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Lanthanide–Crown Ether Mixtures as Chiral NMR Shift Reagents for Amino Acid Esters, Amines and Amino Alcohols

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Two chiral crown ethers, 2,3:4,5-bis[1,2-(3-phenylnaphtho)-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene and 1,2:5,6-di-*O*-isopropylidene-3,4-[(*tert*-butylbenzenediyl)bis(oxyethoxy)ethyl-*3*-mannitol, were evaluated as organic-soluble chiral NMR resolving agents. The crown ethers are useful resolving agents for protonated amino acid esters, amines and amino alcohols. Enantiodiscrimination with the crown ethers is better in methanol than in acetonitrile or chloroform. Organic-soluble lanthanide tetrakis(β-diketonate) anions, which are formed in solution by mixing a lanthanide tris(β-diketonate) and silver β-diketonate, can be added to crown–substrate mixtures to enhance the enantiomeric resolution. The lanthanide-induced enhancement occurs because the enantiomers of the substrate have different association constants with the crown ethers. The enantiomer that associates less favorably with the crown ether is more available to complex with the lanthanide.

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INTRODUCTION

NMR spectroscopy is often used to determine enantiomeric excess. One technique is to synthesize a pair of diastereomers with an optically pure derivatizing agent. The resonances of the diastereomers may then show different chemical shifts in the NMR spectrum. Another method is to add a chiral shift reagent or chiral solvating agent. These function by two possible mechanisms. Association of the solvating agent with the enantiomers forms diastereomeric complexes that may then have different chemical shifts. Alternatively, it is possible that one enantiomer has a larger association constant with the solvating agent, and the different time-averaged environments may then lead to differences in the chemical shifts. Depending on how the interaction between the resolving agent and chiral substrate is understood, it may or may not be possible to assign absolute configurations to the resolved resonances.

Liquid chromatography is also commonly used to separate enantiomers.[1] In certain cases, the interaction between the substrate and chiral phase is well understood, or at least relative retention orders for homologous groups of compounds are known. Thus, soluble analogues of some chromatographic phases have been adapted for use in NMR spectroscopy.[2–10] In many cases, the enantiomeric resolution observed in the NMR spectra is small or non-existent. Pirkle and coworkers[11,12] were the first to report that achiral lanthanide species could be added to mixtures of chiral solvating agents and substrates and cause an enhancement in enantiomeric resolution. An essential component of the enhancement in such mixtures is that the enantiomers exhibit different association constants with the resolving agents. It is also important that the association constant of the substrate with the lanthanide be greater than that of the resolving agent with the lanthanide. Under such conditions, the enantiomer that bonds more weakly to the resolving agent is 'free' in solution to complex with the lanthanide, hence its spectrum will shift further. The utility of adding achiral lanthanide species to mixtures of substrates and resolving agents to enhance enantiomeric resolution has now been extended to other systems.[13,14] An alternative to mixing a lanthanide with the chiral resolving agent is to attach the lanthanide covalently to the resolving agent. Lanthanide ions have been attached in such a manner to water-soluble cyclodextrins through the use of a diethylenetriaminepentaacetic acid moiety.[15]

In this paper, we describe the utility of using two chiral crown ethers, 2,3:4,5-bis[1,2-(3-phenylnaphtho)-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (Crown 1)[16] and 1,2:5,6-di-*O*-isopropylidene-3,4-[(4-*tert*-butylbenzenediyl)bis(oxyethoxy)ethyl)]-D-mannitol (Crown 2),[17] as NMR chiral resolving agents. Crown ethers are organic-soluble compounds capable of undergoing host–guest complexation with suitable substrates. Several chiral crown ethers, mostly 18-crown-6 ethers, have been prepared and examined as chiral resolving agents in liquid chromatography[18,19] and NMR spectroscopy.[20,21] Racemic amines, amino acids, amino esters and amino alcohols can be resolved provided that

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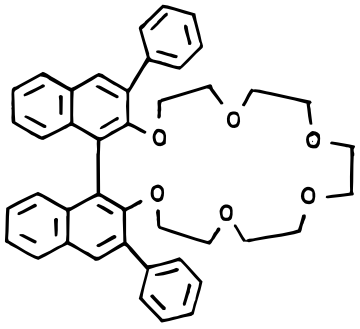
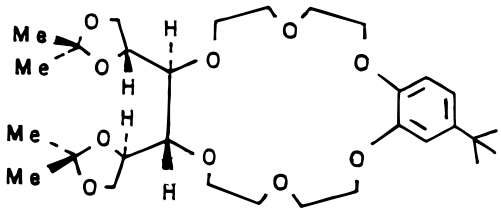


Crown 1



Crown 2

the amine functionality is protonated. The protonated primary amine group has the ability to form three hydrogen bonds in a tripod configuration with the crown cavity. Steric interactions of the substrate with the substituent groups on the crown contribute to the enantiodiscrimination.[1]

Crown 1, first described by Lingenfelter *et al.*,[16] has been shown to function as an NMR chiral resolving agent. Liquid chromatographic columns containing Crown 1 as the stationary phase are commercially available. Crown 2, first described by Joly and coworkers,[17,22] has been the focus of considerably less study. Our work shows that both crown ethers have particular attributes that recommend their use under certain conditions as NMR chiral resolving agents. The benefits of adding suitable lanthanide species to mixtures of the crowns and substrates are also described.

