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(+)-(18-Crown-6)-2,3,11,12-Tetracarboxylic Acid and Its Ytterbium(III) Complex as Chiral NMR Discriminating Agents

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The compound (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid (**I**) and its ytterbium(III) complex are evaluated as chiral NMR discriminating agents. The crown ether is a useful chiral discriminating agent for protonated amino acid esters, amines, and amino alcohols. The crown can also be used with neutral primary amines since amines are protonated through a neutralization reaction with a carboxylic acid moiety of the crown. Enantiodiscrimination with the crown is observed in methanol and acetonitrile. Addition of ytterbium(III) nitrate to crown−substrate mixtures causes upfield shifts in the NMR spectrum of the substrate and often enhances the enantiomeric discrimination. Evidence indicates that the ytterbium(III) bonds to the carboxylic acid moieties of the crown, but enhancements in enantiomeric discrimination result from either the different association constants of the enantiomers with the crown or diastereomeric nature of the resulting crown−substrate complexes. The ytterbium complex with the crown is suitable for use in methanol but precipitates in acetonitrile.

Introduction

Chiral NMR shift reagents are often employed to analyze mixtures of enantiomers. A suitable optically pure reagent is used either to derivatize the enantiomers into a pair of diastereomers or to differentially solvate the enantiomers. A wide variety of chiral NMR shift reagents have been developed.[1,2] For many compounds, enantiomeric discrimination is still often small or nonexistent in the NMR spectra with established chiral shift reagents.

Several reports have shown that enantiomeric discrimination with chiral solvating agents can be enhanced through the use of appropriate lanthanide species.[3−9] The lanthanide ion can either be added to solvating agent−substrate mixtures[3−5,7,8] or bonded to the chiral solvating agent.[6,9] In the former case, the lanthanide species is chosen so that it preferentially complexes with substrate in the bulk solution rather than substrate associated with the chiral solvating agent. The enantiomer that associates more weakly with the chiral solvating agent then exhibits larger lanthanide-induced shifts.

An important family of chiral discriminating agents are host compounds, one subset of which are chiral crown ethers. Crown ethers form complexes with protonated

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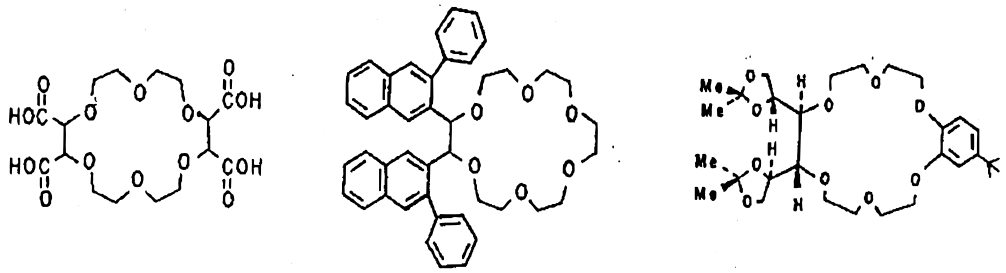
Chart 1



I II III

primary amines, and many chiral crown ethers have been examined for their ability to enantiodiscriminate.[10] Unlike crown ethers, other common chiral solvating agents require a second binding site on primary amines for enantiodiscrimination.[2] Because chiral crown ethers can be used as NMR solvating agents with protonated primary amines, they are easier to use and avoid uncertainties about reaction yields and retention of configuration that are of concern with many chiral derivatizing agents.[1] Often the compound 2,3:4,5-bis[1,2-(3-phenylnaphtho)-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (**II**) (Chart 1) is regarded as the benchmark to which other chiral crown ethers are compared.[11] In a prior report, we described a general scheme for using lanthanide ions to enhance enantiomeric discrimination in the NMR spectra of substrate−crown ether mixtures in chloroform.[8] It was necessary to have an anionic, chloroform-soluble lanthanide species to associate with the ammonium ions. Such a species was achieved by mixing a lanthanide tris(β-diketonate) with a silver β-diketonate, thereby forming an ion pair involving a lanthanide tetrakis(β-diketonate) anion and silver cation. When added to mixtures of crown ethers and amine hydrochloride salts, silver chloride precipitated and an ion pair formed between the organic cation and the lanthanide tetrakis(β-diketonate) anion. A drawback is that these systems are not that effective in polar solvents such as acetonitrile and methanol, a significant restriction given the limited solubility of protonated primary amines in chloroform.

