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of lower metal oxidation states in nonaqueous solvents. This is similar to the results obtained for rhodium porphyrins. However, the data for $[\mathrm{Rh(py)_4Cl_2}]\mathrm{Cl}$ also indicate the electrogenerated species react with several different reagents and that the less rigid ligand set allows observation of new chemical pathways.

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Registry No. TBAP, 1923-70-2; (TBA)(Cl), 1112-67-0; py, 110-86-1; *trans*-$[\mathrm{Rh(py)_4Cl_2}]\mathrm{Cl}$, 14077-30-6; Rh, 7440-16-6; acetonitrile, 75-05-8; water, 7732-18-5; methyl iodide, 74-88-4.

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Solution Conformations of $\mathrm{CaCl_2}$ and $\mathrm{Ca(NO_3)_2}$ Complexes of Chiral Tetramethyl 18-Crown-6 Macrocycles: A 1D and 2D ^{1}H and ^{13}C NMR Investigation

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One- and two-dimensional NMR techniques have been used to investigate the solution structures of (2*S*,6*S*,11*S*,15*S*)-2,6,11,15-tetramethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (I) and (2*R*,3*R*,11*R*,12*R*)-2,3,11,12-tetramethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (II) macrocycle complexes of $\mathrm{CaCl_2}$ and $\mathrm{Ca(NO_3)_2}$ in $\mathrm{CDCl_3}$. Previous chiroptical studies of these and similar crown complexes by circularly polarized luminescence (CPL), total luminescence (TL), and circular dichroism (CD) spectroscopy have shown that the macrocycle asymmetric carbons in these complexes constrain the ring such that the sense of the ring twist in the *S* chiral ring complexes is opposite to that in the *R* chiral ring complexes. These studies have also shown that there is an added chirality element in the di- and trivalent (alkaline earth and lanthanide metal, respectively) nitrate complexes of I and II associated with the twist of the nitrate anions relative to one another as they sterically interact with the ring methyl groups. It has been proposed that channels are created on each face of the macrocycle ring by the axially positioned methyl groups in the solution structures of the I and II complexes and that the planar nitrate anions are constrained to fit in these channels. In this study, we show that the NMR data do indeed support the prominent axial positioning of the methyl groups in the $\mathrm{CaCl_2}$ and $\mathrm{Ca(NO_3)_2}$ complexes of I and II in solution. Furthermore, the NMR data are consistent with the assertion that the *S* chiral ring (I) twists in an opposite sense to the *R* chiral ring in these complexes. The data for this conformational analysis were obtained by exploiting coupling constant information and the nuclear Overhauser effect, observed by using both one- and two-dimensional NMR techniques.

Introduction

Recently reported chiroptical studies of the solution interactions of chiral crown ether hosts with cations have included the total luminescence (TL), circularly polarized luminescence (CPL), and circular dichroism (CD) spectroscopy of complexes of (2*S*,6*S*,11*S*,15*S*)-2,6,11,15-tetramethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (I) and (2*R*,3*R*,11*R*,12*R*)-2,3,11,12-tetramethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (II)[1–4] (Figure 1).

Of particular interest are the complexes of the alkaline-earth-metal nitrates and of europium nitrate. Analysis of the chiroptical spectra of these complexes has led to the hypothesis of an unusual contribution to the chirality due to the relative orientation of the two associated nitrate anions in the complexes. In both the alkaline-earth and lanthanide complexes spectral and other data indicate that two nitrates are bound (or ion paired) through two oxygens, one nitrate on each "face" of the otherwise flat macrocycle complex. The anions form a two-bladed propeller, the pitch of which is proposed to be influenced by steric interaction with the methyl substituents on the macrocycle ring. The difference in spacing of the methyls around the ring in I and II predicts a different pitch for the dinitrate propeller in the complexes of these isomeric macrocycles and thus a different contribution to the total chirality.

The n → π* $\mathrm{NO_3^-}$ CD spectra of the alkali-metal ($\mathrm{M^+ = Li^+}$, $\mathrm{Na^+}$, $\mathrm{K^+}$, $\mathrm{Rb^+}$) nitrate complexes of I and II have a pseudoenantiomorphic, mirror image intensity relationship. However, this relationship is not observed between the corresponding complexes of the alkaline earths ($\mathrm{M^{2+} = Mg^{2+}}$, $\mathrm{Ca^{2+}}$, $\mathrm{Sr^{2+}}$, $\mathrm{Ba^{2+}}$), where two nitrates are associated. Furthermore, in the crystal structure of the $\mathrm{Ca(NO_3)_2}$ complex of II there is a strong indication that the four axially oriented methyl groups in effect create channels across the faces of the macrocycle into which the $\mathrm{NO_3^-}$ anions fit. Although no analogous crystal structure data are available for a complex of I, it is clear that its channels, if they exist, would be oriented at ca. 60° to each other, as opposed to almost parallel orientation in II (Figure 2). The influence of these channels is apparently also seen in the CPL spectra of the $\mathrm{Eu(NO_3)_3}$ complexes of I and II. (Extensive evidence supports a solution structure for the europium complex essentially identical with that of the alkaline-earth nitrate complexes, with one of the three nitrates not associated.) The fact that the CPL spectra of the europium *chloride* complexes of I and II are virtual mirror images, whereas those of the nitrate show no such relationship, again suggests that it is the nitrate anions which are, together, providing an additional source of chirality (not possible for the spherical chlorides).

This conclusion rests in part on the assumption that other sources of chirality in these complexes are substantially the same in I and II and that, for example, the chiral twist of the macrocycle ring differs only in handedness between the calcium or europium nitrate complexes of I and II. Although this is not an unreasonable assumption, it would be interesting to test it directly by probing the solution conformations of the macrocycle rings more directly. That is the purpose of the study reported here.

Although the numerous investigations of the solution conformations of crown ether macrocycles and their complexes have included a significant number of NMR studies,[5–10] these have all

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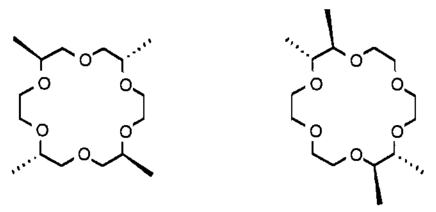

I II

Figure 1. The chiral tetramethyl macrocycles employed in this study.

Ia IIa

Figure 2. Schematic representation of the "channels" formed by the methyl substituents on the faces of the chiral crowns I and II. The methyl groups are represented by spheres, and dashed lines connect those on the same face of the macrocycle. The numbers correspond to those of the structures in Figure 1.

relied on one-dimensional ^1H and/or ^{13}C techniques. In one such investigation, Kleinpeter and co-workers[9] demonstrated that the ^1H–^1H nuclear Overhauser effect (NOE) may be exploited to yield crown macrocycle solution structure information. In that study, 1D NOE difference spectroscopy was used to probe nonbonded proton interactions, illustrating an interesting extension of NMR spectroscopy limited to one dimension. It is clear from such data that valuable insight into the solution structures of crown ethers and crown ether complexes may be obtained by using NMR methods.