EXPERIMENTAL

Reagents

(*R*)-1,1′-Bi-2-naphthol, 1,2:5,6-isopropylidene-D-mannitol and all other chemicals required for synthetic purposes were obtained from Aldrich Chemical (Milwaukee, WI, USA). DL- and L-valine methyl ester hydrochloride, DL- and L-alanine methyl ester hydrochloride, DL- and L-phenylalanine methyl ester hydrochloride and L-proline methyl ester hydrochloride were obtained from Sigma Chemical (St Louis, MO, USA). DL-Leucine methyl ester hydrochloride was purchased from USB Chemical (Valencia, CA, USA). All other substrates were obtained from Aldrich Chemical. Deuterated NMR solvents were obtained from Aldrich Chemical and used as received. Europium(III) and praseodymium(III) complexes of 6,6,7,7,8,8,8-heptafluorooctane-3,5-dione (fod),[23] the silver complex of fod,[24] Crown 1[16] and Crown 2[17] were prepared, purified and characterized according to published procedures. All solvents used in the synthetic preparations were dried by established procedures prior to use.

Salts of primary amines were prepared by dissolving the amine in dry diethyl ether and bubbling hydrogen chloride gas through for 15 min. The precipitate that formed almost immediately was collected by suction filtration, washed with diethyl ether and dried in a vacuum desiccator overnight. Preparation of the desired salt was confirmed by ^{1}H NMR spectroscopy.

Procedures

The appropriate amount of crown ether (typically 0.10 M) and substrate (typically 0.05 M) were weighed and dissolved in the appropriate solvent. Increments of $Ln(fod)_3$ were added using 5 µl aliquots of 0.059 M stock solution. Increments of $Ln(fod)_4^-$ were added by weighing the appropriate amounts of $Ln(fod)_3$ and Ag(fod) into a small test-tube, adding the solution with the crown and substrate and shaking for 1 min. The silver chloride precipitate that formed was removed by centrifugation and decantation of the supernatant into an NMR tube.

Apparatus

All spectra were recorded on a General Electric QE 300 MHz NMR spectrometer at a probe temperature of 20 or 50 °C.

RESULTS AND DISCUSSION

When using an NMR chiral resolving agent, it is preferred that the exchange of the substrate between its free and associated forms be fast on the NMR time-scale. Slow exchange leads to a duplication of all peaks that then complicate analysis for the presence of enantiomeric resolution. Intermediate exchange introduces broadening. The presence of a large lanthanide complex has been shown by Bulsing *et al.*[25] to slow the tumbling rate of the complexed substrate sufficiently, thereby contributing to broadening on a high-field NMR spectrometer. Increasing the temperature of the system can increase the exchange and tumbling rate, thereby decreasing exchange broadening. Previous work with lanthanide–chiral resolving agent systems based on either amino acid or cyclodextrin derivatives showed that recording spectra at 50 °C led to significant reductions in exchange broadening, yet still resulted in enantiodiscrimination.[13–15] Spectra of crown ether–substrate mixtures run in chloroform-*d* at ambient probe temperature often had an excessive amount of

exchange broadening, especially when a lanthanide was introduced. Heating the probe to 50 °C reduced these effects significantly for Crown 2, as seen for the resonances at approximately 1.8 and 4.6 ppm in Fig. 1. In a more polar solvent such as acetonitrile or methanol, exchange broadening is reduced considerably and spectra can be recorded at 20 °C. Presumably the more polar solvent competes more effectively with the substrate for the crown cavity and speeds up the exchange rate.

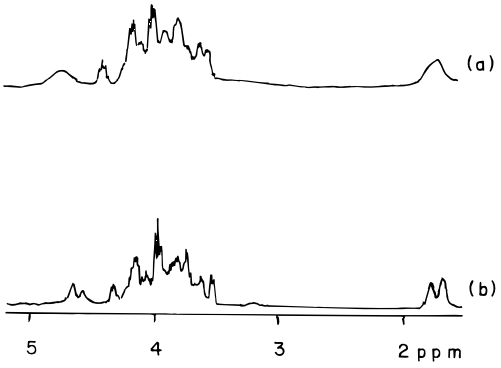


Figure 1. ^{1}H NMR spectrum (300 MHz) of valine methyl ester hydrochloride (0.05 M), Crown 2 (0.10 M), Eu(fod)$_3$ (0.10 M) and Ag(fod) (0.10 M) in chloroform-*d* at (a) 20 °C and (b) 50 °C.

