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Chiral NMR Shift Reagents: Mixtures of Lanthanide Tris (β-diketonates) with Chiral Carboxylate Anions

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Chiral carboxylic acids such as *N*-(*R*)-1-(1-naphthyl)ethylaminocarbonyl-L-*tert*-leucine, *N*-(*R*)-1-(1-naphthyl)ethylaminocarbonyl-L-valine and *N*-(3,5-dinitrobenzoyl)-L-leucine are solubilized in chloroform by the addition of triethylamine. The resulting ion pairs are useful chiral resolving agents for sulfoxides, amines and alcohols. For certain substrates, particularly amines, the ion pairs were more effective chiral resolving agents than the corresponding organic-soluble ester derivatives. Addition of lanthanide tris(β-diketonate) complexes to mixtures of the ion pairs causes enhancements in the enantiomeric resolution in the spectra of certain substrates. Evidence indicates that the chiral carboxylate compound bonds directly to the lanthanide tris(β-diketonate) to form an anionic species. Shifts in the spectra of substrates and enhancements in enantiomeric resolution in the presence of the anionic species appear to be dominated by bonding of the substrate to the carboxylate moiety of the lanthanide complex. These new reagents are therefore complementary to mixtures of lanthanide tris(β-diketonate) complexes with the ester forms of the resolving agents. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

NMR spectroscopy is one of the most common methods of determining enantiomeric excess. Using an optically pure reagent, it is possible to synthesize a pair of diastereomers, the NMR spectra of which may then exhibit different chemical shifts. Alternatively, an optically pure chiral solvating agent can be added. Association of the solvating agent with the enantiomers forms diastereomeric complexes *in situ*, and these complexes may have different shifts in the NMR spectra. Alternatively, it is possible that one enantiomer has a larger association constant with the solvating agent than the other, and the different time-averaged solvation environments may then lead to differences in the chemical shifts.

Another common method for resolving enantiomers is to use liquid chromatography. A large variety of chiral stationary phases have been developed for use in liquid chromatography.[1] Soluble analogues of certain of these materials have also been used as chiral resolving agents in NMR spectroscopy.[2–10] In many instances, the enantiomeric resolution observed in the NMR spectrum with these reagents is small or not observed at all. By coupling a paramagnetic lanthanide ion to these systems, it is possible to enhance the enantiomeric resolution in the NMR spectra. Coupling of lanthanide ions to chiral resolving agents can be achieved in two ways. Pirkle and co-workers[11,12] were the first to show that enantiomeric resolution could be enhanced by mixing a suitable achiral lanthanide species with mixtures of a resolving agent and substrate. Assuming the association constants of the substrate enantiomers with the resolving agent were different, and the lanthanide ion bonded preferentially to the ‘free’ substrate, the spectrum of the enantiomer that exhibited the weaker association with the resolving agent exhibited the larger lanthanide-induced shifts.[11,12] This method has since been extended to other resolving agent systems.[13,14] An alternative strategy is to bond the lanthanide directly to the chiral resolving agent. In this scheme, in addition to enhanced enantiomeric resolution, it is possible to use the magnitude of the lanthanide-induced shifts to obtain information about the geometry of substrate–chiral resolving agent interactions. Such a directly coupled lanthanide–resolving agent system has been described for cyclodextrins.[15]

We have described the use of esters of *N*-(3,5-dinitrobenzoyl)- and 1-(1-naphthyl)ethylurea derivatives of amino acids as organic-soluble chiral NMR resolving agents.[13,14] Mixtures of lanthanides with these resolving agents often resulted in enhanced enantiomeric resolution. One of our goals has been to develop organic-soluble systems in which the lanthanide is bonded directly to the chiral resolving agent, analogous to the previously reported water-soluble cyclodextrin systems.[15] The potential use of 2.2.2 and 2.2.1 cryptands as encapsulating ligands for such a coupling scheme was evaluated. Resolving agents such as *N*-1-(1-naphthyl)ethylurea derivatives of amino acids (**Ia**, **IIa**) and *N*-(3,5-dinitrobenzoyl)-L-leucine (**IIIa**) are solubilized in chloroform in the presence of the cryptands, presumably

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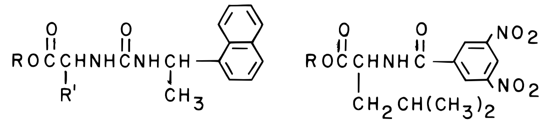


	R	R'	R	
Ia	H	$C(CH_3)_3$	H	IIIa
Ib	CH_3	$C(CH_3)_3$	CH_2CH_3	IIIb
IIa	H	$CH(CH_3)_2$		
IIb	CH_2CH_3	$CH(CH_3)_2$		

Formula 1

owing to the formation of an ion pair between the carboxylic acid and tertiary amine of the cryptand. Work on the cryptand systems was abandoned when evidence indicated that addition of a substrate caused removal of some of the lanthanide from the cavity.