A crown ether increasingly used as a chiral discriminating agent is (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid (**I**) (Chart 1),[12−19] which is easy to synthesize[20,21] and now commercially available. Most applications of **I** for chiral discrimination are in capillary electrophoresis.[12−15] Its use as a chiral NMR discriminating agent is quite limited, having only been evaluated with 1-(1-naphthyl)-ethylamine, alanine-β-naphthylamide,[17] and 3,5-di-*tert*-butyl-4-hydroxyglycine.[18] The purpose of this report is 2-fold. One is to extend the applicability of **I** as a chiral NMR discriminating agent. The other is to examine the coupling of lanthanide ions to enhance enantiomeric discrimination. Of special significance is the presence of the carboxylic acid moieties, which provide potential sites for direct bonding of lanthanide ions to the crown ether.

Experimental Section

Reagents. The sources of substrates and deuterated NMR solvents were described in a prior report.[8] Compound **I** was obtained from Sigma-Aldrich (Milwaukee, WI). The nitrate salts of lanthanides were prepared by established procedures.[22]

Procedures. The appropriate amounts of crown ether (typically 0.025 M) and substrate (typically 0.025 M) were weighed and dissolved in 1 mL of methanol-d_4. Increments of ytterbium(III) nitrate pentahydrate were added either by weight or by 10 μL additions of a 0.5 M stock solution in methanol-d_4. All chemical shift values were referenced to internal tetramethylsilane.

Apparatus. All spectra were recorded on a General Electric QE 300 MHz NMR spectrometer at ambient probe temperature.

Results and Discussion

Enantiomeric discrimination in the NMR spectra of substrates in methanol with **I** is reported in Table 1. Comparable discrimination is obtained whether racemic or enantiomerically enriched mixtures are used. Enantiomeric discrimination previously obtained with 1,2:5,6-di-*O*-isopropylidene-3,4-[(*tert*-butylbenzenediyl)-bis(oxyethoxy)ethyl-3-mannitol (**III**) (Chart 1), which was generally more effective than **II**, is provided in Table 1 as well.[8] With a few exceptions, notably the methoxy resonances of alanine, phenylalanine, and lysine methyl ester hydrochloride, the enantiomeric discrimination with **I** is similar or often significantly larger than that with **III**. Of the 11 substrates examined, the spectra of 9 exhibit enantiomeric discrimination for one or more resonances in the presence of **I**.

Enantiomeric composition can be determined by integration of the NMR spectra. For example, analysis of an enantiomerically enriched mixture of *R*,*S*-phenylglycine (80% *R* by weight) by integration of the CH resonances gave a measured value of 80.8 ± 0.2% for the *R*-enantiomer. It is possible to distinguish as little as 1% of the minor enantiomer of phenylglycine in mixtures with **I**. The enantiomeric discrimination of the H_1 and H_6 resonances of tryptophan with **I** is considerably less than the CH resonance of phenylglycine. Analysis of an