Table 1. Representative shifts (ppm) in the ^{1}H NMR spectra of substrates (0.05 M) and Crown 1 (0.05 or 0.10 M) in chloroform-*d* at 50 °C[a]

Substrate	Resonance	[Crown]/[substrate]	Δδ
Valine methyl	—OCH_3	2:1, 50 °C	−0.05
ester HCl	—CH_3		−0.10
Alanine ethyl	—CH_3	2:1, 50 °C	−0.07
ester HCl	—OCH_2CH_3		−0.03

[a] Negative values represent upfield shifts. Shifts are reported for the L-enantiomer.

Both Crown 1 and 2 shift the resonances of substrates upfield, as shown by the data in Tables 1 and 2. The selection of suitable chiral substrates for our study was based on previous liquid chromatographic data.[19] The crown ethers were effective NMR chiral resolving agents for protonated amino alcohols, protonated aromatic amines and methyl ester hydrochloride salts of amino acids. Enantiomeric resolution is not observed in the spectra of aliphatic amines such as 2-aminooctane and cyclohexylethylamine under the conditions employed.

A reversal of shift order for the enantiomerically resolved resonances is noted in the spectra of a number of different substrates. The enantiodiscrimination

Table 2. Representative shifts (ppm) in the ^{1}H NMR spectra of substrates (0.05 M) in the presence of Crown 2 (0.05 or 0.10 M) at 20 °C[a]

Substrate	Solvent	[Crown]/[substrate]	Resonance	Δδ
Valine methyl ester HCl	Chloroform	2:1	—OCH_3	−0.03
			—CH_3 (upfield)	−0.02
			—CH_3 (downfield)	−0.02
			—CH	−0.04
	Chloroform	1:1	—OCH_3	−0.02
			—CH_3 (upfield)	0
			—CH_3 (downfield)	−0.02
	Acetonitrile	2:1	—OCH_3	−0.07
			—CH_3 (upfield)	−0.09
			—CH_3 (downfield)	−0.06
	Acetonitrile–chloroform (50:50)	2:1	—OCH_3	−0.05
			—CH_3	−0.09
			—CH_3	−0.06
	Methanol	2:1	—OCH_3	−0.06
			—CH_3 (upfield)	−0.20
			—CH_3 (downfield)	−0.16
	Methanol	1:1	—OCH_3	−0.01
			—CH_3	−0.16
			—CH_3	−0.13
Leucine methyl ester HCl	Chloroform	2:1	—OCH_3	−0.03
			—CH_2	−0.10
			—CH	0.02
			—CH_3 (upfield)	−0.06
			—CH_3 (downfield)	−0.06
α-(1-Aminoethyl)-4-hydroxybenzyl alcohol HCl	Methanol	1:1	—OCH_3	−0.06
			—*CH*OH	−0.05
			Aromatic	−0.06
Alanine ethyl ester HCl	Chloroform	2:1	—CH_3	−0.05
Alanine ethyl ester HCl	Chloroform	1:1	—CH_3	−0.02

[a] Shifts are reported for the L-enantiomer.

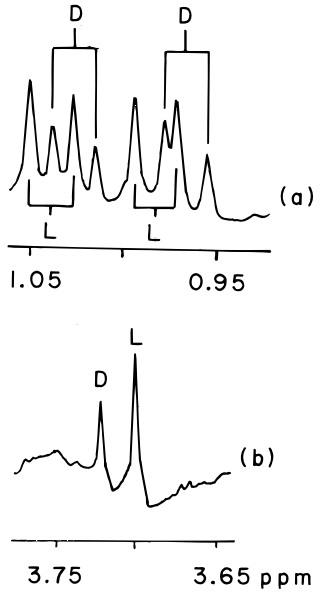


Figure 2. Resonances for the (a) valine methyl and (b) methoxy groups in the ^{1}H NMR spectrum (300 MHz) of valine methyl ester hydrochloride (0.05 M) with Crown 2 (0.10 M) in methanol-d_4 at 20 °C.

observed in the NMR spectra of substrates in the presence of the crowns therefore cannot be due entirely to differences in association constants. For example, with valine methyl ester hydrochloride in acetonitrile, acetonitrile–chloroform and methanol (Fig. 2), the resonance of the L-enantiomer of the methoxy singlet is further upfield, whereas the resonance of the D-enantiomer of the diastereotopic methyl resonances are further upfield. Such a reversal must be caused by differences in the shielding effects of the two diastereomeric substrate–crown complexes.