During this work, mixtures in which triethylamine (TEA) was used to solubilize the chiral carboxylic acid instead of the cryptand were examined for comparison. Certain anomalies between the ester and acid forms of the chiral resolving agents (CRA) were noted when lanthanide tris(*β*-diketonate) complexes with 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione (fod) were added to the solutions. These anomalies led us to propose that the species $[Ln(fod)_3(CRA)]^-HTEA^+$, in which the carboxylate moiety acts as a ligand and bonds directly to the lanthanide, is formed in mixtures of $Ln(fod)_3$, TEA and the acid form of the resolving agents. Enhancements in enantiomeric resolution in the NMR spectra of substrates in the presence of $[Ln(fod)_3(CRA)]^-$ appear to be caused by preferential shifting of the enantiomer that associates more strongly with the chiral carboxylate group of the lanthanide complex. As such, these systems complement those with the ester reagents in which larger lanthanide-induced shifts are observed for the more weakly bonded enantiomer. Evidence for the proposed mechanism will be presented, and the effectiveness of CRA^-HTEA^+ ion pairs as chiral resolving agents is described.

EXPERIMENTAL

Reagents

The compounds (*R*)-(+)- and (*S*)-(−)-*α*-methylbenzylamine, (*R*)-(+)- and (*S*)-(−)-1-(1-naphthyl)ethylamine, (*R*)-(+)- and (*S*)-(−)-methyl *p*-tolyl sulfoxide, (*R*)-(+)- and (*S*)-(−)-*sec*-phenethyl alcohol, (*R*)-(+)- and (*S*)-(−)-*α*-methyl-1-naphthalenemethanol, dinitrobenzoyl chloride, benzoyl chloride, L-valine, L-*tert*-leucine, (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate and *N*-(3,5-dinitrobenzoyl)-L-leucine were obtained from Aldrich Chemical (Milwaukee, WI, USA). Lanthanide complexes of 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione $[Ln(fod)_3]$ were prepared by reported procedures.[16] The preparations of *N*-(*R*)-1-(1-naphthyl)ethylaminocarbonyl-L-*tert*-leucine methyl ester (**Ib**), *N*-(*R*)-1-(1-naphthyl)ethylaminocarbonyl-L-valine ethyl ester (**IIb**) and 3,5-dinitrobenzoyl-L-leucine ethyl ester (**IIIb**) have been described previously.[13,14] *N*-(*R*)-1-(1-Naphthyl)ethylaminocarbonyl-L-*tert*-leucine (**Ia**) and *N*-(*R*)-1-(1-naphthyl)ethylaminocarbonyl-L-valine (**IIa**) were prepared by a literature method.[17]

Preparation of 3,5-dinitrobenzoyl and benzoyl derivatives of amines

A solution of the appropriate amine (2.2 mmol) in 20 ml of dry tetrahydrofuran was placed in a three-necked, round-bottomed flask fitted with a nitrogen inlet. Propylene oxide (0.38 g, 6.6 mmol) and then dinitrobenzoyl chloride (0.5 g, 2.2 mmol) were added in one portion and the solution was stirred for 15 min. The solvent was removed by rotary evaporation, resulting in a brown oil that solidified on standing. The pure product was obtained by recrystallization from acetonitrile. Benzoyl derivatives of amines were prepared by a similar procedure using benzoyl chloride.

Procedures

The appropriate amount of substrate and chiral resolving agent were weighed into an NMR tube and dissolved in chloroform-*d*. After recording the initial spectrum, the lanthanide complex was added in small portions either by weight or by 5 µl additions of a concentrated stock solution. Shifts were recorded relative to tetramethylsilane. NMR spectra were recorded on a General Electric QE 300 MHz instrument at ambient probe temperature unless specified otherwise.

RESULTS AND DISCUSSION

Comparison of Ia and IIa with Ib and IIb

Representative spectra from the series obtained when increments of $Eu(fod)_3$ are added to a mixture of methyl *p*-tolyl sulfoxide, triethylamine and **Ia** are shown in Fig. 1. The spectra obtained by adding $Eu(fod)_3$ to a mixture of **Ib** and methyl *p*-tolyl sulfoxide are shown for comparison in Fig. 2. The europium-induced shifts in the spectra of methyl *p*-tolyl sulfoxide with **Ib** are considerably larger than those with **Ia**. It is assumed that the free substrate bonds to the europium when using **Ib**, a conclusion substantiated by the large shifts of the sulfoxide methyl group.[18] Since the sulfoxide methyl resonance of the *S*-isomer exhibits the larger lanthanide-induced shifts with **Ib**, the *R*-isomer presumably bonds more strongly to the resolving agent. It is noteworthy that when $Eu(fod)_3$ is added to mixtures of **Ia** and methyl *p*-tolyl sulfoxide, the sulfoxide methyl resonance of the *R*-isomer shifts further. The resonance of the *R*-enantiomer is initially at a lower frequency in the mixture of **Ia** with methyl *p*-tolyl sulfoxide [$\Delta\Delta\delta = 2.1$ Hz, Fig. 1(a)]. On addition of $Eu(fod)_3$ the larger shift of the *R* resonance causes the sulfoxide methyl peaks to coalesce and then eventually the resonance of the *R*-enantiomer appears at a higher frequency [Fig. 1(b) and (c)].

