

## Synthesis of Two Stereochemically Distinct Chiral Di-nitroxide Crown Ethers

Hermann Dugas\*<sup>a</sup> and Marius Ptak<sup>b</sup>

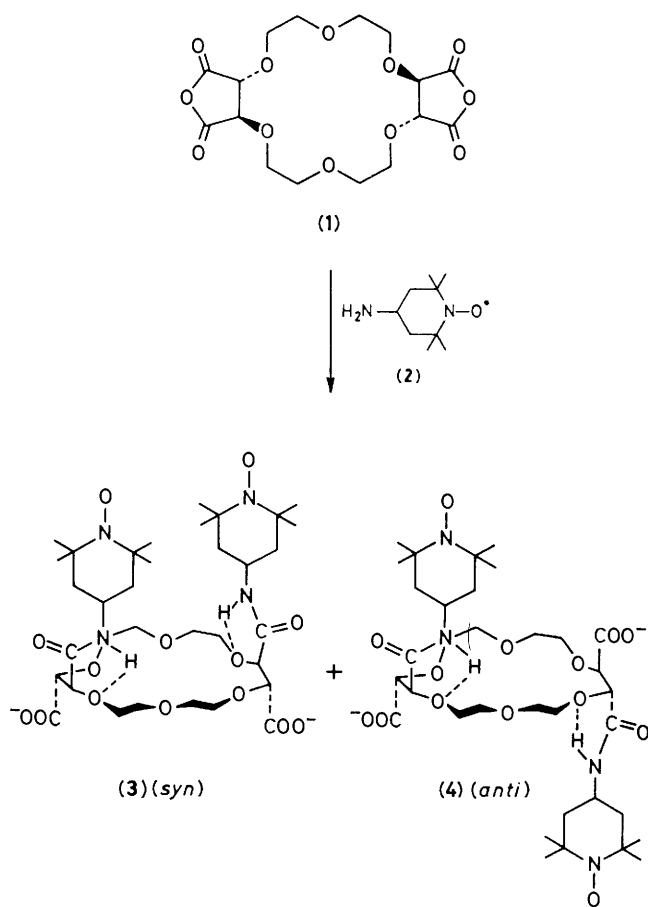
<sup>a</sup> *Département de Chimie, Université de Montréal, Montréal, Québec, Canada H3C 3V1*

<sup>b</sup> *Centre de Biophysique Moléculaire, C.N.R.S., 45045 Orléans Cédex, France*

The first synthesis of two stereochemically distinct di-nitroxide-18-crown-6 ethers, the *syn*-(**3**) and *anti*-(**4**) isomers is described and the presence of a spin-spin interaction for the *syn*-isomer (**3**) is used as a spectral parameter to follow the binding of K<sup>+</sup> ion to the crown ether.

Spin labelling of crown ethers could be of considerable help in the understanding of their intrinsic structural properties as well as their cation-complexing and possibly cation-transporting behaviour. To date, only a few mono-spin-labelled crown ethers have been synthesized and used to investigate alkali-

metal complexation by e.s.r. spectroscopy.<sup>1,2</sup> We now report the first synthesis of the two chiral di-nitroxide-di-acid-18-crown-6 ethers (**3**) and (**4**). The guiding assumption for this work was that in a diradical the spin-spin interaction, which depends on the respective positions and motions of the



Scheme 1

nitroxide groups, should enable us to analyse conformations of the molecule alone or interacting with a cation.

The controlled introduction of a nitroxide radical on either side of the crown ether ring was based on a modification of a chiral tetra-functionalized macrocycle recently developed by Lehn and co-workers.<sup>3,4</sup> As shown in Scheme 1, the di-nitroxides were obtained by reaction of the (+)-(*R,R*)-di-anhydride (1) with 4-amino-2,2,6,6-tetramethylpiperidine 1-oxyl (2) at room temperature in dichloromethane according to the procedure of Behr *et al.*<sup>5,6</sup> In this way a mixture (85% yield) of about equal amounts of the *syn*-(3) and *anti*-(4) isomers was obtained as an orange oil. However, in the presence of an excess of triethylamine,<sup>4</sup> the *syn*-isomer (3) was formed almost exclusively (90% yield). The compounds were purified by chromatography on silica gel (elution with chloroform-methanol) and then by a Dowex 50-X8 (H<sup>+</sup> form) ion-exchange column.† The structural assignments are based on previous work by Lehn's group.<sup>4</sup>