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Table 1. Enantiomeric Discrimination (Hz) in the ^{1}H NMR Spectra of Substrates (0.025 M) in the Presence of I (0.025 M) in Methanol-d_4 at 20 °C

substrate	resonance	I	III[a]
valine methyl	$-CH_3$	13.2	4.5
ester HCl	$-CH_3$	3.0	0.6
	$-OCH_3$	4.5	4.8
leucine methyl ester HCl	$-OCH_3$	3.9	0
alanine methyl	$-CH_3$	9.3	7.2
ester HCl	$-OCH_3$	0	5.7
phenylalanine methyl ester HCl	$-OCH_3$	0	2.4
phenylglycine	$-OCH_3$	6.0	9.6
methyl ester HCl	$-CH$	84.6	2.1
tryptophan methyl	$-H_1$	14.7	0
ester HCl	$-H_6$	30.0	0
	$-OCH_3$	6.0	4.8
lysine methyl ester HCl	$-OCH_3$	0	1.8
1-(1-naphthyl)-	$-CH_3$	24.3	3.0
ethylamine HCl	$-CH$	57.6	0
	−aromatic	47.7	0
1-phenylethyl-	$-CH_3$	12.6	2.4
amine HCl	$-CH$	22.6	0
1-cyclohexylethylamine HCl	$-CH_3$	16.5	0
(1*S*,2*R*)- and (1*R*,2*S*)-	$-CH_3$	1.8	2.1
α-(1-aminoethyl)-	−aromatic (3′)	7.8	3.3
4-hydroxybenzyl	$-CH$	19.5	5.4
alcohol HCl			

[a] Enantiomeric discrimination with **III** (0.050 M) and substrate (0.050 M) in methanol-d_4.[8]

enantiomerically enriched mixture of DL-tryptophan (80% L by weight) provided values of 82.4% ± 0.4% (H_6) and 83.0 ± 0.4% (H_1) for the L-enantiomer.

Figure 1 shows the diastereotopic methyl resonances of DL-valine methyl ester hydrochloride (enriched in the L-enantiomer) as increasing quantities of **I** are added. One of the methyl resonances shifts upfield on addition of the crown, whereas the other shifts downfield. The methoxy resonance, which is not shown in the figure, experiences a slight upfield shift on addition of the crown and exhibits enantiomeric discrimination. Inconsistencies in the direction substrate resonances shift in mixtures with the crown are common. Association of valine methyl ester hydrochloride with the crown leads to both diastereotopic and enantiomeric discrimination of the methyl groups; however, the enantiomeric discrimination is considerably more pronounced for one of the methyl groups than the other. Only modest gains in enantiomeric discrimination are obtained at ratios of crown-to-substrate above 1. This behavior is consistent with other substrates examined, so either 1:1 or 2:1 ratios of crown-to-substrate are appropriate.

The environment about the ammonium group is important in influencing the extent of enantiomeric discrimination. The enantiomeric separation of 1-(1-naphthyl)ethylamine was greater than 1-phenylethylamine using **I** as a mobile phase additive in capillary electrophoresis.[15] Furthermore, enantiomeric separation of leucine was better than valine when **I** was used as a liquid chromatographic stationary phase[16] or pseudostationary phase in capillary electrophoresis.[12] The elution orders of these compounds with **I** can be explained by the influence of steric effects on the relative association constants, a common factor in enantioseparations using chiral crown ethers.[11,19,23] 1-Phenylethylamine hydrochloride, 1-(1-naphthyl)ethylamine hydrochloride, 1-cyclohexylethylamine hydrochloride, and α-(1-aminoethyl)-4-hydroxybenzyl alcohol ($HOC_6H_4CH(OH)CH(CH_3)NH_2$) hydrochloride contain ethylamine groups. The greater enantiomeric discrimination observed for the methyl and methine resonances of 1-(1-naphthyl)ethylamine hydrochloride may reflect the increased steric hindrance of the naphthyl ring relative to the phenyl, cyclohexyl, and benzyl groups in the other substrates, although a greater difference in the magnetic anisotropies of the diastereomeric crown−substrate complexes cannot be ruled out.