Evidence that the mode of association of substrates with the acid and ester forms of these resolving agents is similar is demonstrated by the data in Tables 1–3. Table 1 lists the shifts in the spectra of representative substrates in mixtures with **Ia**, **Ib**, **IIa** and **IIb**. The sub-

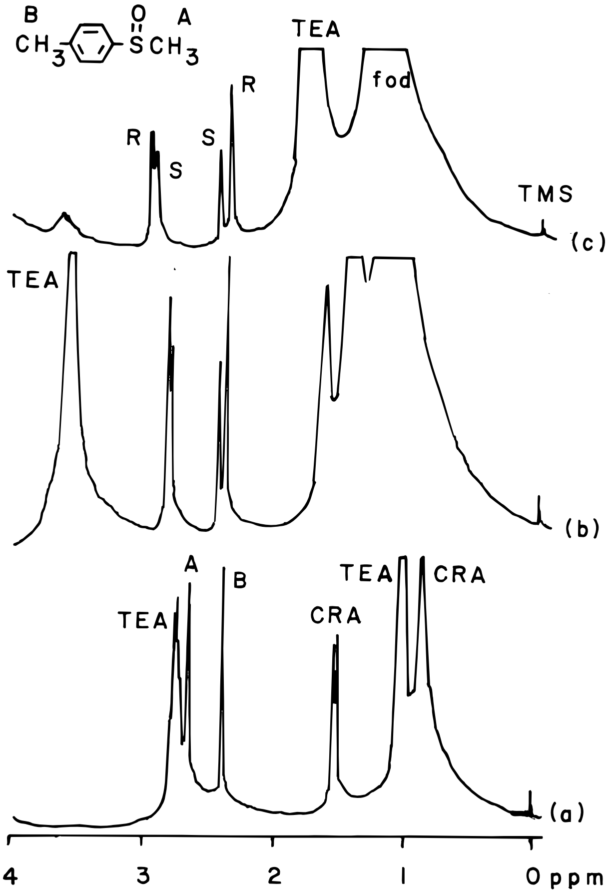


Figure 1. ^{1}H NMR spectrum (300 MHz) of methyl *p*-tolyl sulfoxide (0.06 M *R*- and 0.04 M *S*-enantiomer), triethylamine (0.20 M) and **Ia** (0.20 M) in chloroform-*d* at 20 °C with (a) no Eu(fod)$_3$, (b) 0.12 M Eu(fod)$_3$ and (c) 0.20 M Eu(fod)$_3$.

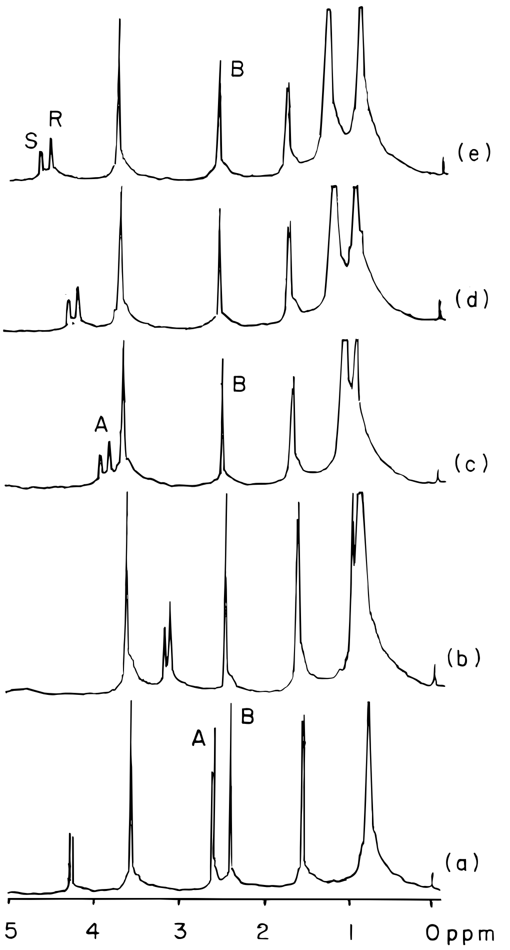


Figure 2. ^{1}H NMR spectrum (300 MHz) of methyl *p*-tolyl sulfoxide (0.06 M *R*- and 0.04 M *S*-enantiomer) and **Ib** (0.20 M) in chloroform-*d* at 20 °C with (a) no Eu(fod)$_3$, (b) 0.04 M Eu(fod)$_3$, (c) 0.10 M Eu(fod)$_3$, (d) 0.14 M Eu(fod)$_3$ and (e) 0.18 M Eu(fod)$_3$.

strate resonances shift to lower frequency and, even though there are some variations, the magnitudes of the shifts are generally similar with either form of the resolving agent.

Table 2 shows the shifts in the spectra of **IIa** and **IIb** with several substrates. Certain resonances of the resolving agent consistently exhibit shifts to either lower or higher frequencies; however, the direction and magnitude are similar for both **IIa** and **IIb**. The amide hydrogens exhibit pronounced shifts to higher frequencies that, except for amine substrates, are smaller with the acid form. The only other notable difference is that H-8 and H-9 shift to lower frequencies for **IIa** but higher frequencies for **IIb** in the presence of amine-containing substrates.