However, one-dimensional NMR techniques are limited in their ability to consistently provide unambiguous results when NMR is the sole spectroscopic tool being used to probe molecular structure. The limitations of 1D NMR spectroscopy stem largely from the overlap of resonances, making accurate chemical shift and coupling constant assignments difficult. Furthermore, 1D techniques such as double-irradiation experiments and NOE difference spectroscopy are also limited by resonance overlap because of the requirement of selectivity for resonance irradiation.[11] By spreading the signal into the second dimension, 2D NMR spectroscopy is often able to overcome the obstacle of overlapping resonances. Extension into two dimensions of such techniques as COSY[12-14] NOESY,[15-17] and DQCOSY (double-quantum-filtered, phase-sensitive COSY)[18,19] further enhances the conformational analysis potential of NMR spectroscopy.

The goal of the study reported here was to probe the solution structures of the $CaCl_2$ and $Ca(NO_3)_2$ complexes of the tetramethyl 18-crown-6 macrocycles I and II by using both one- and two-dimensional NMR techniques. It is believed that conclusions about structure drawn from the study of the calcium complexes may be generalized to include the corresponding europium complexes as well. In this study we show that the NMR data are indeed consistent with the hypothesis that channels are created on each face of the complexed rings as the methyl groups protrude axially. While this investigation focused primarily on the relative orientations of the methyl groups in these complexes, the conformation of the entire carbon–hydrogen backbone was also considered, in light of the assertion that the *S* chiral ring (I) twists in an opposite sense from the *R* chiral ring (II).[1,4] Dipolar interactions were the most useful in our analysis because coupled nuclei need not be connected through-bond to provide information about one another. Hence, the 2D NOESY experiment[15-17] was the most important tool in this conformational analysis, with 1D NOE difference experiments[20-22] being referred to primarily for consistency with the 2D results. Finally, an advanced variation on the standard COSY experiment, double-quantum-filtered, phase-sensitive COSY (DQCOSY),[18,19] was necessary to obtain the chemical shift and *J*-coupling data reported in Table I (vide infra).

Experimental Section

All ^1H and ^{13}C NMR experiments reported for the $CaCl_2$ and $Ca(NO_3)_2$ complexes of (2*S*,6*S*,11*S*,15*S*)-2,6,11,15-tetramethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (I) and (2*R*,3*R*,11*R*,12*R*)-2,3,11,12-tetramethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (II) were performed at 25 °C, unless otherwise specified. All NMR samples were prepared under nitrogen in a dry glovebox with use of 100 atom % $CDCl_3$ (Sigma Chemical Co.).

The 2D homonuclear, double-quantum-filtered, phase-sensitive COSY (DQCOSY) experiments and homonuclear, phase-sensitive NOESY experiments reported for the above complexes were recorded by using 256 × 2K data points with zero-filling to 2K × 2K data points. All reported NOESY experiments were performed with a 200-ms mixing time to allow for evolution of the NOE. The 1D difference spectra were performed by irradiating the selected nucleus with low-power spectrometer decoupling for 5.0 s and recording the FID. A base-line FID recorded by irradiating a region of the spectrum far removed from all proton resonances was then subtracted from the proton-irradiated FID, and the resulting FID was Fourier-transformed to provide the difference spectrum. Except for 1D ^1H spectra of the $CaCl_2$–I and $Ca(NO_3)_2$–I complexes, all NMR experiments were performed at 300 MHz with a Varian XL-300 spectrometer. In order to verify the magnitudes of *J* values measured for the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I, ^1H spectra were taken at 500 MHz with a General Electric GN-500 spectrometer.

The crown ethers I and II used in this investigation were recovered from complexes prepared for previous studies,[1-4] and their purification was accomplished by dissolution of the complexes in freshly deionized water and subsequent extraction of the crown into carbon tetrachloride. Following rotary evaporation of the carbon tetrachloride solvent, the crowns were distilled under reduced pressure at 100 °C by using a Kugelrohr apparatus. The $CaCl_2$ and $Ca(NO_3)_2$ complexes of I and II were prepared by dissolving the freshly distilled crown in dry CH_2Cl_2, under nitrogen in a dry glovebox. Excess $CaCl_2$ or $Ca(NO_3)_2$ salt was added to the crown/CH_2Cl_2 solution, and the combined mixture was stirred for 24–48 h. The mixture was subsequently filtered through a sintered-glass frit to remove uncomplexed salts, and the solvent was then evaporated under reduced pressure to give the crude crown complex. The complex was further purified by twice recrystallizing it from 50% CH_2Cl_2/50% DME mixed solvent at room temperature. Samples of the complexes were dried under high vacuum prior to dissolution in $CDCl_3$ for NMR study.

The $CaCl_2$ and $Ca(NO_3)_2$ salts were dried in an Abderhalden drying apparatus at 101 °C and 0.01–0.005 Torr for 5 days prior to use with $Mg(ClO_4)_2$ as a desiccant. Methylene chloride used in the preparation of the crown complexes was dried over calcium hydride, and dimethoxyethane (DME) was dried over Na/benzophenone. Both DME and CH_2Cl_2 were distilled under dry N_2 prior to use and stored over molecular sieves. DME and CH_2Cl_2 used in this study were reagent grade and commercially available (Aldrich Chemical Co.). Solvents and salts were handled only under dry N_2 subsequent to drying so as to rigorously exclude moisture contamination.

Results

Before we focus on the data obtained from each crown complex, a brief description of some general characteristics of the NMR results is in order. In each ^1H NMR spectrum of the complexed I and II, a clearly resolved upfield doublet appears, while downfield multiplets appear with varying degrees of resolution. In each case, the single upfield doublet is assigned to the methyl protons of the

