EPR detection of alkali-metal cations using novel spin-labelled macrocyclic sensors

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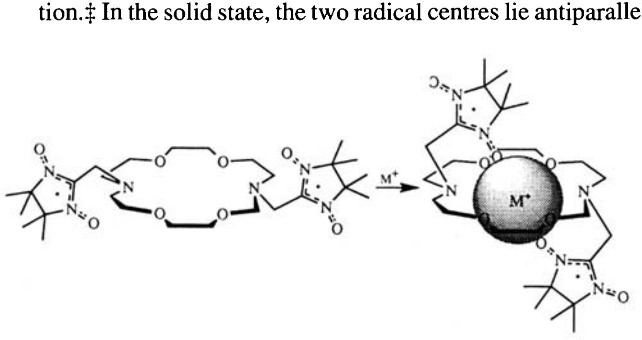
The efficacy with which polyazamacrocycles grafted with multiple nitronyl nitroxide spin labels function as EPR-active sensors for metal cations depends upon the ability of the cation to disrupt spin–spin exchange interactions between adjacent radical centres.

Recent studies have resulted in the design of spin-labelled crown ethers and cryptands possessing one or more sterically hindered nitroxo radicals appended to the macrocycle.[1–3] In several cases, cation insertion into the central cavity is accompanied by interaction between the nitroxide O atom and the guest. These realizations suggest that sensitive EPR-based probes for alkali-metal cations could be constructed by combining the unique complexing properties of macrocyclic receptors with the magnetic properties of nitroxo radicals. In this respect, the ability to attach multiple radical centres to the macrocycle provides the opportunity to use the encapsulated cation as a template with which to organize the internal structure and thereby modulate mutual coupling between radicals (Scheme 1). Although spin-labelled benzo-15-crown-5 derivatives are known to give triplet EPR spectra upon complexation with alkali or alkaline-earth cations[4] this is a simple hydrophobic effect that is unrelated to spin–spin exchange between the radical sites.[5]

Following our synthetic strategy developed for the preparation of high-spin calix[4]arene sensors,[6] a series of related spin-labelled polyazamacrocycles has been prepared (Fig. 1). The mono-radical based molecular fragments **1** and **2** provide important controls and, in particular, **2** allows discrimination between hydrophobic and cavity effects.[5] The macrocycles were selected so as to give a small range of differing affinity towards alkali-metal cations; note that **3** possesses both N and O macrocyclic donor sites. The proposed binding mode (Scheme 1) demands that the radical centre lies close to the macrocyclic cavity but retains rotational mobility. Compounds **3–5** were obtained by reacting the corresponding polyazamacrocycle (1 equiv.) with monoradical **1**, with KI as catalyst and K_2CO_3 as base. The polyradicals, being EPR-active, were obtained as deep-red crystals.†

Macrocycle **3**, which is the most interesting of the new sensors and has been termed *kryptospin* by analogy with its 18-N_2O_4 kryptofix precursor, was studied by X-ray diffraction.‡ In the solid state, the two radical centres lie antiparallel on opposite sides of the macrocyclic cavity, without obscuring the central void (Fig. 2). The macrocyclic donor atoms occupy the twist-boat structure commonly found in crown ethers,[7] with the oxygen atoms directed towards the centre. This configuration is particularly favourable for complexation of added cations and we note that the respective bond distances and angles are such that the appended radicals should approach a bound cation. Any resulting interaction (Scheme 1) could assist stabilization of the complex and, in fact, unequivocal evidence for side-arm coordination to a sequested cation has been reported for a related, but non-paramagnetic, macrocycle.[8] The nitroxyl rings