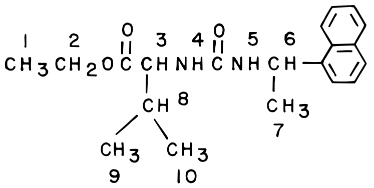
Table 3 shows $\Delta\Delta\delta$ values for representative substrates with **Ia**, **Ib**, **IIa** and **IIb**. For sulfoxides, the ester

Table 1. Shifts (ppm) in the ^{1}H NMR spectra (300 MHz) of substrates (0.1 M) in the presence of resolving agents (0.2 M) in chloroform-*d* at 20 °C[a]

		Ia	Ib	IIa	IIb
Methyl	SCH$_3$	−0.04	−0.12	−0.04	−0.10
p-Tolyl	PhCH$_3$	−0.03	−0.02	−0.02	−0.02
Sulfoxide	*ortho*	—[b]	—[b]	—[b]	−0.04
α-Methyl-1-	CH$_3$	−0.07/−0.11	−0.06	−0.07/−0.11	−0.04
naphthalenemethanol	CH	—[b]	−0.12	—[b]	—[b]
1-(1-naphthyl)ethylamine	CH$_3$	−0.11/−0.20	−0.04	−0.10/−0.20	−0.05
	CH	−0.09/−0.18	−0.04	−0.08/−0.16	−0.06
	H-8′	—[b]	−0.03	—[b]	−0.06

[a] Two values are reported when enantiomeric resolution is observed. Negative values represent shifts to lower frequency.
[b] Overlaps with a resonance of the resolving agent.

Table 2. Shifts (ppm) in the ^{1}H NMR spectra (300 MHz) of IIa and IIb (0.2 M) in the presence of representative substrates (0.1 M) in chloroform-*d* at 20 °C[a]



	Substrate					
	Methyl *p*-tolyl sulfoxide		α-Methylbenzylamine		α-Methyl-1-naphthalene methanol	
Resonance	IIa	IIb	IIa	IIb	IIa	IIb
H-3	0.05	0.01	−0.08	0	0.05	−0.01
H-4	0.34	0.57	0.57	0.51	0.18	0.44
H-5	0.47	0.70	0.58	0.66	0.31	0.54
H-6	0.01	0	−0.01	0	0.01	0.02
H-7	−0.04	−0.06	−0.06	−0.07	−0.04	−0.07
H-8	0.02	0.02	−0.06	0.03	0.03	−0.01
H-9	0.03	0.05	−0.01	0.03	0.01	0.01
H-10	0.01	0.05	−0.02	0	0.01	0.01
Aromatic	−0.01	0.01	−0.05	−0.04	−0.05	—[b]
Aromatic	−0.02	−0.04	−0.04	−0.04	−0.01	—[b]
Aromatic	−0.05	−0.05	0	0	0.01	—[b]

[a] Negative values represent shifts to lower frequency.

[b] Obscured by substrate peaks.

form of the reagent causes better enantiomeric resolution. For alcohol and amine substrates, however, certain resonances exhibit larger enantiomeric resolution with the acid forms of the reagents. Except for the anomalous behavior of the methine resonance of *sec*-phenethyl alcohol, the relative magnitude of the shifts for resonances of the *R*- and *S*-enantiomers is similar for the acid and ester forms.

The most noteworthy feature of Fig. 1 is the enantiomeric resolution of the tolyl methyl group that occurs on addition of Eu(fod)$_3$ to mixtures of **Ia** and methyl *p*-tolyl sulfoxide. Enantiomeric resolution of this resonance had not been observed with any other resolving agent we had previously examined, either with or without a lanthanide present.[13,14] The europium-induced shifts of the tolyl methyl resonance in Fig. 1 are less than those of the sulfoxide methyl resonance; however, in contrast to the sulfoxide methyl group, the resonance of the *S*-enantiomer shifts further.

A plausible explanation for the enantiomeric resolution and lanthanide-induced shifts of the methyl resonances observed in Fig. 1, as they compare with the results in Fig. 2, is that **Ia** bonds directly to Eu(III) forming the anionic species [Eu(fod)$_3$(CRA)]$^-$. The

Table 3. Enantiomeric resolution (Hz) in the ^{1}H NMR spectrum (300 MHz) of substrates (0.1 M) with resolving agents (0.2 M) in chloroform-*d* at 20 °C[a]

		Ia	Ib	IIa	IIb	IIIa
Methyl *p*-tolyl sulfoxide	SCH$_3$	0	5.7 (*R*)	2.1 (*R*)	7.0 (*R*)	0
	PhCH$_3$	0	0	0	0	0
	ortho	0	0	0	2.6 (*R*)	0
α-Methylnaphthalenemethanol	CH$_3$	—[b]	—[c]	—[b]	0	0.9
	CH	—[b]	—[c]	0	—[b]	6.7
	H-8′	—[b]	—[c]	—[b]	—[b]	2.5
sec-Phenethyl alcohol	CH$_3$	7.2 (*R*)	1.2 (*R*)	6.3 (*R*)	1.3 (*R*)	0
	CH	5.6 (*R*)	12.6 (*R*)	3.7 (*R*)	3.5 (*S*)	0
α-Methylbenzylamine	CH$_3$	31.8 (*R*)	0	28.2 (*R*)	2.0 (*R*)	0
	CH	0	—[d]	0	—[b]	0
1-(1-Naphthyl)ethylamine	CH$_3$	29.7 (*R*)	—[b]	30.0 (*R*)	1.7 (*R*)	0
	CH	26.7 (*R*)	—[d]	26.3 (*R*)	0	0

[a] The resonance that shifter further (*R* or *S*) is noted for samples enriched in one enantiomer.