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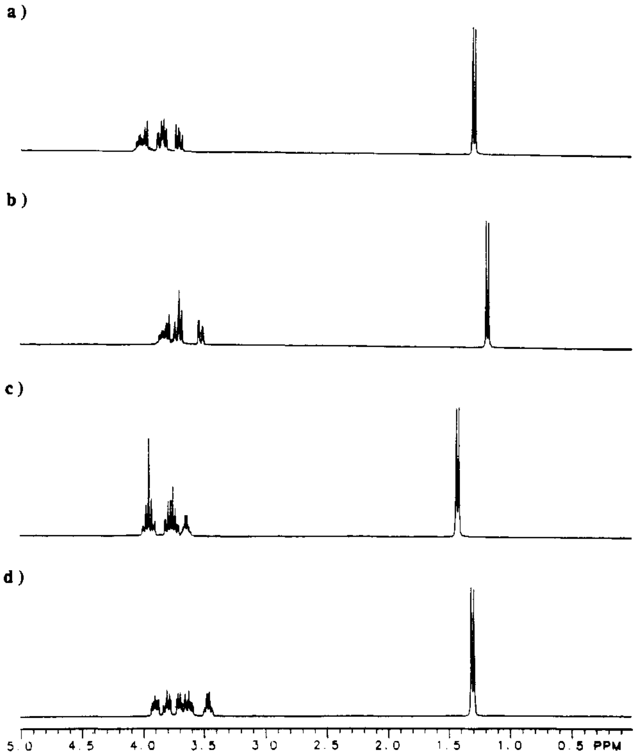


Figure 3. 300-MHz ^{1}H NMR spectra for (a) $CaCl_2$–I, (b) $Ca(NO_3)_2$–I, (c) $CaCl_2$–II, and (d) $Ca(NO_3)_2$–II complexes in $CDCl_3$ at 25 °C.

crown complex. This corresponds to one equivalent resonance for all 12 methyl protons in the complex. Integration of each ^{1}H NMR spectrum gives the expected 3:5 (12:20) ratio between the methyl protons and the remaining protons in the spectrum.

The ^{13}C NMR spectra of the complexes of I and II each show only four resonances with one peak upfield from the rest. This resonance is assigned to the methyl carbon in each case. The ^{13}C NMR spectra of the $Ca(NO_3)_2$ complexes of I and II at −55 °C show that these four peaks persist at low temperature as well, with no indication of additional peaks being "frozen out". These four carbon signals do, however, lose intensity at this lowered temperature, but this is attributed to decreased solubility. The remaining three ^{13}C resonances are assigned to the methine signal and two nonequivalent methylene signals, consistent with a conformation having four equivalent methyl carbons, methine carbons, and two groups of four equivalent methylene carbons, with no indications of signal averaging.

The pattern of equivalence observed in the ^{13}C NMR spectra is also seen in the homonuclear DQCOSY spectra of the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I and II. In each complex, only one methyl resonance, one methine resonance, and four nonequivalent methylene resonances are observed in the ^{1}H spectrum, which when integrated, correspond to 12 equivalent methyl protons, four equivalent methine protons, and four groups of four equivalent methylene protons, respectively. The four methylene resonances have been arbitrarily labeled H_{a-d} in order of decreasing chemical shift. In each complex, the combined results of the ^{1}H and ^{13}C NMR and DQCOSY spectra indicate a highly symmetrical solution structure.

The proton chemical shifts of the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I and II are shown in Table I, and the 1D ^{1}H spectra for each complex are shown in Figure 3. In both complexes of I, the DQCOSY spectra (Figure 4) indicate that the methylene protons H_a and H_c are coupled to one another, as are H_b and H_d. Furthermore, the methine proton in each of these complexes is coupled to H_a, in addition to the methyl protons. Only the DQCOSY spectrum of the $Ca(NO_3)_2$ complex of I, however, shows coupling between the methine proton and H_c. The expected methine/H_c cross-peak is absent from the DQCOSY spectrum of the $CaCl_2$–I complex. In both complexes of II, the DQCOSY spectra (not shown) show coupling only between the methyl and methine resonances and between the four methylene resonances H_{a-d}.

Table I. ^{1}H Chemical Shifts (δ, ppm)[a] for the $CaCl_2$ and $Ca(NO_3)_2$ Complexes of I and II in $CDCl_3$ at 25 °C

	complex of I		complex of II	
	$CaCl_2$	$Ca(NO_3)_2$	$CaCl_2$	$Ca(NO_3)_2$
methyl	1.261	1.182	1.413	1.301
methine	3.997	3.858	3.637	3.462
methylene				
H_a	3.667	3.536	3.721	3.622
H_b	3.782	3.699	3.791	3.690
H_c	3.828	3.720	3.925	3.808
H_d	3.947	3.816	3.977	3.905

[a] The reported chemical shifts have a digital resolution of ±0.003 ppm.

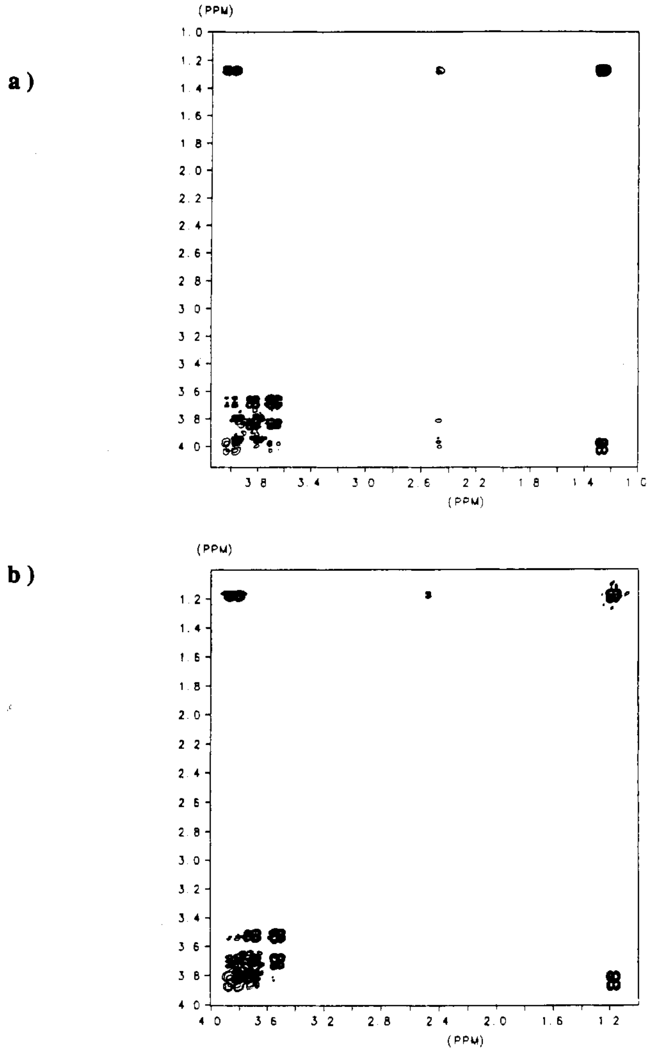


Figure 4. 300-MHz double-quantum-filtered, phase-sensitive COSY spectra of (a) $CaCl_2$–I and (b) $Ca(NO_3)_2$–I complexes in $CDCl_3$ at 25 °C.