The effect of solvent on enantiomeric resolution is shown by the data in Table 3 for valine methyl ester hydrochloride with Crown 2. In general, enantiomeric resolution is greater the more polar is the solvent. This finding is consistent with other work on crown ethers. The use of acetonitrile–chloroform as the organic phase instead of chloroform in liquid–liquid extraction techniques resulted in better enantiodiscrimination with phenylglycine.[22] The data show that the resonances of the substrate in the presence of the crown exhibit considerably larger upfield shifts in methanol than in chloroform.

One possible explanation for the solvent effect is that the cationic substrates are less favorably solvated in chloroform and both enantiomers associate more fully with the crown. In a more polar solvent, better solvation of the substrate may possibly lead to a greater distinction between the enantiomer that associates more strongly with the crown and the one that does not. The larger induced shifts caused by the crown in methanol would seem contradictory, however, to this mechanism.

An alternative explanation is to consider the degree of solvation of the anion. Different anions have been found to influence the degree of chiral recognition produced by chiral crown ethers.[20,26] Presumably the anion is solvated to a greater degree in methanol than in chloroform, thereby causing the cation and anion to associate in an outer-sphere arrangement in methanol. In a solvent such as chloroform, the anion may associate with the cation–crown complex in an inner-sphere manner, which may influence the association constants or the geometry of association of the cation with the crown. Either one may alter enantiodiscrimination of the substrate.

The choice of whether to use Crown 1 or Crown 2 as a chiral resolving agent is dependent on several factors. Crown 1 is soluble in chloroform and acetonitrile, whereas Crown 2 is soluble also in methanol. Since many amine substrates, as their hydrochloride salts, are not soluble in either chloroform or acetonitrile, the utility of Crown 1 is more limited than Crown 2. In addition, neither Crown 1 nor Crown 2 is commercially available, and the two-step preparation of Crown 2 is considerably easier to carry out than the five-step preparation of Crown 1. In cases when solubility is not a problem, Crown 1 is known from liquid chromatographic investigations to resolve a wide variety of enantiomers. As shown by the data in Table 4, Crown 1 did cause a larger enantiomeric resolution for the methoxy resonance of valine methyl ester hydrochloride; however, Crown 2 caused a better enantiomeric resolution of the methyl resonances of the valine group. It is also interesting to note the reversal in the shift order of the enantiomerically resolved methoxy resonances for valine methyl ester hydrochloride with Crown 1 and Crown 2. In all cases examined, the enantiomeric resolution was better at crown-to-substrate ratios of 2:1 than at 1:1.

Even though the crowns do produce some enantiomeric resolution in the NMR spectra of substrates, adding a suitable lanthanide species to crown–substrate solutions does enhance the enantiomeric resolution of certain resonances. Since the lanthanide preferentially shifts the spectrum of the free substrate, enantiomeric resolution in the presence of a lanthanide allows resolved resonances to be assigned to the more strongly or weakly associated enantiomer.

The crown systems are different to any previous reports on lanthanide–chiral resolving agent mixtures because of the cationic nature of the substrates. Previous work has shown that lanthanide tetrakis-β-diketonate anions [Ln(fod)$_4^-$] are useful NMR shift

Table 3. Enantiomeric resolution (Hz) in the ^{1}H NMR spectrum of valine methyl ester hydrochloride (0.05 M) and Crown 2 (0.10 M) with different solvents[a]

Solvent	Resonance	$\Delta\Delta\delta$
Chloroform-*d*	—OCH_3	0
	—CH_3 (upfield)	0
	—CH_3 (downfield)	0
Acetonitrile-d_3–chloroform-*d* (50:50)	—OCH_3	5.1 (L)
	—CH_3 (upfield)	3.9 (D)
	—CH_3 (downfield)	0
Acetonitrile-d_3	—OCH_3	6.6 (L)
	—CH_3 (upfield)	3.6 (D)
	—CH_3 (downfield)	4.8 (D)
Methanol-d_4	—OCH_3	9.6 (D)
	—CH_3 (upfield)	6.3 (D)
	—CH_3 (downfield)	0

[a] The resonance that shifted further (L or D) is noted.

Table 4. Enantiomeric resolution (Hz) in the ^{1}H NMR spectra of substrates (0.05 M) and Crown 2 (0.05 M) in methanol-d_4 at 20 °C[a]

Substrate	Resonance	$\Delta\Delta\delta$	
Valine methyl	—OCH_3	4.8 (L)	13.2 (D)[b]
ester HCl	—CH_3 (upfield)	4.5 (D)	
	—CH_3 (downfield)	0.6 (D)	
Alanine methyl	—OCH_3	5.7 (L)	
ester HCl	—CH_3	7.2 (D)	
Phenylglycine methyl	—OCH_3	9.6 (S)	
ester HCl	—CH-	2.1 (S)	
Phenylalanine methyl ester HCl	—OCH_3	2.4 (S)	
Tryptophan methyl ester HCl	—OCH_3	4.8 (L)	
(±)-α-(1-Aminoethyl)-4-hydroxybenzyl alcohol HCl	—CH_3	2.1	
	—CHO	5.4	
	Aromatic	3.3	
Lysine methyl ester HCl	—OCH_3	1.8 (L)	
Methylbenzylamine HCl	—CH_3	2.4	
1-(1-Naphthyl)ethylamine HCl	—CH_3	3.0	