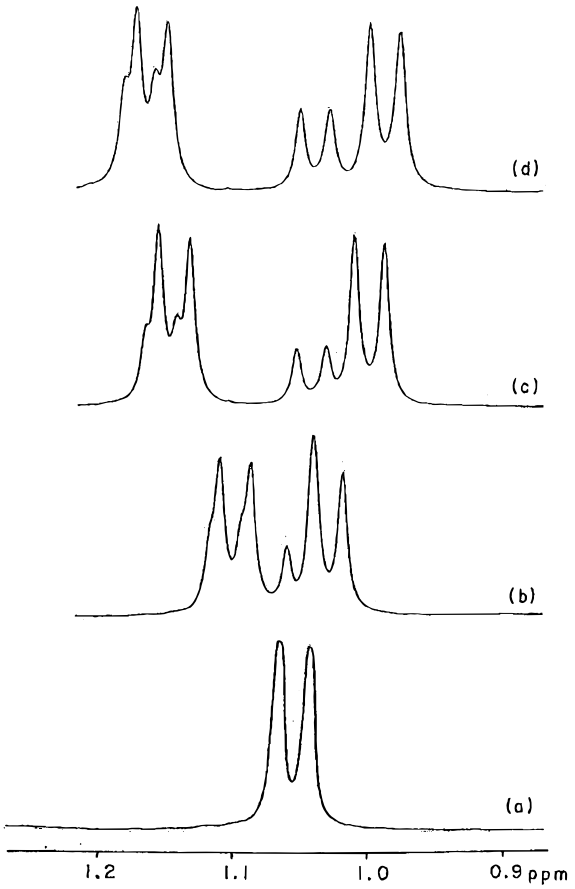

Figure 1. Resonances for the valine methyl groups in the ^{1}H NMR spectrum (300 MHz) of DL-valine methyl ester hydrochloride (0.025 M, enriched in L-enantiomer) in methanol-d_4 at 20 °C with (a) no **I**, (b) 0.0125 M **I**, (c) 0.025 M **I**, and (d) 0.050 M **I**.

For example, in contrast to the chromatographic data, the diastereotopic methyl groups of leucine methyl ester hydrochloride exhibit less enantiodiscrimination in the NMR spectra than valine methyl ester hydrochloride. The methyl groups in leucine are further from the chiral center and ammonium group than in valine, which presumably accounts for the reduced diastereotopic and enantiomeric discrimination in NMR spectra with **I**. As these results demonstrate, chromatographic and NMR spectroscopic methods sometimes complement each other in analyzing mixtures of enantiomers.

Compound **I** is soluble in methanol, acetonitrile, and dimethyl sulfoxide. The chemical shifts and enantiomeric discrimination in the spectra of substrates in methanol and acetonitrile are quite similar. No shifts or enantiomeric discrimination are observed in the spectrum of substrates with **I** in dimethyl sulfoxide.

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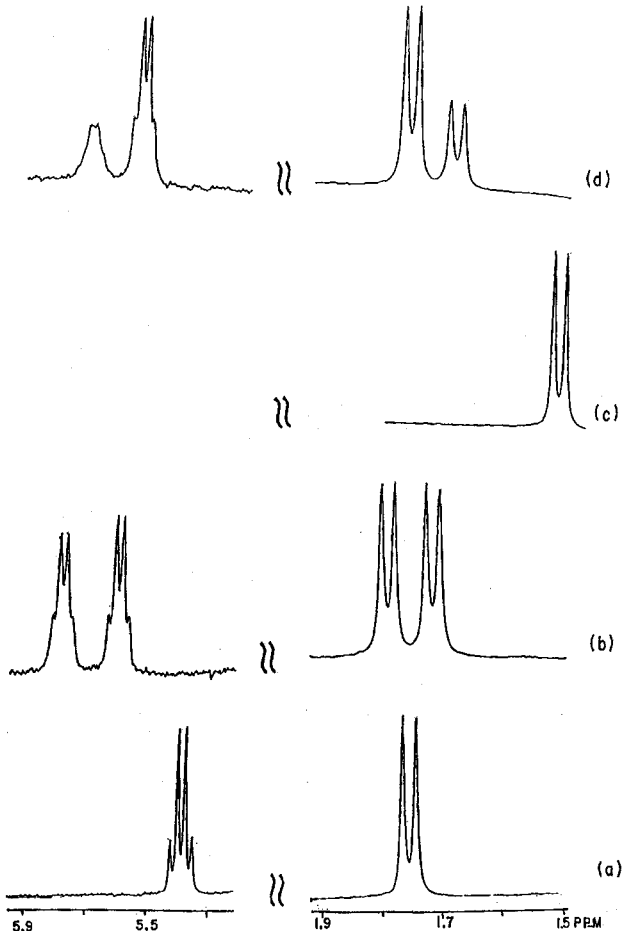