Some coupling constants were also measured for selected resonances in the complexes of I. In the 1D 300-MHz ^{1}H NMR spectrum of the $CaCl_2$–I complex, the H_a and H_c quartets were each well enough resolved to allow analysis of their coupling constants by direct measurement from the 1D spectra. Three J values were measured (digital resolution ±0.1 Hz): $J_{a/c} = -9.4$ Hz, $J_{a/\mathrm{methine}} = 6.3$ Hz, and $J_{c/\mathrm{methine}} = 3.2$ Hz. The geminal coupling constant $J_{a/c}$ was easily assigned by the coupling patterns of H_a and H_c (and therefore reported as negative in sign), and the vicinal coupling constants $J_{a/\mathrm{methine}}$ and $J_{c/\mathrm{methine}}$ were assigned by a process of elimination. The magnitudes of these J values were verified and found to be constant in the 500-MHz ^{1}H spectrum (±0.1 Hz) of the complex. Only the H_a quartet in the

Table II. Dipolar Proton Couplings Observed in the 2D NOESY Spectra of the $CaCl_2$ and $Ca(NO_3)_2$ Complexes of I and II in $CDCl_3$ at 25 °C (τ_m = 200 ms)

	obsd NOE cross-peaks	
resonance[a]	$CaCl_2$ complex	$Ca(NO_3)_2$ complex
	complexes of I	
Me	H_a, H_b, H_c, H_d, Meth	H_a, H_b, H_c, H_d, Meth
Meth	Me, H_a, H_b, H_c	Me, H_a, H_b, H_c
methylene		
H_a	Me, H_b,[b] H_c, Meth	Me, H_c, Meth
H_b	Me, H_a,[b] H_d, Meth	Me, H_d, Meth
H_c	Me, H_a, H_d,[b] Meth	Me, H_a, Meth
H_d	Me, H_b, H_c[b]	Me, H_b
	Complexes of II	
Me	Meth, H_a, H_b, H_c	Meth, H_a, H_b, H_d
Meth	Me, H_a, H_c	Me, H_a, H_d
methylene		
H_a	Me, H_c, H_d	Me, Meth, H_b, H_c, H_d
H_b	Me, H_c, H_d	Me, H_a, H_c, H_d
H_c	Me, Meth, H_a, H_b	H_a, H_b, H_d
H_d	H_a, H_b	Me, Meth, H_a, H_b, H_c

[a] Where Me = Methyl, Meth = Methine. [b] Cross-peaks of only very weak intensity detected.

300-MHz ^1H spectrum of the $Ca(NO_3)_2$–I complex was well enough resolved to permit coupling constant analysis. These two J values were also directly measured from the 1D spectrum (±0.1 Hz): $J_{a/c} = -10.0$ Hz and $J_{a/\mathrm{methine}} = 3.1$ Hz. The geminal coupling constant $J_{a/c}$ (again reported negative in sign) was assigned on the basis of its magnitude, and the vicinal coupling constant $J_{a/\mathrm{methine}}$ was once again assigned by a process of elimination. These J values were also found to be constant in the ^1H spectrum at 500 MHz (±0.1 Hz). J values for the complexes of II were not measured.

The results of the 2D NOESY experiments (spectra not shown) performed on the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I and II are shown in Table II. The 2D data were supported by 1D NOE difference experiments.[20-22] Because of the natural limitations of the 1D technique, namely the requirement that resonances be well enough resolved to permit exclusive irradiation, the 2D NOESY experiment is the preferred technique to study NOE's. Indeed, only the methyl and H_a resonances in the complexes of I and the methyl and methine resonances in the complexes of II are adequately resolved in the 1D ^1H NMR spectra (Figure 3) to permit study by the 1D NOE difference technique. Nevertheless, the 1D NOE data were found to be consistent with the 2D data shown in Table II.

Discussion

Initial Assumptions. Consideration of the crystal structure of the $Ca(NO_3)_2$ complex of II,[4] as well as of the previous conformational studies of 18-crown-6 complexes[10] and NMR studies of similar crown complexes,[5,6] supports the assumption that the –OCCO– torsion angles in the Ca complexes of I and II in solution are gauche. If this is so, then the $-OCH_2CH_2O-$ and $-OCH_2CH(CH_3)O-$ ethylene subunits must be staggered, and in fact, the two conformational features of primary interest, the orientation of the methyl groups and the twist of the macrocycle ring, are specifically coupled. To the extent that the methyls are axial, the twist of the rings must be effectively opposite in the complexes of I (*S* chiral centers) and II (*R* chiral centers).

The results of the preliminary 1D ^1H experiments indicate that the solution conformations of all four complexes are either statically or dynamically highly symmetric. In fact, the symmetry must be very close to, if not exactly, D_2. All 12 methyl protons in each complex have the same chemical shift in the ^1H (and DQCOSY) spectra, appearing as a lone, upfield doublet (Figure 3). This is indicative of conformational equivalence of all the methyl groups in each complex.

In addition to the lone upfield doublet appearing in the 1D ^1H NMR and 2D DQCOSY spectra of each of these complexes, only one methine and four nonequivalent methylene resonances are observed. Integration of each 1D ^1H spectrum shows that each resonance signal corresponds to four equivalent protons. This pattern of equivalence is observed in the ^{13}C spectra (not shown) as well. For each of the complexes studied, only four carbon signals are detected. These are assigned to the methyl, the methine, and two nonequivalent methylene carbons. Low-temperature ^{13}C experiments, performed on the $Ca(NO_3)_2$ complexes of I and II by cooling the samples in increments to −55 °C, showed no additional peaks in the carbon spectrum. If signal averaging is taking place at room temperature, presumably resulting from rapid rotamer interconversion, cooling would be expected to slow the interconversion on the NMR time scale. The signal-averaged carbon resonances would then be expected to become nonequivalent. The lack of additional signals (or even significant peak broadening) in the low-temperature carbon spectra provides evidence that no signal averaging is taking place.

Rapid rotamer interconversion would also be expected to average the methylene proton signals in the ^1H spectrum. Protons rapidly interchanging axial/equatorial positions would be expected to give averaged methylene signals, as observed in the ^1H spectra of the free crowns (not shown) and reported in the literature for similar macrocycles.[5,6] Clearly, this is not supported in the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I and II. If we then assume static D_2 symmetry for all the complexes, this requires that in each complex the methyls be equally axial. The conformational factor of interest is then the degree of axiality in each of the complexes. Steric interaction would clearly favor more axial orientation in the complexes of II than in those of I, and in fact, the methyls are fully axial in the crystal structure of the $Ca(NO_3)_2$–II complex.[34]

In order to assess the degree of axiality of the methyls, the most potent data are NOE's and coupling constants. However, with the assumption of D_2 symmetry, it can be seen that the NOE data will only distinguish between axial and equatorial methyls in the complexes of II. In II, equatorial methyls located at the 2,3,11,12-positions would be expected to be too remote from the methylene protons bonded to carbons 6, 8, 15, and 17 to show NOE's between them. However, if the methyls were oriented axially, they would be proximally located to the axially oriented protons at the 6,8,15,17-positions, and an NOE could be expected. On the other hand, the 2,6,11,15-positions of the methyl groups in I locate them proximally to *all* the methylenes regardless of axial/equatorial orientation.

