, and consequently no mutual interactions at the electrochemical level, either electrostatic or face-to-face, between the two cyclam moieties. However, Table 1 clearly indicates that the presence of two cations {2 [M(II)cyclam]} induces a positive redox shift, *ca.* $\Delta E'_0 \approx 230$ mV, of the ferrocene system. It might be fortuitous that the M(III)/M(II) systems (M = Cu, Ni) are also both shifted by an approximately equal amount. This indicates that both systems are under an electronic effect. The influence of *N*-substitution on the oxidation potential of metal cyclam derivatives is weak,[4,8,12] and the substitution on the cyclopentadienyl does not affect the Fc^+/Fc system, as shown by compound **3** (Table 1). The positive shift of both systems can thus be ascribed to a mutual electrostatic repulsive interaction between the ferrocene moiety and the two cyclam complexes. Such an effect has been recorded in the case of a ferrocene mono-substituted cyclam but to a much lower extent.[4] The present shift is comparable to that recorded for a monometallic complex of the ferrocene-disubstituted cyclam,[1] but the geometry of that compound and its coordination ability are totally different. Molecular mechanics calculations indicate, in the case of free ligand **3** (Fig. 2), that the cofacial geometry with a centre-to-centre distance of about 6 Å is a stable configuration, adequate for direct face-to-face interactions and bridged substrate when complexed by two metallic cations.[7]

In summary, we have developed a practical and straightforward method for the synthesis of a new redox-active biscyclam ligand potentially leading to cofacial metal complexes. The positive potential shift of the M(III)/M(II) system reveals an important redox switching effect of the ferrocene linking bridge.[1] An intermetallic site is made available for a bridging substrate for multinuclear tandem activation, eventually under the control of the switching effect of the ferrocene moiety. Properties of additional complexes are currently under investigation.

Experimental

Synthesis of 1,1′-bis(chloromethyl)ferrocene 2

1,1′-Ferrocenedimethanol **1** (247 mg, 1 mmol) in dichloromethane (30 mL) was added to a ice-cooled solution of oxalyl chloride (350 μL, 4 mmol) in dichloromethane (5 mL). The cold reaction mixture was stirred overnight at room temperature. The solvent and the excess of oxalyl chloride were evaporated. The residue (yellow powder) was used without purification (100%). ^1H NMR ($CDCl_3$, δ) 4.43 (s, 4H, $CpCH_2Cl$), 4.21–4.28 (m, 8H, H_{Cp}); ^{13}C NMR ($CDCl_3$, δ) 43.1 ($CpCH_2Cl$), 69.5, 69.7, 85.0 (C_{Cp}).

Synthesis of biscyclam-ferrocene 3

Cyclamphosphoryl (490 mg, 2 mmol), Na_2CO_3 and 1,1′-bis(chloromethyl)ferrocene (1 mmol) were added to DMF (15 mL) and heated at 100 °C for 4 h. After evaporation to dryness and addition of dichloromethane, the mixture was filtered. The filtrate was evaporated and the residue was stirred in 4 M hydrochloric solution (5 mL) for 3 h at room temperature. The solution was reduced to half under vacuum and ethanol (20 mL) was added. The precipitate was washed by ethanol and dried (yield of isolated hydrochloride: 63%). The residue was dissolved in water (2 mL) and liberated on an Amberlyst A-26 ion-exchange resin. The basic aqueous solution was evaporated to dryness. The crude product was recrystallised from acetonitrile to yield the biscyclam-ferrocene as a yellow solid in 47% yield. APCIMS: 611.5 $(M + H)^+$; mp 106–108 °C; ^1H NMR ($CDCl_3$, δ): 1.65–1.75 (m, 8H, CH_2CH_2N), 2.35–2.75 (m, 32H, CH_2N), 3.00 (m, 6H, NH), 3.55 (s, 4H, $CpCH_2N$), 4.00–4.04 (m, 8H, H_{Cp}); ^{13}C NMR ($CDCl_3$, δ): 25.8, 29.0 (CH_2CH_2N), 47.2, 48.0, 49.0, 49.5, 49.9, 50.3, 50.8, 51.9, 53.9 (CH_2N), 68.4, 70.7, 81.1 (C in Cp). Anal. calcd. for $C_{32}H_{58}N_8Fe \cdot H_2O$: C, 61.12; H, 9.62; N, 17.83; Fe, 8.88. Found: C, 61.14; H, 9.73; N, 17.53; Fe, 8.95.

Synthesis of dinuclear complexes

$M(BF_4)_2$ (0.6 mmol) in ethanol (3 mL) was added to a solution of biscyclam-ferrocene **3** (183 mg, 0.3 mmol) in ethanol (5 mL). The mixture was refluxed for 0.5 h. The metallation reaction was controlled by UV-Visible spectrophotometry $[\lambda_{max}([Ni_2(3)](BF_4)_4) = 452$ nm, $\lambda_{max}([Cu_2(3)](BF_4)_4) = 553$ nm]. The mixture was then cooled, the precipitate was recovered by filtration and recrystallised in methanol. Anal. calcd. for $C_{32}H_{58}N_8FeCu_2B_4F_{16}$: C, 35.42; H, 5.39; N, 10.33; Cu, 11.71; Fe, 5.15. Found: C, 35.52; H, 5.65; N, 10.17; Cu, 11.41; Fe, 5.46. Anal. calcd. for $C_{32}H_{58}N_8FeNi_2B_4F_{16}$: C, 35.76; H, 5.44; N, 10.42; Ni, 10.92; Fe, 5.19. Found: C, 35.84; H, 5.51; N, 10.21; Ni, 10.60; Fe, 5.04.

Computational procedure

Molecular modeling of **3** was accomplished with the program SYBYL on a Silicon Graphics station.[13] Trial structures of the various conformers of **3** were generated and a conformational search was made to find its optimum geometry.

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