Figure 2. Resonances for the methyl and methine groups in the ^{1}H NMR spectrum (300 MHz) of (a) racemic 1-(1-naphthyl)-ethylamine hydrochloride (0.025 M), (b) racemic 1-(1-naphthyl)ethylamine hydrochloride (0.025 M) and **I** (0.025 M), (c) *R*,*S*-1-(1-naphthyl)ethylamine (0.025 M, enriched in *S*-enantiomer), and (d) *R*,*S*-1-(1-naphthyl)ethylamine (0.025 M, enriched in *S*-enantiomer) and **I** (0.025 M) in methanol-d_4 at 20 °C.

With a few exceptions,[24] crown ethers do not strongly associate with neutral primary amines. Primary amines in the presence of **I** are converted to their corresponding ammonium ion through a neutralization reaction with a carboxylic acid moiety of the crown. Figure 2 shows the methyl and methine regions of the spectra of *R*,*S*-1-(1-naphthyl)ethylamine (enriched in the *S*-enantiomer) and racemic 1-(1-naphthyl)ethylammonium ion with and without **I**. The significant downfield shifts of the methyl and methine resonances of 1-(1-naphthyl)ethylamine that occur when it is mixed with **I** (Figure 2d) are consistent with protonation of the amine group (the methine resonance is not seen in Figure 2c since it is considerably upfield and overlaps with the HOD resonance at approximately 4.8 ppm). Comparable enantiomeric discrimination of the methyl and methine resonances is observed when either the amine (Figure 2d) or ammonium ion (Figure 2b) are mixed with the crown. 1-Phenylethylamine and 1-cyclohexylethylamine and their corresponding ammonium salts show similar results, although the enantiomeric discrimination with the neutral amine is slightly less than when the ammonium ion is analyzed. Presumably, the protonated amine formed in situ through the neutralization reaction associates as an ion pair to some extent with the carboxylate group, thereby diminishing its association within the crown cavity. The use of 2:1 crown-to-substrate ratios is recommended when neutral primary amines are added to **I**.

Lanthanide(III) ions are well-known for their properties as NMR shift reagents.[25] The magnitude and direction of the shifts vary with the identity of the ion and exhibit a significant dependence on solvent. In noncoordinating solvents such as chloroform, lanthanide-induced shifts are quite large for an associated compound, and ions such as europium or praseodymium are preferable. In coordinating solvents such as water and methanol, lanthanide ions that produce larger shifts are often necessary. Ions that cause larger shifts also cause more broadening, so selection of the appropriate lanthanide ion requires a balancing of shift and broadening effects.

Even though the crown is an effective enantiomeric discriminating agent in acetonitrile, addition of lanthanide salts to crown−substrate mixtures in acetonitrile resulted in the formation of a precipitate. The precipitate is believed to be a lanthanide−crown complex. No appreciable lanthanide-induced shifts are observed with these systems in methyl sulfoxide.

The shifts caused by europium(III) and praseodymium-(III) in **I**−substrate mixtures in methanol are too small to be of much practical utility. The broadening with ions such as thulium(III) and dysprosium(III) is so great at the field strength employed that coupling information is absent from the spectrum. Ytterbium(III) provides the most appropriate balance between the magnitude of the shifts, which are upfield with these systems, and broadening effects. The magnitude of the ytterbium-induced shifts are not that large (approximately 0.1−0.2 ppm) but are sizable enough to cause significant enhancements in enantiomeric discrimination with several substrates.