Fortunately, although the NOE data cannot be used to determine the orientation of the methyls in the complexes of I, coupling constant data may be employed to determine their orientation relative to the methylene protons at the 3,5,12,14-positions. This may be done by relating the methylene/methine proton J value to the torsion angle between them. Equatorial methyls would require axial methine protons. Because of the staggered orientation assumed for the ethylene subunits, the methine would have a trans diaxial relationship with one of the methylene protons bonded to the adjacent carbon, and this would be characteristically reflected in the coupling constant. Conversely, axial methyls would require equatorial methine protons. In addition, a gauche relationship would be expected between the methine proton and both neighboring methylenes, which should also be reflected in the magnitude of the coupling constants. Thus, our conformational analysis will center around the NOE data for the complexes of II, while for the complexes of I, the coupling constant data will be our primary source of information.

Having proposed relevant NMR data required to determine the axial/equatorial orientation of the methyls in the complexes of I and II, criteria for evaluation of the ring twist in these complexes should be discussed. Because the sense of the ring twist in each complex is associated with the orientation of the methyl groups, by defining the orientation of the methyl groups in these complexes, the sense of the ring twist will also be defined. In our analysis, the sense of the ring twist will be addressed in terms of the signs of the gauche –OCCO– torsion angles. In particular, it is the orientation of the ethylene ether subunits containing the methyl groups, which is directly linked to the orientation of the methyls. If it can be shown that the NMR data are indeed consistent with axial methyls, then the ring twist sense of the ethylene subunits containing the methyls will also be shown to be opposite in the *R* chiral complexes and the *S* chiral complexes. This then would be independent support for the model of additional chirality associated with the relative orientation of the two NO_3^- anions as the source of the distinct *non*-mirror-image relationship between the chiroptical spectra of complexes of I and II with nitrate salts; i.e., in spite of approximately equal and opposite ring twists.[1,4] In addition, to the extent that the NMR data are consistent with axial methyls, they provide further support for the two-bladed NO_3^- propeller model in that only axial methyls could be expected to control the pitch of the NO_3^- "blades".

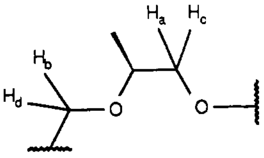
Preliminary Considerations of the NMR Data. The homonuclear 2D NOESY experiment was used to simultaneously map out all the proton NOE's in the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I and II. These interactions were most important in determining the crown ring conformations in the complexes of II. In particular, those NOE's between the methyl and methylene resonances were qualitatively interpreted to provide distance information.

For certain resolved resonances, the 2D NOESY data were supported by 1D NOE difference spectra.[20-22] It was found that the data obtained from this technique were consistent with those obtained from the 2D experiment. Furthermore, the positive NOE's observed in the 1D NOE difference spectra of the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I and II indicate that these compounds are in the extreme narrowing limit and that $\omega_0\tau_c$ (the product of the Larmor frequency and the correlation time) is less than 1 for these complexes.

The homonuclear DQCOSY experiment was used to assign chemical shifts and identify *J*-coupled resonances. The persistence of cross-peaks due to *J* coupling in NOESY spectra is a well-documented problem, and several methods for avoiding this problem have been proposed.[23-25] Alternatively, if little or no structural information is to be gained by identifying NOE's between protons that are *J*-coupled (as in this study), cross-peaks due to *J* coupling may be identified by using a COSY experiment, and then these cross-peaks can be ignored in the NOESY spectrum (although they are still reported in Table II).

The coupling constant data obtained for the complexes of I were measured directly from the 1D ^1H spectra of these complexes. In order to be certain that the system is first order and that second-order distortions are not present, the coupling constants were measured at two different field strengths (300 and 500 MHz). Values were found to be the same within experimental error.

Complexes of I. The ^1H NMR and DQCOSY spectra of the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I (parts a and b of Figure 4, respectively) are very similar. As previously discussed, the proton spectra show an upfield methyl doublet and five nonequivalent downfield resonances. Each DQCOSY spectrum of the I complexes clearly shows the methyl resonance coupled to the farthest downfield multiplet via a mutual cross-peak, unambiguously identifying this resonance with the (four equivalent) methine protons. The remaining four nonequivalent proton resonances must be the methylene signals and are arbitrarily assigned as H_{a-d} in order of decreasing chemical shift (as are the methylenes in the spectra of the complexes of II). Furthermore, in both spectra the methine resonance shows a cross-peak to the methylene H_a, which in turn shows a cross-peak to H_c. The methylene protons H_b and H_d show only one mutual cross-peak, indicating that they are geminally coupled, as are H_a and H_c. All of these assignments are summarized in structure **1**.

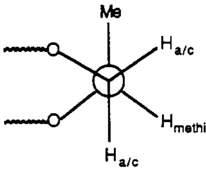


1

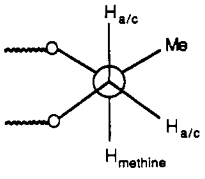
A potential ambiguity in both $CaCl_2$–I and $Ca(NO_3)_2$–I DQCOSY spectra (Figure 4) exists concerning the H_c/methine cross-peak. The cross-peak does not appear in the spectrum of the $CaCl_2$–I complex, while it appears distorted in the $Ca(NO_3)_2$–I spectrum. The reason for the lack of a cross-peak between the methine proton and H_c in the $CaCl_2$–I DQCOSY spectrum is open to speculation. However, on the basis of the magnitude of the $H_c/H_{methine}$ coupling constant (3.2 Hz), it is unlikely that it is due to a coupling magnitude dependent effect, such as the cancellation of anti-phase pairs due to ineffective resolution. The distorted cross-peak between H_c and the methine proton in the $Ca(NO_3)_2$–I spectrum may be indicative of second-order effects between the two resonances, which also appear as distorted resonances in the 1D ^1H NMR spectrum (Figure 3).