[b] Overlaps with a resonance of the resolving agent.

[c] Spectrum not recorded.

[d] Severely broadened.

lanthanide-induced shifts in the spectrum of the substrate occur through substrate association with the CRA of $[\mathrm{Eu(fod)_3(CRA)}]^-$. The formation of tetrakis chelate anions of the type $\mathrm{Eu}(\beta\text{-dik})_4{}^-$ is well documented.[19] Species of the form $\mathrm{Ag[Eu(fod)_4]}$ have been used as NMR shift reagents for olefins, aromatics, halogenated compounds and phosphines.[20–24] Shift reagents for organic cations have been developed by adding species such as $\mathrm{Ag[Eu(fod)_4]}$ to halide salts of the cations.[25,26] The silver halide precipitates and is removed, thereby leaving the organic cation paired with the lanthanide tetrakis chelate anion. Anionic lanthanide species of the form $\mathrm{Ln}(\beta\text{-dik})_3(\mathrm{carboxylate})^-$ have also been used for transporting carboxylate salts across liquid membranes.[27]

The relatively small europium-induced shifts seen in the spectra in Fig. 1 compared with those in Fig. 2 presumably reflect steric crowding around the $[\mathrm{Eu(fod)_3CRA}]^-$ species, which limits the ability of the substrate to bond to the resolving agent. Also, since the substrate does not bond directly to the lanthanide as is typically observed, the shifts are expected to be smaller.[20,24] The larger lanthanide-induced shifts of the sulfoxide methyl resonance of the *R*-isomer are consistent with this mechanism. The reversal in shift order for the tolyl methyl resonance of the *R*- and *S*-isomers similarly supports something other than direct bonding of the free substrate to the lanthanide, since, in such a case, one would expect all of the resonances of one isomer to exhibit the larger lanthanide-induced shifts. The reversal of shift order must reflect the diastereomeric nature of the lanthanide–resolving agent–substrate complexes.

The shifts in the spectrum of a substrate in the presence of a lanthanide ion ($\Delta\delta$) are dominated by a dipolar shift mechanism[28] and predicted according to the equation

$$\Delta\delta = K(3\cos^2\theta - 1)/r^3 \qquad (1)$$

where r is the distance between the lanthanide and nucleus of interest, θ is the angle between the principal magnetic axis and the line connecting the lanthanide to the nucleus of interest and K is a constant for a particular lanthanide ion. Presumably the *R*- and *S*-enantiomers of methyl *p*-tolyl sulfoxide have differing orientations with respect to the lanthanide that cause the reversal in shift order for the two sets of methyl resonances. Even through the *R*-enantiomer associates more strongly with the resolving agent, the geometry of the *S*-enantiomer may be such that the tolyl methyl group is considerably closer to the europium than for the *R*-enantiomer, thereby causing larger shifts for this resonance of the *S*-enantiomer.

Examining the behavior of $\Delta\Delta\delta$ as a function of the lanthanide to substrate ratio (L:S) provides additional evidence that the lanthanide-induced shifts and enhancement in enantiomeric resolution in the spectra of substrates with mixtures of $\mathrm{Eu(fod)_3}$ with **Ia** or **IIa** occur predominantly through bonding of the substrate to $[\mathrm{Eu(fod)_3CRA}]^-$. The plots of $\Delta\Delta\delta$ *vs.* L:S for substrates with **Ib** and **IIb** exhibit a maximum. Considering that the free substrate bonds to the lanthanide with **Ib** and **IIb**, high lanthanide concentrations strip the substrate from the resolving agent, thereby reducing the enantiomeric resolution. This behavior has been well characterized in previous work.[11,13,14] With **Ia** or **IIa**, however, plots of $\Delta\Delta\delta$ *vs.* L:S increase and then gradually level off, as would be expected if the substrate associates with the CRA group of $[\mathrm{Eu(fod)_3CRA}]^-$.

The methyl resonances of 1-(1-naphthyl)ethylamine and α-methylbenzylamine exhibit a relatively small shift to lower frequency and minimal enantiomeric resolution with **Ib** and **IIb** [Table 3 and Fig. 3(b)], whereas the shifts and enantiomeric resolution with **Ia** and **IIa** are substantially larger [Table 3 and Fig. 3(c)]. Enantiomeric resolution is confirmed by comparing a racemic with enantiomerically enriched mixture for 1-(1-naphthyl)ethylamine [Fig. 3(c) and (d)]. The reason why **Ia** and **IIa** are so much more effective than **Ib** and **IIb** at causing enantiomeric resolution in the spectra of these amines is not understood. The enhanced steric hindrance of the triethylammonium cation compared with the methoxy group of the ester may play a role; however, enantiomeric resolution is expected to occur mostly through the chiral amino acid and ethylnaphthyl moieties. Protonation of the amine group of the substrates in the presence of **Ia** and **IIa** seems unlikely given the stronger basicity of triethylamine, and because protonation of amines usually causes pronounced shifts to higher frequency of adjacent methylene groups, which is not observed in these mixtures.[29] Because of