The e.s.r. spectrum of the *anti*-isomer (4) showed no spin-spin exchange signal for the ligand or the K<sup>+</sup>-complex since the distance between the nitroxide groups on either side of the crown ether ring exceeds 18 Å. On the other hand, a spin-spin exchange interaction was readily detected at room temperature in the e.s.r. spectrum of the *syn*-isomer (3), which is very sensitive to the presence of alkali metals. As shown in Figure 1, one can then follow qualitatively the complexation of K<sup>+</sup> in ethanolic solution in which the stability constant should be especially high (values in the range of 10<sup>4</sup> l mol<sup>-1</sup> have been found for parent compounds such as the *syn*-di-anilide<sup>4</sup>).

On addition of K<sup>+</sup> (KSCN), small broad intermediate lines ( $M_1 = \pm 1$ ) become visible between the main lines ( $M_1 = \pm 2$ ) which clearly demonstrate that the spin-spin exchange is modified by the complexation process. The presence of common points of intersection or isoclinic points<sup>7</sup> in the first-derivative spectra is characteristic of an equilibrium between two spectrally active states. Notice that the maximal spectral change is obtained for  $K^+/(3) > 3$ , *i.e.* in the presence of an

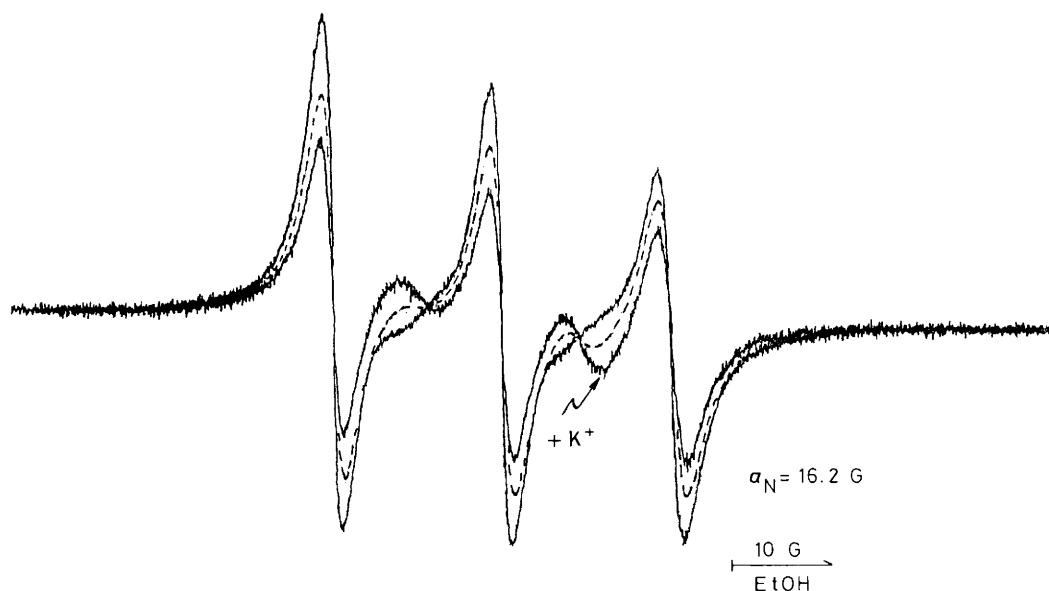
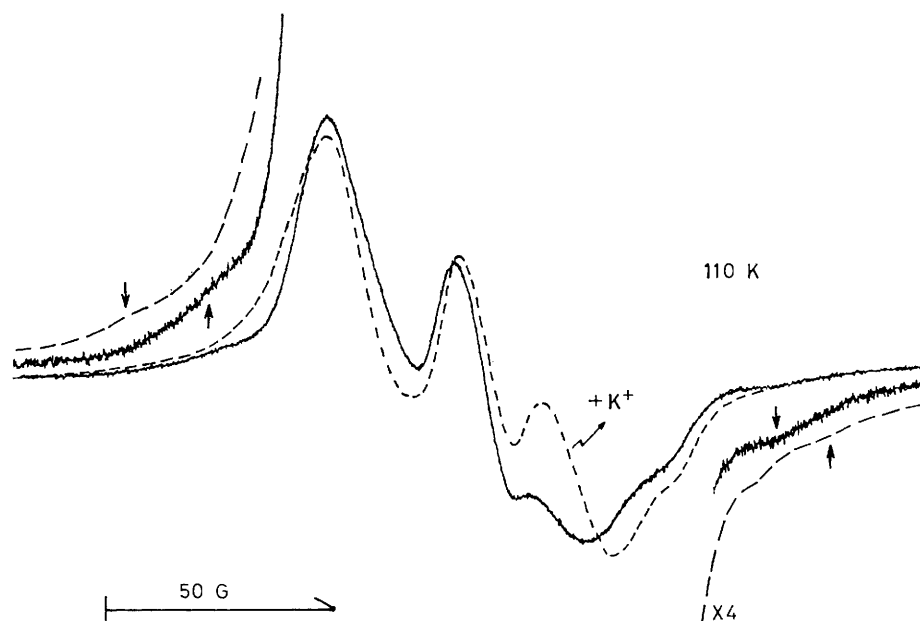