[a] The resonance that shifted further (L or D) is noted for samples enriched in one enantiomer.
[b] Spectrum recorded with Crown 1 in acetonitrile-d_3.

reagents for organic cations.[27,28] The anionic species is formed in solution by the addition of a lanthanide tris-β-diketonate and silver β-diketonate:

$$\mathrm{Ln(fod)_3 + Ag(fod) \rightarrow Ag[Ln(fod)_4]} \quad (1)$$

Addition of a chloride salt of an organic cation results in the precipitation of silver chloride and formation of an ion pair between the lanthanide tetrakis-β-diketonate anion and the organic cation:

$$\mathrm{Ag[Ln(fod)_4] + R^+X^- \rightarrow AgX(s) + R^+[Ln(fod)_4]^-} \quad (2)$$

Lanthanide tris-β-diketonates of fod [$Ln(fod)_3$] were also examined in combination with the crown–substrate mixtures, because the amino acid substrates contain a carbonyl group that can potentially complex directly with the lanthanide ion.

The alanine methyl resonance of alanine methyl ester hydrochloride (0.05 M) exhibits enantiomeric resolution ($\Delta\Delta\delta = 4.8$ Hz) in the presence of Crown 2 (0.10 M). Addition of $Eu(fod)_4^-$ causes the alanine methyl resonance to broaden to the point that no further enantiomeric resolution is apparent. The triplet of the ethoxy methyl group shows no enantiomeric resolution in the presence of Crown 2, but with increasing amounts of $Eu(fod)_4^-$ exhibits enantiomeric resolution (Table 5). Larger lanthanide-induced shifts are observed for the resonance of the L-enantiomer, preliminarily indicating that the L-enantiomer exhibits weaker association with the crown. This conclusion is in agreement with liquid chromatographic retention data,[22] and supports the proposal that the lanthanide ion does preferentially bond to the free substrate in these systems. When $Eu(fod)_3$ is added to a mixture of alanine ethyl ester hydrochloride and Crown 2 in chloroform, the lanthanide-induced shifts are smaller than with $Eu(fod)_4^-$ and no enantiomeric resolution is observed for the methyl resonance of the ethoxy group. The anionic lanthanide tetrakis-β-diketonate species is therefore a better choice than lanthanide tris-β-diketonates for studies with these systems.

The spectrum of valine methyl ester hydrochloride (0.05 M) with Crown 2 (0.10 M) in chloroform exhibits no enantiomeric resolution. Addition of $Eu(fod)_4^-$ causes the enantiomeric resolution of both diastereotopic valine methyl groups and the methoxy resonance, as seen in Fig. 3 and Table 5. As shown in Fig. 3, the diastereotopic valine methyl resonances undergo substantial shifts and the enantiomeric resolution causes the methyl doublets to appear as triplets. Virtually identical results for the valine methyl resonances are observed when $Eu(fod)_4^-$ is added to mixtures of valine methyl ester hydrochloride and Crown 1 in chloroform. The resonances of the L-enantiomer shift further downfield, again in agreement with liquid chromatographic retention data.[22] The spectrum of Crown 2 (0.05 M) and valine methyl ester hydrochloride (0.05 M) mixed in equimolar amounts shows no distinct enantiomeric resolution of any resonance either with or without $Eu(fod)_4^-$. The diastereotopic valine methyl resonances

Table 5. Enantiomeric resolution (Hz) in the ^{1}H NMR spectra of substrates (0.05 M) and Crown 2 (0.10 M) in chloroform-d with added $Eu(fod)_4^-$

Substrate	Resonance	$[Eu(fod)_4^-]$ (M)	$\Delta\Delta\delta$ (Hz)
Alanine ethyl ester HCl	—OCH_2CH_3	0.035	6.6 (L)
Valine methyl ester HCl	—OCH_3	0.035	8.4 (L)
	—CH_3		6.9 (L)
Leucine methyl ester HCl	—CH_3 (upfield)	0.030	3.3 (L)
	—CH_3 (downfield)		3.0 (L)
Valine methyl ester HCl[a]	—CH_3 (upfield)	0.030	7.5 (L)
	—CH_3 (downfield)		7.2 (L)
	—OCH_3	0.035	10.2 (L)

[a] The resonance that shifted further (L or D) is noted.
[b] Sample recorded with Crown 1.