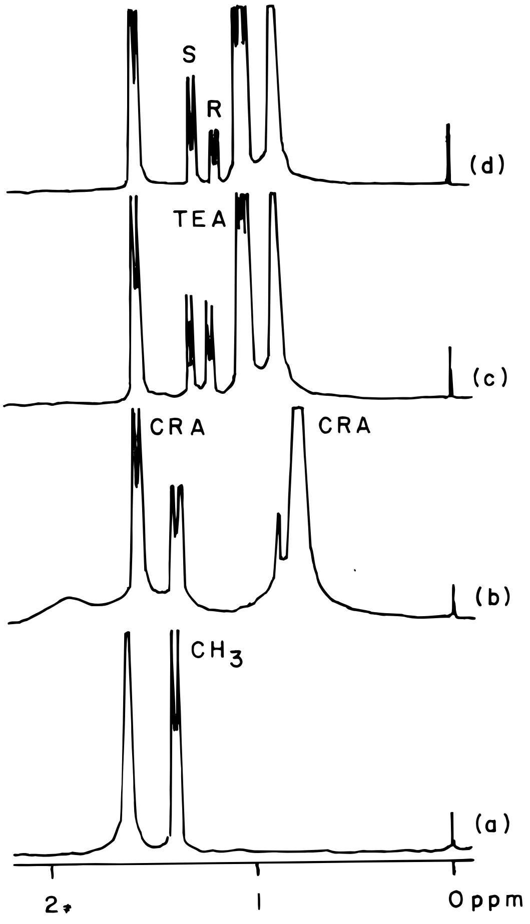


Figure 3. ^{1}H NMR spectrum (300 MHz) of 1-(1-naphthyl)ethylamine (0.10 M) in chloroform-*d* at 20 °C with (a) no chiral resolving agent, (b) 0.20 M **Ib**, (c) 0.20 M **Ia**, 0.20 M TEA (racemic mixture of substrate) and (d) 0.20 M **Ia**, 0.20 M TEA (70:30 mixture of *S*- and *R*-entiomers of substrate).

the substantial shifts of the methyl resonances of these amines in the presence of **Ia** and **IIa**, the lower frequency resonance is presumably that of the enantiomer more strongly associated with the chiral resolving agent. Addition of Eu(fod)$_3$ to mixtures of **Ia** or **IIa**, TEA and α-methylbenzylamine or 1-(1-naphthyl)ethylamine causes the lower frequency methyl resonance to shift further, leading to a reduction of $\Delta\Delta\delta$ and a coalescence of the signals, precisely the expectation if the substrate associates with the CRA group of [Eu(fod)$_3$CRA]$^-$.

It is known from liquid chromatographic retention data that the *R*-enantiomers of dinitrobenzoyl (DNB) derivatives of α-methylbenzylamine and 1-(1-naphthyl) ethylamine bond more strongly to the enantiomeric form of **II** used in our work.[17,30] Addition of **IIa** or **IIb** to DNB derivatives of these compounds causes enantiomeric resolution of the resonances for the methyl and DNB ring hydrogens. Figure 4(a), which is typical of the results that are obtained, shows the spectra of the methyl and DNB resonances of the DNB derivative of 1-(1-naphthyl)ethylamine in the presence of **IIa**. In every case, the resonances of the *R*-enantiomer are at lower frequency in the presence of **IIa** or **IIb**. Addition of Eu(fod)$_3$ to the mixtures with **IIa** causes severe broadening and substantial shifts of the resolving agent resonances, which indicate of significant bonding to the Eu(III). An example of the broadening is seen for the resonance of **IIa** at about 1.5 ppm in the spectra in Fig. 4. The resonances of the *R*-enantiomer shift further on addition of Eu(fod)$_3$ [Fig. 4(b)–(f)], again consistent with a mechanism in which the Eu(III)-induced shifts in the spectrum of the substrate are the result of bonding to the CRA of [Eu(fod)$_3$(CRA)]$^-$.

A similar observation was seen, however, when Eu(fod)$_3$ was added to mixture of **IIb** and the DNB derivatives of α-methylbenzylamine or 1-(1-naphthyl) ethylamine. The resonances of the *R*-enantiomer shifted further than those of the *S*-enantiomer on addition of Eu(III), and the spectrum of the resolving agent shifted and broadened. These observations are inconsistent with the expectation that the free form (*S*-enantiomer) of the substrate preferentially bonds to Eu(fod)$_3$ in mixtures with **IIb**. Instead, it appears as if **IIb** is bonding directly to Eu(fod)$_3$ and the substrate then bonds to the CRA unit in the neutral species Eu(fod)$_3$CRA. Figure 5 shows a plot of $\Delta\delta$ *vs.* L:S for several resonances of the DNB derivative of 1-(1-naphthyl)ethylamine and one resonance of **IIb** that is not too severely broadened. The plots are significantly different for the resolving agent and substrate and indicate that **IIb** preferentially binds at low concentrations of Eu(III). Only at higher concentrations of Eu(III) do the data indicate direct bonding of the substrate to the lanthanide. The electron-withdrawing nature of the nitro groups in the substrate reduces the direct association with Eu(III).[31]