The series of spectra in Figure 3 show the effect of adding ytterbium to a mixture of DL-alanine methyl ester hydrochloride (enriched in the L-enantiomer) and **I**. As the concentration of ytterbium is increased, enantiomeric discrimination of the methyl resonance improves from 9.3 to 32.4 Hz; the methoxy resonance, from 0 to 12.0 Hz. The effect of adding ytterbium to a mixture of racemic (1*S*,2*R*)- and (1*R*,2S)-α-(1-aminoethyl)-4-hydroxybenzyl alcohol hydrochloride and the crown is shown in Figure 4. The methyl and one aromatic resonance exhibit complete enantiomeric discrimination on addition of ytterbium. The other aromatic resonance is partially resolved in the presence of ytterbium. A summary of the enhancements in enantiomeric resolution caused by adding ytterbium to substrate−**I** mixtures is provided in Table 2.

Certain resonances such as the methine group of 1-(1-naphthyl)ethylamine hydrochloride, the methyl group of valine methyl ester hydrochloride, the methine group of phenylglycine methyl ester hydrochloride, and H_6 of tryptophan methyl ester hydrochloride shift downfield on addition of the crown. In these cases, the upfield shifts induced by the ytterbium cause a reduction in enantiomeric discrimination. For the aromatic resonance of α-(1-aminoethyl)-4-hydroxybenzyl alcohol hydrochloride at about 7.3 ppm (Figure 4b), the signal further downfield

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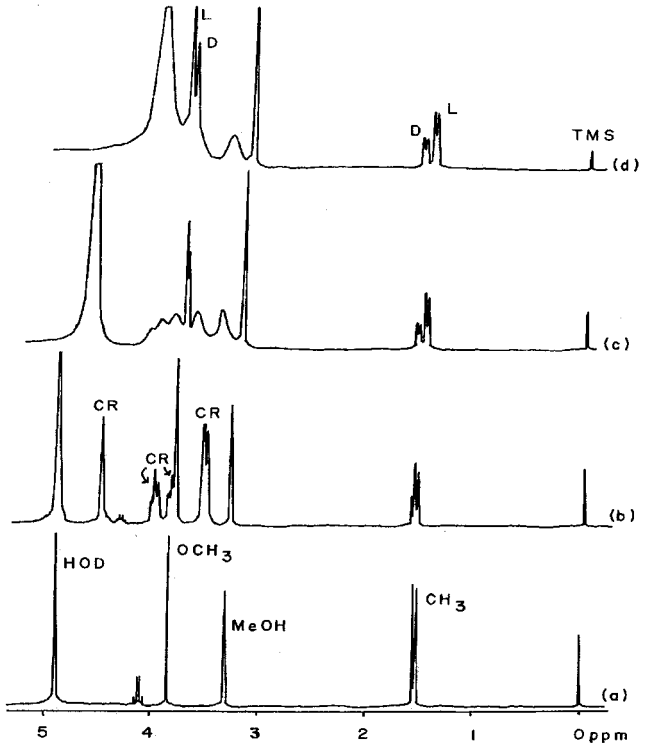

Figure 3. ^{1}H NMR spectrum (300 MHz) of (a) DL-alanine methyl ester hydrochloride (0.025 M, enriched in L-enantiomer) in methanol-d_4 at 20 °C with (b) **I** (0.025 M), (c) **I** (0.025 M) and ytterbium(III) nitrate (0.035 M), and (d) **I** (0.025 M) and ytterbium(III) nitrate (0.125 M). CR denotes crown ether resonances.