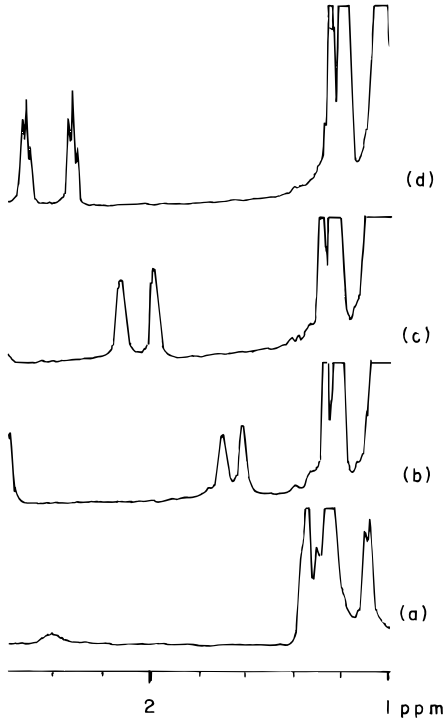


Figure 3. ^{1}H NMR spectrum (300 MHz) of valine methyl ester hydrochloride (0.05 M) with Crown 2 (0.10 M) in chloroform-*d* at 50 °C with (a) no Eu(fod)$_3$ or Ag(fod), (b) Eu(fod)$_3$ (0.01 M) and Ag(fod) (0.01 M), (c) Eu(fod)$_3$ (0.025 M) and Ag(fod) (0.025 M) and (d) Eu(fod)$_3$ (0.035 M) and Ag(fod) (0.035 M).

did have very slight shoulders at a Eu(fod)$_4^-$ concentration of 0.040 M.

The spectrum of leucine methyl ester hydrochloride (0.05 M) with Crown 2 (0.10 M) in chloroform at 20 °C exhibits slight enantiomeric resolution of the methoxy resonance ($\Delta\Delta\delta = 2.7$ Hz) and no enantiomeric resolution of the leucine methyl resonance. No enantiomeric resolution is observed in the spectrum at 50 °C. The series of spectra obtained on addition of Eu(fod)$_4^-$ at 50 °C is shown in Fig. 4. The methoxy resonance could not be followed in the series because of overlap with the crown resonances. Of particular interest, though, are the doublets for the two diastereotopic methyl groups of the leucine. These resonances shift considerably and clearly show enantiomeric resolution in the presence of Eu(fod)$_4^-$. The enantiomeric resolution is enhanced up to a europium concentration of 0.04 M (Table 5), after which it diminishes as more europium is added. Such behavior has been observed before and is characteristic of systems in which the lanthanide bonds to the free substrate.[11,13,14] Association of the lanthanide with the substrate at high lanthanide concentrations effectively strips the substrate from the resolving agent, thereby reducing the enantiomeric resolution. The larger lanthanide-induced shifts for the resonances of the L-enantiomer agree with previous liquid chromatographic retention data.

When adding Eu(fod)$_4^-$ to Crown 2 (0.10 M)–substrate (0.05 M) mixtures, significant shifts of the crown resonances are observed at europium concentrations greater than 0.045 M [Fig. 5(a) and (b)]. Presumably the Eu(III) is complexing with the crown and causing the shifts. The reactions shown in Eqns (3)–(6),

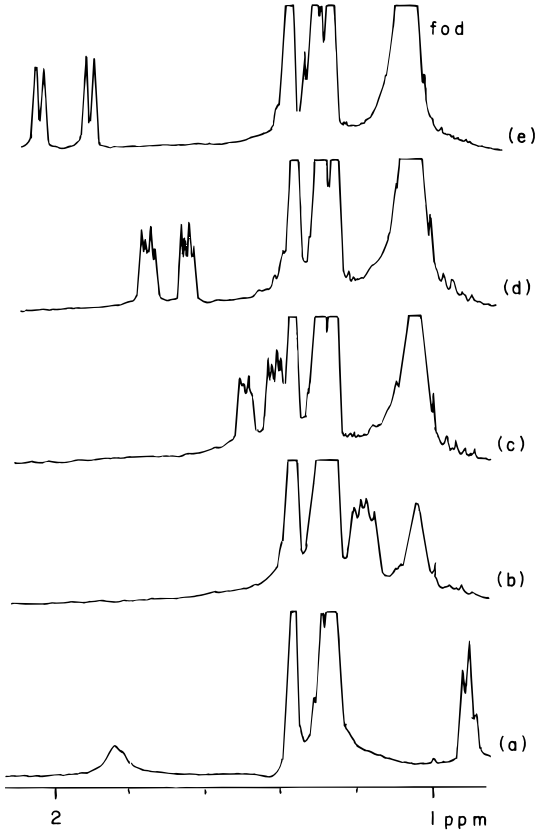


Figure 4. ^{1}H NMR spectrum (300 MHz) of leucine methyl ester hydrochloride (0.05 M) with Crown 2 (0.10 M) in chloroform-*d* at 50 °C with (a) no Eu(fod)$_3$ or Ag(fod), (b) Eu(fod)$_3$ (0.01 M) and Ag(fod) (0.01 M), (c) Eu(fod)$_3$ (0.02 M) and Ag(fod) (0.02 M), (d) Eu(fod)$_3$ (0.03 M) and Ag(fod) (0.03 M) and (e) Eu(fod)$_3$ (0.04 M) and Ag(fod) (0.04 M).