The assignments in **1** are consistent with the fine structure of the methylene resonances in the $CaCl_2$–I and $Ca(NO_3)_2$–I 1D ^1H NMR spectra (Figure 3). In the $CaCl_2$–I spectrum, these resonances consist of a well-resolved quartet, a slightly overlapped doublet and quartet, and another doublet (H_a, H_b, H_c, and H_d, respectively). Except for the distorted H_c and methine resonances, the fine structure of the methylene resonances in the 1D ^1H NMR spectrum of the $Ca(NO_3)_2$–I complex is identical with that of the $CaCl_2$–I complex (i.e., the proton H_a appears as a well-resolved quartet and H_b and H_d appear as doublets). These results show that the methine and the methylene H_{a-d} resonances each correspond to four magnetically equivalent protons in the NMR spectrum, consistent with D_2 symmetry in the solution structures of the complexes of I.

As discussed above, the critical conformational analysis of these compounds by the 2D NOESY technique is inconclusive because the same NOE's are expected in a ring conformation with axial methyls as in a conformation with all the methyl groups equatorial. This circumstance is a direct result of the magnetic equivalence present in the compounds and the 2,6,11,15-positions of the methyls. A Newman projection of the ethylene ether subunit containing the methyl group is shown with the methyl group axial (**2a**) and equatorial (**2b**). As shown in **2a** and **2b**, the methylenes are assumed to be staggered with the methyl group, but the 60° dihedral angles are only convenient approximations. Initial examination of the two structures leads to the expectation of an NOE between the axial methyl group and the equatorial proton only of the H_a/H_c pair (H_a and H_c are at this point unassigned to axial and equatorial positions). On the other hand, the equatorial methyl group in **2b** would be expected to show NOE's to both methylenes. If a similar orientation relating the axial methyl group and the H_b and H_d protons on the adjacent ethylene subunit is assumed, a similar conclusion may be drawn: the trans axial orientation of the methyl group and the axial proton of the H_b/H_d geminal pair would appear to make these protons too remote to show an NOE between them. Alternatively, an equatorial methyl group would be proximally located to both H_b and H_d. However, the staggered structure shown schematically in **3**, with axial methyls and H_a and H_b tentatively assigned to axial positions, shows that, while the methyl group may be remote from H_a and H_b, it is proximally located to the magnetically equivalent partners of these methylenes (H_a' and H_b'). Thus, NOE's are expected between the methyl group and all the methylene resonances, regardless of axial/equatorial methyl or methylene orientations.



2a



2b

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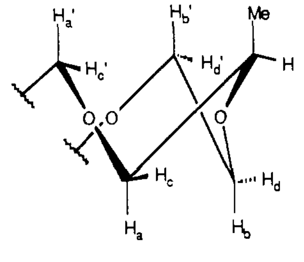


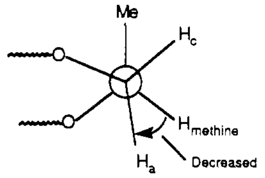
3

On the other hand, the measured J values in the complexes of I are sensitive to the orientation of the methyl groups in these complexes. The $H_a/H_{methine}$ (6.3 Hz) and $H_c/H_{methine}$ (3.2 Hz) coupling constants observed in the $CaCl_2$–I complex are inconsistent with a solution structure having equatorial methyl groups. For a structure such as **2b**, a large anti/anti vicinal coupling would be expected between the methine proton and the axially oriented proton of the H_a/H_c geminal pair. A reasonable approximation of this value may be obtained from the J-value data on the $-CH_2CH_2-$ fragment in *trans*-2,3-dimethyl-1,4-dioxane, considered to exist entirely in the chair conformation with the methyl groups equatorial.[26] Abraham and Gatti report the axial/axial vicinal coupling to be 11.51 Hz in magnitude, clearly much greater than either of the vicinal couplings observed in the $CaCl_2$–I complex. Thus, the J-coupling data support a solution structure for the $CaCl_2$–I complex resembling that shown in **2a**, with axial methyl groups.

The two electronegative oxygens in *trans*-2,3-dimethyl-1,4-dioxane contribute to the large diaxial coupling constant observed,[26] and similar effects are expected in the complexes of both I and II. Studies of the effect of electronegative substituents on the magnitude of vicinal –CHCH– couplings show that these effects are dependent upon the orientation of the substituents relative to the coupling protons.[26-29] For staggered $-XCH_2CH_2Y-$ fragments (where X and Y are electronegative substituents), electronegative substituents that are oriented planar trans to vicinally coupled protons decrease the magnitude of the coupling constant, while electronegative substituents not in this orientation tend to increase the J value. Orientations in which only one (of a pair of vicinally coupled protons) is oriented planar trans to an electronegative substituent are expected to produce intermediate effects. The $H_a/H_{methine}$ and $H_c/H_{methine}$ J values for the $CaCl_2$–I complex are both consistent with gauche torsion angles.

Unfortunately, however, only the $H_a/H_{methine}$ J value (3.1 Hz) could be measured for the $Ca(NO_3)_2$–I complex. The H_c/methine coupling constant in the $Ca(NO_3)_2$–I complex could not be measured by available methods due to apparent second-order distortions. As previously stated, both the H_c and methine resonances appear to be distorted in the 1D ^1H NMR spectrum of this complex, presumably because of second-order effects due to their proximity to each other. Because second-order effects persist in the 2D J-resolved experiment,[30,31] a more rigorous 2D experiment would be needed to deduce this information, such as E COSY[32] or PE COSY.[33] Unfortunately, these experiments are beyond the present capabilities of this study, and the magnitude of the $H_c/H_{methine}$ coupling constant was not pursued.

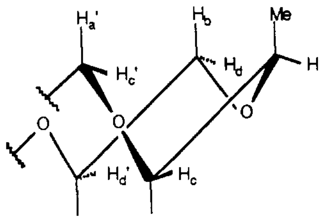
The $H_a/H_{methine}$ coupling constant observed in the $Ca(NO_3)_2$–I complex is consistent with a gauche torsion angle between these protons, supporting axial methyl orientations in the solution structure of this complex as well. The decreased magnitude of the J value indicates that complexation of I to $Ca(NO_3)_2$ induces changes in the crown ether ring conformation different from those in the $CaCl_2$–I complex. In earlier substituent effect studies by Pachler on monosubstituted ethane,[27] it was found that the maximum decrease of vicinal couplings occurred when the –CX– bond and –CH– bond of the coupled proton, bonded to the same carbon, are perpendicular to the two bonds not involved in the coupling. A staggered structure with a decreased torsion angle between H_a and the methine (**4**) would approach this conformation, consistent with the observed decreased $Ca(NO_3)_2$–I $H_a/H_{methine}$ coupling constant. However, it should be noted that, because the $H_c/H_{methine}$ J value in the $Ca(NO_3)_2$–I complex could not be measured, the possibility of axial/axial coupling between these two protons, and a solution structure with equatorial methyl groups, cannot be definitively ruled out.