Scheme 1

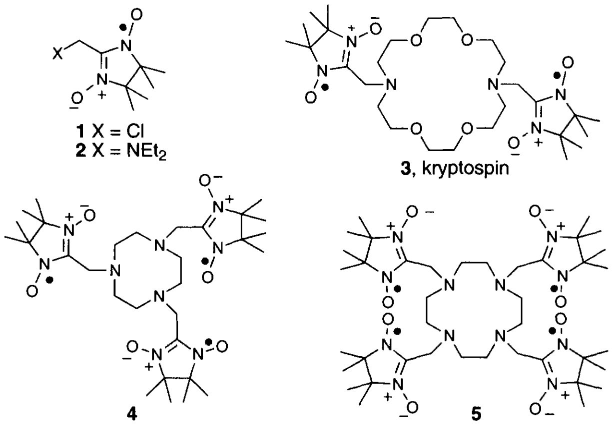


Fig. 1

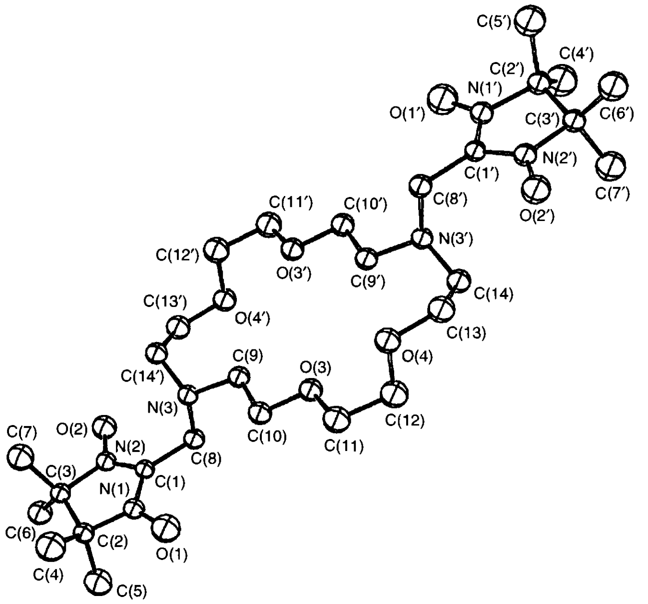


Fig. 2 ORTEP plot of the crystal structure of kryptospin **3**

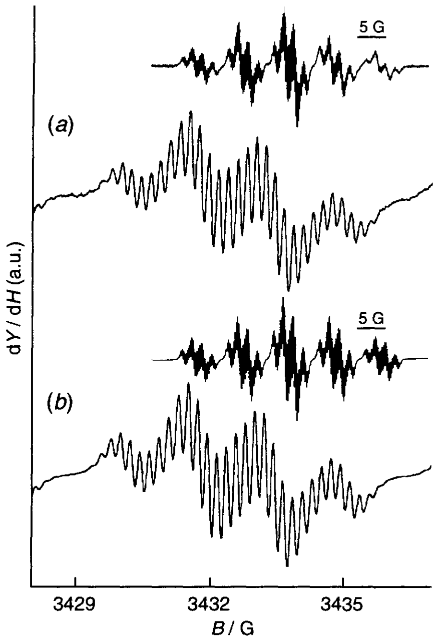


Fig. 3 Central lines of the EPR spectra of radical **2** at room temperature [10^{-4} mol dm^{-3} in dichloromethane–toluene (1 : 1)]: (*a*) experimental and (*b*) simulated spectra [a_N(ONCNO) = 7.45 G, a_N(NEt$_2$) = 0.84 G, $a_{\alpha\text{-H}}$(CH$_2$) = 1.50 G, a_H(CH$_3$) = 0.205 G]. The best simulation is achieved for the individual nearly Gaussian line shape with the line width ΔB_{pp} = 0.18 G. The whole spectra, exhibiting five-line structures, are represented in the insets.

are non-planar with equivalent N–O bond lengths [1.275(3), 1.279(3) Å] due to delocalization of the odd electron.

Room-temperature EPR studies were performed at X-band irradiation with magnetically dilute solutions in deoxygenated dichloromethane–toluene. The EPR spectrum of **2**, this being a reference compound, together with its simulation is shown in Fig. 3. Precise simulation requires that the two nitroxide groups are equivalent and that there is pronounced hyperfine coupling between the radical centre and (*i*) the acyclic nitrogen, (*ii*) the acyclic methylene protons and (*iii*) the twelve methyl protons.[9,10] In contrast, EPR spectra recorded for the free ligand **3** exhibited an obvious nonet band shape, which can only arise from mutual spin–spin interaction between the two appended nitroxo radicals. Because these experiments are conducted with magnetically dilute solutions it is clear that this coupling involves through-space interaction. Orbital contact between the radical centres requires that the macrocycle is highly flexible in solution.