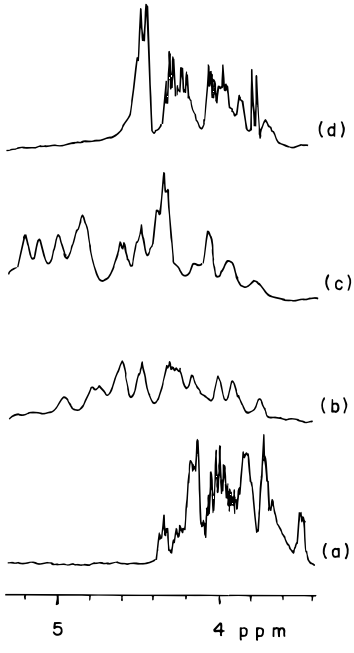


Figure 5. ^{1}H NMR spectrum (300 MHz) in chloroform-*d* of (a) Crown 2 (0.05 M), (b) Crown 2 (0.10 M), leucine methyl ester hydrochloride (0.05 M), Eu(fod)$_3$ (0.07 M) and Ag(fod) (0.07 M), (c) Crown 2 (0.05 M), Eu(fod)$_3$ (0.03 M) and Ag(fod) (0.03 M) and (d) Crown 2 (0.05 M), Eu(fod)$_3$ (0.03 M), Ag(fod) (0.03 M) and K(fod) (0.03 M).

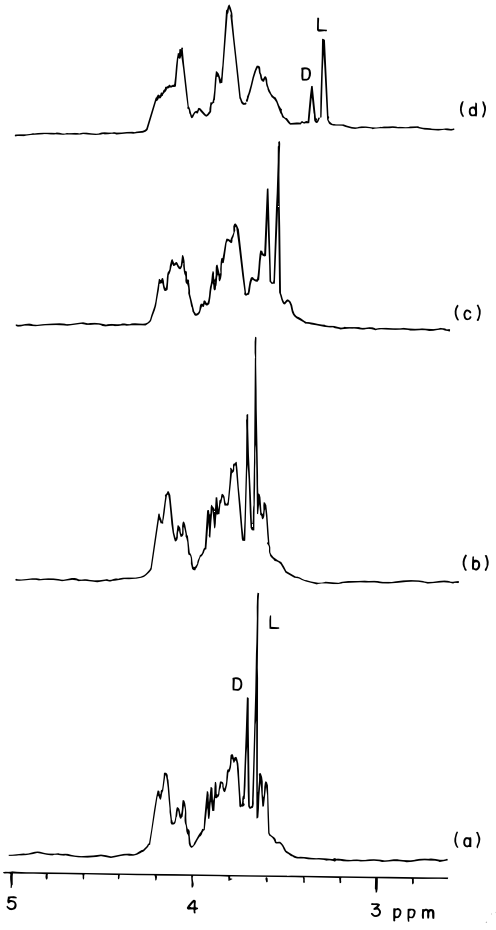


Figure 6. ^{1}H NMR spectrum (300 MHz) of valine methyl ester hydrochloride (0.05 M) with Crown 2 (0.10 M) in acetonitrile-d_3–chloroform-d (50:50) at 20 °C with (a) Pr(fod)$_3$ (0.005 M) and Ag(fod) (0.005 M), (b) Pr(fod)$_3$ (0.01 M) and Ag(fod) (0.01 M), (c) Pr(fod)$_3$ (0.025 M) and Ag(fod) (0.025 M) and (d) Pr(fod)$_3$ (0.05 M) and Ag(fod) (0.05 M).

in which S represents the substrate, do not completely describe the system, but are the most important ones to consider in these mixtures.

$$\text{crown} + \text{S} \rightarrow \text{crown–S} \quad (3)$$

$$\text{crown} + \text{Ag(I)} \rightarrow \text{crown–Ag(I)} \quad (4)$$

$$\text{crown} + \text{Eu(III)} \rightarrow \text{crown–Eu(III)} \quad (5)$$

$$\text{Eu(fod)}_4^- + \text{S} \rightarrow [\text{Eu(fod)}_4^-]\text{S} \quad (6)$$

The reaction in Eqn (4) is only important when the concentration of Ag(Eu(fod)$_4$] is greater than that of the substrate, since at lower concentrations the silver ion precipitates from solution as silver chloride.