4

Finally, NOE's between nongeminal methylene protons are also observed in the NOESY spectrum of the $CaCl_2$–I complex (Table II). By inspection of 1D traces parallel to ω_2 in the NOESY spectrum (not shown) weak cross-peaks between H_a and H_b and between H_c and H_d can be detected. On the basis of the inferred proximity of these nuclei, the conformation shown schematically in **3**, having gauche –OCCO– torsion angles of the same sign, is consistent with these observed NOE's. Furthermore, the magnetic equivalence of the protons observed in the NMR data would support a completely symmetrical crown ring in this complex, consisting of four conformationally equivalent, four-carbon subunits. This is shown schematically in Figure 5, in which the ring is symmetric about both C_2 axes.

Although the NMR data for the $Ca(NO_3)_2$–I solution structure are not as conclusive as those for the $CaCl_2$–I complex, the observed magnetic equivalence is consistent with the structure shown in Figure 5. No NOE's between nongeminal methylene resonances are observed in this complex, and the magnitude of the $H_a/H_{methine}$ J value is decreased. This evidence suggests the conformation of the ring in the $Ca(NO_3)_2$–I complex may resemble that shown schematically in **5**, or a conformation somewhere between **5** and **3**. Thus, as expected, some differences appear to exist in the ring conformations of the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I.



5

Complexes of II. The proton magnetic equivalence observed in the complexes of I is only approximate in the complexes of II. As in the ^1H NMR spectra of the I complexes, one upfield methyl doublet and five downfield resonances are observed in the ^1H NMR spectra of the $CaCl_2$ and $Ca(NO_3)_2$ complexes of II (Figure 3). Integration of the 1D $CaCl_2$–II and $Ca(NO_3)_2$–II proton

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(34) Another assumption underlying the analysis concerns the location of the chloride ions in the $CaCl_2$ complexes of I and II. It is assumed that each Cl^- is centrally located on a C_2 axis that is perpendicular to the mean plane of the crown ring and passes through the calcium. This orientation is consistent with D_2 symmetry of the solution structures of these complexes. Hence, NMR data supporting D_2 symmetry in these complexes also reinforces our assumption of the positions of the chlorides in these complexes.

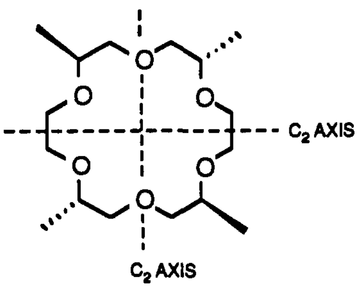


Figure 5. Schematic representation of the symmetry elements present in the macrocycle ring of the I complexes. Symmetry about both C_2 axes defines a ring structure consisting of four conformationally equivalent four-carbon subunits. (A third C_2 axis is, of course, perpendicular to the other two.)

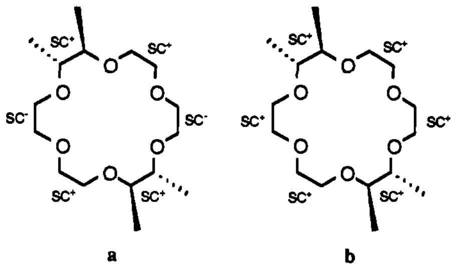
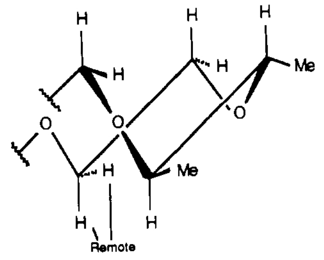


Figure 6. *Schematic representations for the macrocycle rings in the* complexes of II, indicating the signs of the gauche (sc$^+$ and sc$^-$) -OCCO- torsion angles.

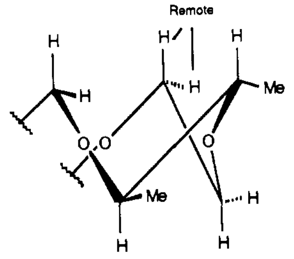
spectra shows that each of the five downfield resonances corresponds to four chemical-shift-equivalent nuclei. Furthermore, the DQCOSY spectra of each of these complexes (not shown) show coupling patterns consistent with the chemical-shift equivalence of these protons. Specifically, the lone methyl doublet shows coupling to a single methine resonance and the four nonequivalent methylene resonances show coupling to one another. However, the fine structure of the methine and methylene multiplets in the ^{1}H NMR spectra of these two complexes show small but significant splittings, indicating slight distortion from exact D_2 symmetry.

The distortions observed in the methylene resonances of the II complexes are not surprising. The large couplings between these protons, combined with their close proximity of chemical shifts, would be expected to produce significant second-order effects. However, a single, resolved quartet would be expected for four magnetically equivalent methine protons, instead of the distorted pseudoquartet observed. The single methine resonance in the ^{1}H NMR spectrum of each complex of II more closely resembles a quartet of triplets, indicating different coupling environments for the chemical-shift-equivalent protons. Thus, although the solution structures of the II complexes do not appear to be quite as symmetrical as those of I, the chemical-shift equivalence of the methine and methylene protons (four resonances corresponding to four protons each) and the methyl protons appearing as a lone upfield doublet show that the symmetry is still approximately D_2. This is also indicated by the ^{13}C NMR spectrum of each complex (not shown), which shows only a single methyl and methine carbon resonance, and two nonequivalent methylene carbons, consistent with a symmetrical crown ring.

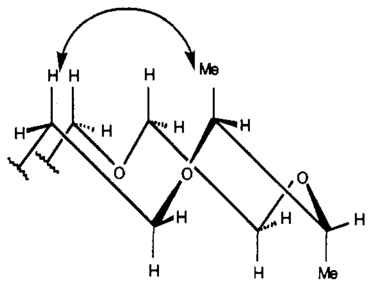
For both complexes of II, the observed NOE's are more diagnostic of the preferred conformation in solution than are the coupling constants, by virtue of the 2,3,11,12-locations of the methyl groups. Because of the lone methyl doublet appearing in each ^{1}H NMR spectrum, it can be concluded that all the methyl groups are equivalently axial. In the completely equatorial orientation, the methyl groups would be too remote from two of the methylene protons to show NOE's to either. This is shown schematically in **6a** and **6b**. Alternatively, methyl groups oriented axially would be proximally located to at least one of these protons such that an NOE could be observed (**7a** and **7b**). Hence, NOE's observed between the methyl resonance and three of the four methylene protons would be more consistent with a solution structure having axial methyl groups. Furthermore, the implied equatorial orientation of the methine protons in a solution structure containing axial methyl groups would proximally locate the methine to both of the geminal protons bonded to the carbon, immediately opposite the ring oxygen, in the adjacent ethylene subunit. Observed NOE's between the methine proton and both of these methylene resonances would not only support a structure containing axial methyls but also would permit assignment of the methylene geminal partners.