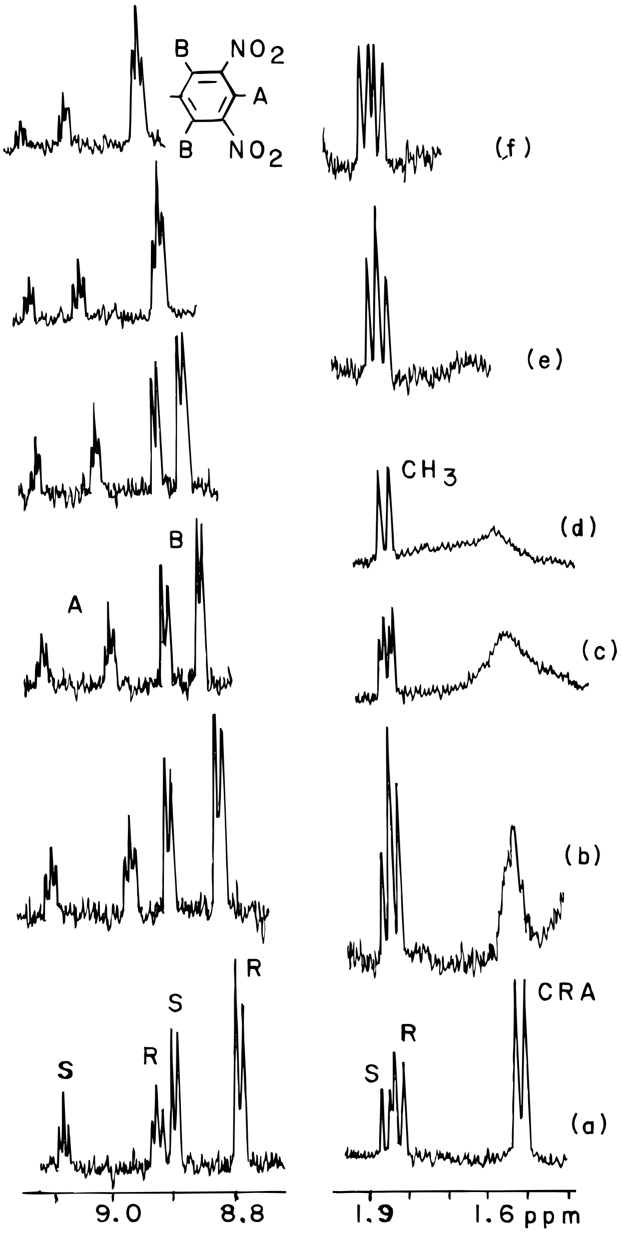


Figure 4. ^{1}H NMR spectrum (300 MHz) of the dinitrobenzoyl derivative of 1-(1-naphthyl)ethylamine (9.0×10^{-4} M *R*- and 6.0×10^{-4} M *S*-enantiomer), **IIa** (3.0×10^{-3} M) and TEA (3.0×10^{-3} M) in chloroform-*d* at 20 °C with (a) no Eu(fod)$_3$, (b) 6×10^{-4} M Eu(fod)$_3$, (c) 1.2×10^{-3} M Eu(fod)$_3$, (d) 1.5×10^{-3} M Eu(fod)$_3$, (d) 2.4×10^{-3} M Eu(fod)$_3$ and (f) 3.0×10^{-3} M Eu(fod)$_3$.

Comparison of IIIa with IIIb

Addition of **IIIb** to the benzoyl derivatives of 1-(1-naphthyl)ethylamine or α-methylbenzylamine causes shifts to lower frequencies and enantiomeric resolution of the methine and methyl resonances. The larger shifts of the *S*-enantiomers indicate that they bond more strongly to **IIIb**, which agrees with liquid chromatographic retention data.[32,33] Addition of Eu(fod)$_3$ increases the enantiomeric resolution of the methyl group by causing pronounced shifts that are larger for the *R*-enantiomer. A plot of $\Delta\Delta\delta$ *vs.* the L:S ratio for the methyl resonance of both benzoyl derivatives shows a maximum, which indicates that Eu(III) preferentially bonds to the free substrate. Furthermore, at low concentrations of Eu(III), the substrate resonances exhibit much larger shifts than those of **IIIb** (Fig. 6). Only when the concentration of Eu(III) exceeds that of the substrate do the resonances of **IIIb** show significant shifts (Fig. 6).

The behavior using **IIIa** is markedly different. Once again the substrate peaks shift to lower frequency on

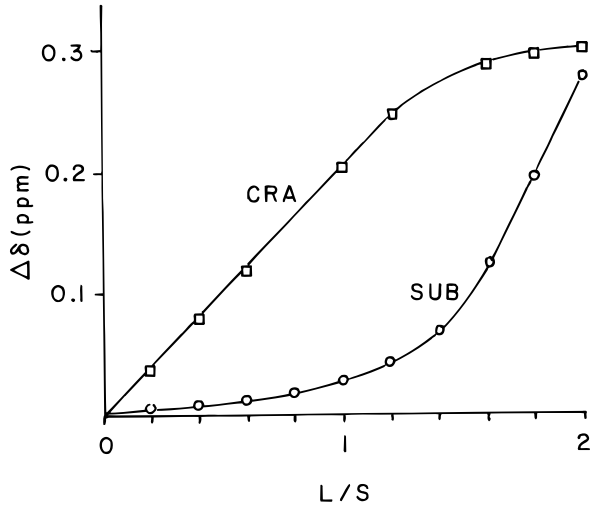


Figure 5. Plot of the lanthanide-induced shifts (Δδ) of the ethoxy methyl resonance of **IIb** (3.0×10^{-3} M) and the methyl resonance of the dinitrobenzoyl derivative of 1-(1-naphthyl)ethylamine (1.5×10^{-3} M) as a function of the lanthanide to substrate (L/S) ratio.