The relative extent of complexation of different ions in mixtures with a crown depends on the size and shape of the host and guest, and also the concentrations of the competing species. Generally, the closer the match in size between the host crown and guest cation, the higher is the association constant. The potassium cation, with an ionic diameter of 2.66 Å, is known to associate strongly with 18-crown-6 ethers, which have cavity diameters of 2.6–3.2 Å.[29] Europium(III) and Ag(I) have ionic diameters of 1.90 and 2.52 Å, respectively, so both metal ions fit inside the crown cavity. The size of Ag(I) is more complementary to an 18-crown-6 ether than Eu(III), but unlike Ag(I), Eu(III) is a hard Lewis acid, which complements the hard Lewis basicity of the crown oxygen atoms.

The crown ether resonances in the NMR spectra of mixtures of Crown 2 (0.05 M) with only Ag[Eu(fod)$_4$] (0.03 M) (Fig. 5c) or Eu(fod)$_3$ (0.03 M) show appreciable downfield shifts. The shifts were larger with Eu(fod)$_3$, presumably because of competition of the silver ion for the crown with Ag[Eu(fod)$_4$]. Addition of K(fod) to either mixture causes a significant reduction in the magnitude of the europium-induced shifts [Fig. 5(d)]. Potassium(I), because of its strong association with 18-crown-6 ethers, is expected to displace the europium from the cavity. These data clearly support the conclusion that Eu(III) complexes with the crown.

The crown resonances remain essentially constant in intensity and chemical shift for mixtures of crown (0.10 M), substrate (0.05 M) and lanthanide concentrations less than 0.045 M. Under these conditions, the substrate apparently competes with Eu(III) for the crown and the reactions in Eqns (3) and (6) predominate. Only when Eu(III) is added in concentrations equal to or greater than that of the substrate do appreciable shifts of the crown resonances occur. A 1:1 substrate-to-lanthanide ratio is therefore the upper limit on useful lanthanide concentrations to bring about enhancements in enantiomeric resolution.

The solubility of certain of the cationic substrates in chloroform is limited. Compounds such as octyl- or *n*-butyltryptophan hydrochloride, which were expected to be more soluble in non-polar solvents, still did not dissolve to acceptable levels. Attempts at exchanging the chloride ion with more organic-soluble anions such as pentanesulfonate did increase the solubility of the substrates in chloroform, but not to the concentrations desired. The additional resonances of the pentanesulfonate also obscured important portions of the spectrum. The utility of adding lanthanide ions to crown–substrate mixtures of acetonitrile and acetonitrile–chloroform mixtures was therefore examined with valine methyl ester hydrochloride.

The magnitudes of the lanthanide-induced shifts are considerably smaller in polar solvents. Europium-induced shifts as large as 2 ppm are observed in chloroform with these systems, whereas the largest shifts in acetonitrile and acetonitrile–chloroform mixtures are of the order of 0.12 ppm. Presumably the acetonitrile bonds directly to the lanthanide ion in Ln(fod)$_4^-$ and the competition of solvent molecules for the lanthanide significantly reduces the association of the substrates with the lanthanide. This conclusion is consistent with previous studies of other lanthanide shift reagent systems.[30]

Nevertheless, addition of Eu(fod)$_4^-$ to mixtures of Crown 2 (0.10 M) and valine methyl ester hydrochloride (0.05 M) in acetonitrile did enhance the enantiomeric resolution of the valine and methoxy methyl resonances. The enantiomeric resolution of the more upfield of the two diastereotopic valine methyl resonances increased to 12.0 Hz from an initial value of 3.6 Hz. Addition of Eu(fod)$_4^-$ or Pr(fod)$_4^-$ to mixtures of Crown 2 and valine methyl ester hydrochloride in 50:50 acetonitrile–chloroform causes similar enhancements in enantiomeric resolution. The series of spectra shown in Fig. 6

illustrate another potential benefit of adding a lanthanide species to crown–substrate mixtures in polar solvents. In this example, the upfield shifts caused by the Pr(III) move the methoxy resonances away from the crown resonances so that the signals no longer overlap. Also, because of the faster exchange rate, spectra with lanthanides in polar solvents can be recorded at 20 °C without significant broadening.

CONCLUSION

Crown 1 and Crown 2 are both useful chiral NMR resolving agents for protonated amines, amino alcohols and amino acid esters. Crown 2, because of its ease of preparation and solubility in a wider range of solvents, is often the preferred choice. Addition of a lanthanide species of the form $Ln(fod)_4^-$, which is formed in solution by mixing $Ln(fod)_3$ and Ag(fod), is often useful at enhancing the enantiomeric resolution of certain resonances of the substrate.

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