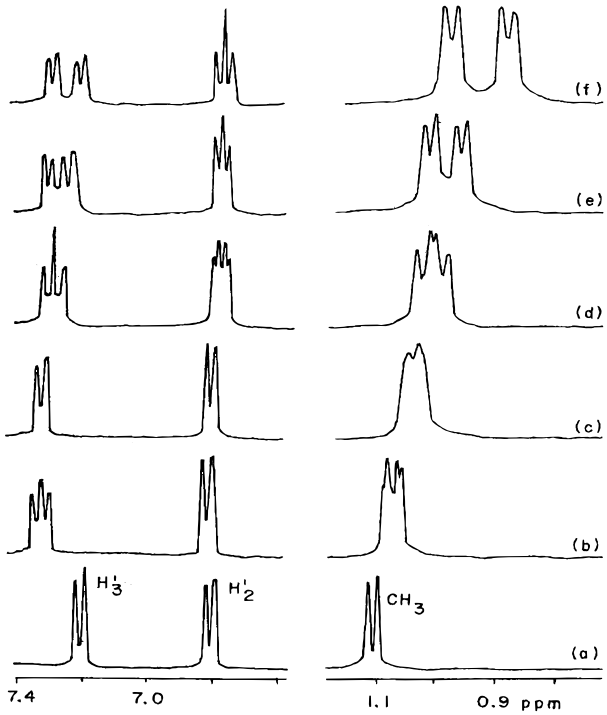

Figure 4. Resonances for the aromatic and methyl groups in the ^{1}H NMR spectrum (300 MHz) of (a) racemic (1*R*,2*S*)- and (1*S*,2*R*)-α-(1-aminoethyl)-4-hydroxybenzyl alcohol hydrochloride (0.025 M) in methanol-d_4 at 20 °C with (b) **I** (0.025 M), (c) **I** (0.025 M) and ytterbium(III) nitrate (0.005 M), (d) **I** (0.025 M) and ytterbium(III) nitrate (0.025 M), (e) **I** (0.025 M) and ytterbium(III) nitrate (0.050 M), and (f) **I** (0.025 M) and ytterbium(III) nitrate (0.100 M).

exhibits the larger ytterbium-induced shifts such that the resonances of the enantiomers initially coalesce (Figure 4c) and then reverse positions (Figure 4d−f).

Evidence indicates that ytterbium(III) preferentially bonds to the crown when added to solutions of **I** and protonated amine substrates. First, the crown resonances show considerably more broadening than the resonances of the substrate on addition of ytterbium(III) (Figure 3). Second, plots of $\Delta\Delta\delta$ as a function of ytterbium concentration increase and eventually level off at a limiting value, which is in contrast with lanthanide−chiral solvating agent systems in which the lanthanide preferentially bonds to the substrate in the bulk solution.[3,5,7] In the latter case, the value of $\Delta\Delta\delta$ goes through a maximum as the increasing concentration of lanthanide eventually strips sufficient quantities of the substrate from the solvating agent. Finally, several of the substrates including 1-(1-naphthyl)ethylamine hydrochloride, 1-phenylethylamine hydrochloride, and 1-cyclohexylethylamine hydrochloride, which only have a cationic group, would not be expected to bond to the lanthanide cation. Also, the ester functionality of the amino acid derivatives examined in this study would not bind well to ytterbium(III) in methanol.[24]

At the concentrations employed in our work (0.025 M for crown and substrate), and assuming crown−substrate association constants of approximately 1000,[18] about 20% of the substrate is not associated with the crown. Prior chromatographic, NMR spectral, and crystallographic data has shown that the *R*-enantiomer of 1-(1-naphthyl)-ethylamine associates more strongly with **I**.[15,18,19] The *R*-enantiomer of 1-(1-naphthyl)ethylamine shifts further when ytterbium is added to mixtures with the crown. On the basis of liquid chromatographic data, the D isomers of amino acids used in our study associate more strongly with **I**.[16] In most cases, larger ytterbium-induced shifts are observed for the D isomer of amino acid methyl ester hydrochloride salts; however, the results in Figure 3 for alanine methyl ester hydrochloride are unique in exhibiting the opposite behavior. Differential shifts of the