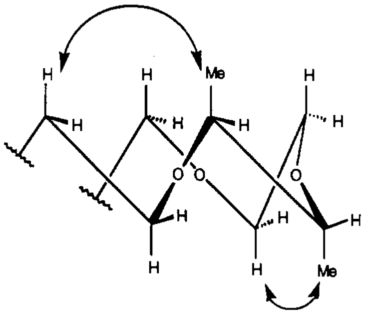
6a



6b



7a



7b

The 2D NOESY experiment performed on the CaCl$_2$ complex of II shows methyl NOE's to the methylene H$_a$, H$_b$, and H$_c$ resonances, consistent with a solution structure containing axial methyl groups (Table II). In addition, the methine resonance shows NOE's to both the H$_a$ and H$_c$ resonances, further supporting a structure having axial methyl groups and identifying H$_a$ and H$_c$ as geminal methylene protons. As in the NOESY data of the complexes of I, these NOE assignments have been checked by

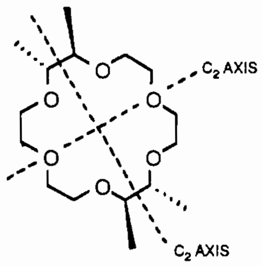
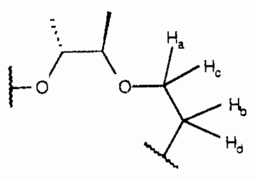


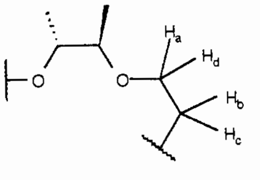
Figure 7. Possible symmetry elements present in the $CaCl_2$–II and $Ca(NO_3)_2$–II complexes.

examining traces parallel to the ω_2 axis in the NOESY spectrum.

The NOE assignments for the $CaCl_2$ complex of II are consistent with both structure conformations shown in **7a** and **7b** and with the proton assignments shown in **8a**. The relative orientations of the methylene protons in the remaining ethylene subunits are considered to be symmetrical to those shown in **8a**, on the basis of the chemical-shift equivalence observed in the ^1H NMR and the DQCOSY spectra.



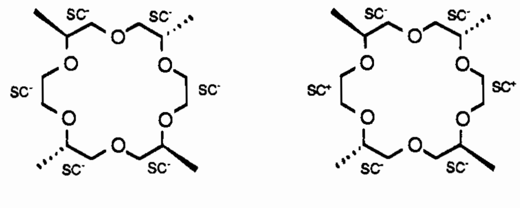
8a



8b

The $Ca(NO_3)_2$–II complex also shows NOE's between the methyl resonance and three of the four methylene protons in the 2D NOESY spectrum (data reported in Table II). The methyl group shows NOE's to the H_a, H_b, and H_d methylene resonances, while the methine proton shows NOE's to H_a and H_d. Once again, a solution structure having axial methyls, as in **7a** and **7b**, is consistent with the observed NOE's in this complex. The methylene proton assignments consistent with the NOE data are shown in **8b**. The methine NOE's to H_a and H_d allow these protons to be assigned as geminal partners proximally located to the methine nucleus. Hence, the H_d resonance in the $Ca(NO_3)_2$–II complex corresponds to the H_c protons in the $CaCl_2$ complex of II, and the converse is also true.

Because of the reported symmetry present in the $Ca(NO_3)_2$–II crystal structure,[4] the proposed symmetry of the solution structures of the $Ca(NO_3)_2$–II complex and the $CaCl_2$–II complex is not unexpected. The crown ring in the crystal structure is reported to be symmetrical such that the calcium and nitrate nitrogen and nonbonded oxygen lie on a 2-fold axis relating half of the ring to the other. Furthermore, the crystal structure of the $Ca(NO_3)_2$–II complex has been shown to contain dihedral angles about the –CC– bonds of approximately 65° (synclinal, sc) and dihedral angles about the –CO– bonds in the range of 180° (antiperiplanar, ap), with the methyl groups oriented axially. The carbon–hydrogen backbone reported for this crystal structure is shown schematically in Figure 6a, where sc^+ and sc^- indicate the signs of the gauche –OCCO– torsion angles. The ring conformation in Figure 6a corresponds to the structure shown schematically in **7a**.



a b

Figure 8. Schematic representations for the macrocycle rings in the complexes of I, indicating the signs of the gauche (sc^+ and sc^-) –OCCO– torsion angles.

The 2D NOESY data for each complex of II show that the solution structures of these complexes could be very close to that reported for the crystal structure of the $Ca(NO_3)_2$–II complex. A conformation similar to that in **7a** would be consistent with the observed chemical-shift equivalence of the ring protons but lack of magnetic equivalence. Alternatively, the NOESY data are also consistent with structures symmetric about either or both C_2 axes shown in Figure 7, similar to the complexes of I. A conformation symmetrical about both C_2 axes would have a ring conformation as shown in Figure 6b and correspond to the structure in **7b**. Thus, while the NOESY data support solution structures for the complexes of II with axial methyl groups, more than one possible conformation of the ether subunits containing the methylene groups appear to be consistent with the observed NOE's.

Twist of the Crown Rings in I and II. Finally, the question of the ring twist remains. In the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I, the data indicate highly symmetric crown rings consisting of four conformationally equivalent four-carbon subunits. Although small differences among the complexes are apparent, solution structures having axial methyl groups and staggered $-OCH_2CH(Me)O-$ ethylene subunits are consistent with the NMR data. The weak NOESY cross-peaks observed between the nongeminal methylene protons of the $CaCl_2$–I complex (H_a and H_b, and H_c and H_d) suggest proximity of these protons and, hence, gauche (synclinal) –OCCO– torsion angles of the same sign (negative) only in this complex. This ring conformation for I is shown schematically in Figure 8a. However, these NOE's are not observed in the $Ca(NO_3)_2$–I complex, and there is no evidence that the two H_b/H_d ethylene subunits are constrained to have gauche –OCCO– torsion angles of the same sign as the other four ethylene subunits. Therefore, the NOE data for this complex would also be consistent with a ring conformation shown schematically in Figure 8b.

Inspection of the ring conformations as deduced from the NMR data, and shown schematically in Figures 6 and 8, shows that the sense of the ring twist in the complexes of I is indeed opposite to that of the complexes of II. The I complexes have ring conformations containing gauche –OCCO– torsion angles that are all or mostly all negative, while those for the II complexes are all or mostly all positive. Thus, the NMR data are consistent not only with the hypothesis that the methyl groups in the solution structures of the $CaCl_2$ and $Ca(NO_3)_2$ complexes of I and II are oriented axially but also with the proposal that the sense of the ring twist in the *R* chiral ring complexes is opposite to that in the *S* chiral ring complexes.

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