Addition of a cation (Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$) to the solution of kryptospin **3** had a dramatic effect on the EPR spectrum; no such changes are observed with the reference compound **2**. In the extreme cases, the spectrum observed in the presence of Li$^+$ is a quintet while that observed in the presence of Cs$^+$ shows the same quintet but with well resolved hyperfine coupling superimposed onto the main lines (Fig. 4). Detailed analysis of the latter spectrum required hyperfine coupling constants of a_N(ONCNO) = 7.60 G, $a_{\alpha\text{-H}}$(CH$_2$) = 1.60 G and a_N(NCH$_2$) = 0.65 G for proper simulation. Intermediate cases showed that increasing the cationic radius resulted in a gradual enhancement of the resolution of the superimposed hyperfine coupling (Fig. 4).

Under the conditions of these experiments the cation is complexed by the crown ether, with larger cations providing a more rigid macrocyclic core. On this basis the effect of Li$^+$ is to diminish the extent of through-space spin–spin exchange interaction between the two radical centres. The larger Cs$^+$ cation can itself interact with individual radicals according to Scheme 1. This situation provides for increased stabilization of the inclusion complex by way of metal to oxygen bonding but provides a steric barrier that prevents coupling between the terminal radical centres. In this way the size of the included cation controls the extent of spin–spin coupling by simple steric factors with the larger cations preventing free rotation of the side arms.

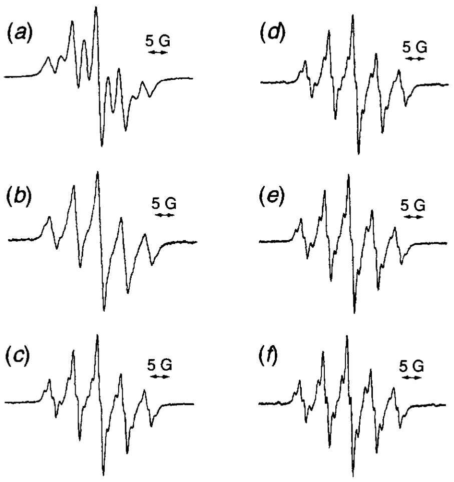


Fig. 4 EPR spectra of diradical **3** at room temperature [10^{-4} mol dm^{-3} in dichloromethane–toluene (1 : 1)]: (*a*) in the absence of alkali-metal salts, and in the presence of (*b*) Li$^+$, (*c*) Na$^+$, (*d*) K$^+$, (*e*) Rb$^+$, (*f*) Cs$^+$

Interestingly, the presence of donor oxygen atoms within the macrocycle itself is mandatory for formulation of effective sensors. This is clearly demonstrated by the observation that added cations do not significantly perturb the level of spin–spin exchange in polyazamacrocycles **4** and **5**. With these receptors, whose EPR properties closely resemble those of **3**, there is little or no inclusion of the cation into the central void. By combining the observations made with **2** and **4** it becomes apparent that only macrocycles having high binding affinities can be considered as suitable scaffolds for development of EPR-based sensors.

Footnotes

† Compounds were characterized by FAB$^+$, UV–VIS, IR, susceptibility measurements and gave satisfactory elemental analyses for C, H, N in agreement with their structure.

‡ *Crystal data* for **3**: $C_{28}H_{52}N_6O_8$, M_r = 600.8, monoclinic, space group $P2_1/n$, a = 6.185(1), b = 23.480(7), c = 11.028(3) Å, β = 102.17(2)°, U = 1565.5 Å^3, Z = 2, D_c = 1.274 g cm^{-3}, R = 0.047, R_w = 0.068 for 1889 reflections with $I > 3\sigma(I)$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/254.

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