Table 2. Enantiomeric Discrimination (Hz) in the ^{1}H NMR Spectra of Substrates (0.025 M) in the Presence of I (0.025 M) in Methanol-d_4 at 20 °C with and without Ytterbium(III) Where Resonances Listed Are Those for Which Enhancements Occurred

substrate	resonance	**I**	Yb	Yb/s[a]
valine methyl ester HCl	$-CH_3$	3.0	6.6	2
alanine methyl ester HCl	$-CH_3$	9.3	32.4	6
	$-OCH_3$	0	12.0	5
phenylalanine methyl ester HCl	$-OCH_3$	0	8.1	1
phenylglycine methyl ester HCl	$-OCH_3$	6.0	15.9	2
tryptophan methyl ester HCl	$-H_4$	0	8.7	2
	$-OCH_3$	6.0	11.7	2
lysine methyl ester HCl	$-OCH_3$	0	4.5	2
1-(1-naphthyl)ethylamine HCl	$-CH_3$	24.3	37.8	2
1-phenylethyl-amine HCl	$-CH_3$	12.6	22.8	2
	−CH	22.6	37.8	0.4
	−ortho	0	18.6	0.8
1-cyclohexylethylamine HCl	$-CH_3$	16.5	21.6	2
(1*S*,2*R*)- and (1*R*,2*S*)-	$-CH_3$	1.8	37.8	6
α-(1-aminoethyl)-	−aromatic (3′)	7.8	30.6	6
4-hydroxybenzyl	−aromatic (2′)	0	9.0	6
alcohol HCl	−CH	19.5	120.0	6

[a] Ytterbium−substrate ratio.

enantiomers caused by the binding of ytterbium to the crown therefore appear to be a mix of relative association constants and the diastereomeric nature of the crown−substrate complexes.

Binding of Yb(III) to the monocarboxylate form of the crown, prepared by either mixing a primary amine with the crown or adding 1 equiv of sodium bicarbonate to a solution of the crown and warming to expel carbon dioxide, is much greater than binding to the neutral crown. For example, broadening in the spectrum of amines is much worse than occurs in the spectra of the corresponding amine hydrochlorides with the crown, even if the concentration of ytterbium with the amine hydrochloride is 10 times higher. Presumably the broadening in the spectrum of the monocarboxylate species is severe even at low concentrations of ytterbium because several crown ligands bind at a time. In almost all cases, the ytterbium-induced broadening that occurs with the anionic crown precludes the measurement of enantiomeric discrimination. One exception occurs with phenylalanine methyl ester hydrochloride. In this case there is an indication that the methine resonance is enantiomerically distinguished in the presence of the neutral and anionic crown (prepared by adding 1 equiv of sodium bicarbonate to the crown); however, significant overlap with a resonance of the crown precludes an unequivocal determination. With the anionic crown, addition of ytterbium causes such significant broadening of the crown resonances relative to those of the substrate that the enantiomeric discrimination of the methine signal is apparent. With the neutral crown, the broadening is not sufficient to distinguish the methine resonance from that of the crown.

Conclusion

Chiral crown ethers represent one of the few examples of NMR solvating agents for chiral primary amines. The compound (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid is an especially effective NMR chiral solvating agent for protonated primary amines, amino alcohols, and amino acid esters in methanol or acetonitrile. The magnitude of enantiodiscrimination and solvent compatibility of **I** is better than previously reported crown ethers.[8] The use of **I** as a chiral NMR solvating agent for primary amines avoids the uncertainties about yield and retention of configuration that can characterize the use of chiral derivatizing agents for amines. Amines can be added to **I** in either their protonated or neutral form. Neutral amines undergo a neutralization reaction with **I** to generate the protonated form. Addition of ytterbium(III) nitrate to crown−substrate solutions in methanol causes shifts in the NMR spectrum of the substrate that often lead to enhancements in the extent of enantiomeric discrimination.

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