Figure 1. E.s.r. spectra (Bruker ER 200 D; 9.40 GHz, 3350 G) of the di-nitroxide *syn*-isomer (3) in ethanol ( $10^{-3}$  mol l<sup>-1</sup>) at 20 °C (undegassed), with and without potassium ion (KSCN). The dotted spectrum is for  $K^+/(3) = 3$  and that indicated by the arrow corresponds to the presence of a large excess of K<sup>+</sup>.

† Both compounds gave satisfactory elemental analyses.



**Figure 2.** E.s.r. spectra of the di-nitroxide *syn*-isomer (3) in ethanol at 110 K. The dotted lines correspond to the spectrum of the crown ether- $K^+$  complex. The dipolar splitting was evaluated from the distance between the arrows.

excess of  $K^+$  ion. This observation is not unusual since it emphasizes the crucial role played by the carboxy-groups on one side of the crown ether ring, where their state of ionization and their interaction with counterions seem to influence the distance between the two nitroxide groups on the other side of the ring. This environmental effect is likely to be superimposed on the specific cavity effect. A sound method of analysis is required to correlate these spectral modifications to changes in the conformation of the molecule or to intramolecular motion since the linewidths of the  $M_I = \pm 1$  lines are strongly dependent on the modulation of the exchange integral.<sup>8</sup>

To evaluate the distance between the nitroxide groups, the e.s.r. spectrum (Figure 2) of the *syn*-isomer (3) was recorded in a frozen matrix of ethanol at 110 K (at this temperature, the  $\Delta M_s = 2$  transition was also observed at 1662 G). The largest splitting (arrows) corresponds to the dipolar interaction for the  $z$ -axis and the values estimated were:  $2D = 121 \pm 4$  G and  $153 \pm 5$  G in the presence of  $K^+$ . The average distance between the unpaired electrons of each nitroxide group was calculated in the point-dipole approximation.<sup>9</sup> Using the equation  $D_{\text{obs}} = 12.74 + 2.009 \times 10^4/r^3$  it was estimated that  $r = 7.4 \pm 0.2$  Å for (3) and  $6.8 \pm 0.2$  Å in the presence of  $K^+$ . Although the error in the evaluation of the  $D$ -parameter is rather large, a marked difference is seen between the complexed and non-complexed forms of (3). Furthermore, the distance of 7.4 Å observed between the two nitroxide groups agrees quite well with an average distance of 7.2 Å found for the corresponding *syn*-di-anilide-compound, an  $X$ -ray diffraction study of which showed that the functionalized groups are approximately perpendicular (axially oriented) to the plane of the

crown ether ring.<sup>4,6</sup> Such a conformation could be stabilized by hydrogen bonds between the N-H of the amide functions and an oxygen of the crown ether ring.<sup>10</sup>

The spin-spin exchange observed for molecule (3) is affected by temperature, solvent polarity, hydration, the state of ionization of the carboxy-groups, *etc.* and this will be discussed elsewhere.

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