addition of the resolving agent, although the methine and methyl resonances do not exhibit enantiomeric resolution. Addition of Eu(fod)$_3$ causes substantial broadening of the resonances of **IIIa** and smaller shifts of the substrate resonances than observed with **IIIb**. Enantiomeric resolution of the methyl and methine resonances is first observed at Eu(fod)$_3$ concentrations of 0.03 and 0.04 M, respectively; however, the signals of the *S*-enantiomers exhibit the larger shifts, which supports a mechanism whereby the substrate bonds to the CRA in [Eu(fod)$_3$CRA]$^-$.

The initial spectrum of **IIIb** with α-methyl-1-naphthalenemethanol exhibits no enantiomeric resolution. Addition of Eu(fod)$_3$ to the mixture causes substantial shifts for all resonances of the substrate, significant enantiomeric resolution for H-8′ [Fig. 7(a)–(c)] and slight enantiomeric resolution for the methine resonance. The methine and H-8′ resonances of the *S*-enantiomer both exhibit larger shifts in the presence of Eu(III). The initial spectrum of **IIIa** with α-methyl-1-naphthalenemethanol exhibits slight enantiomeric resolution for both the methine and H-8′ resonance. Addition of Eu(fod)$_3$ to the mixture causes shifts in the spectrum of the substrate, but they are much smaller than for the mixture with **IIIb** [Fig. 7(d)–(f)]. Of particular significance is the observation that the methine and H-8′ resonances of the *R*-enantiomer exhibit larger shifts in the presence of Eu(III) and **IIIa**. The reversal of the relative order of shifts when Eu(III) is added to **IIIa** and **IIIb** with this substrate provides further evidence for direct association of the substrate with the CRA of [Eu(fod)$_3$CRA]$^-$ when **IIIa** is used.

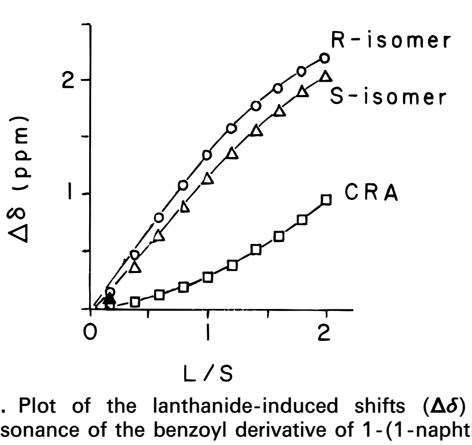


Figure 6. Plot of the lanthanide-induced shifts (Δδ) of the methyl resonance of the benzoyl derivative of 1-(1-naphthyl)ethylamine (0.05 M) and the ethoxy methylene resonance of **IIIb** (0.10 M) as a function of the lanthanide to substrate (L/S) ratio.

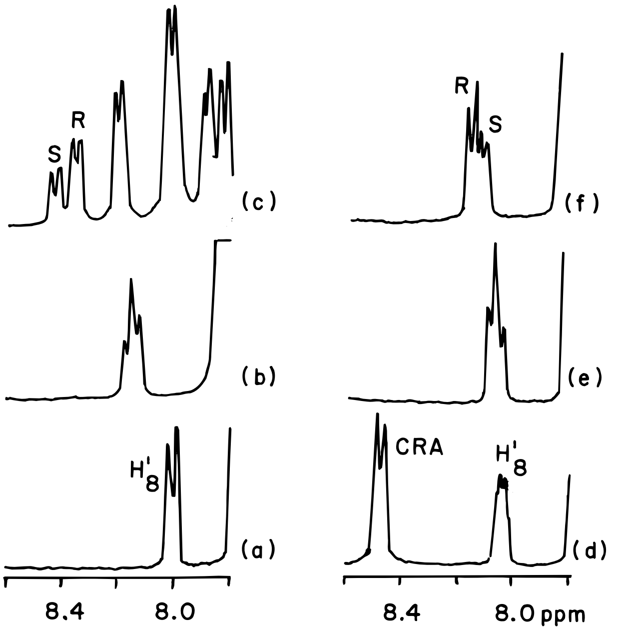


Figure 7. ^{1}H NMR spectrum (300 MHz) of α-methyl-1-naphthalenemethanol (0.06 M *R*- and 0.04 M *S*-enantiomer) in chloroform-*d* at 20 °C with (a) **IIIb** (0.20 M), (b) **IIIb** (0.20 M) and Eu(fod)$_3$ (0.02 M), (c) **IIIb** (0.20 M) and Eu(fod)$_3$ (0.04 M), (d) **IIIa** (0.20 M) and TEA (0.20 M), (e) **IIIa** (0.20 M), TEA (0.20 M) and Eu(fod)$_3$ (0.08 M) and (f) **IIIa** (0.20 M), TEA (0.20 M) and Eu(fod)$_3$ (0.20 M).

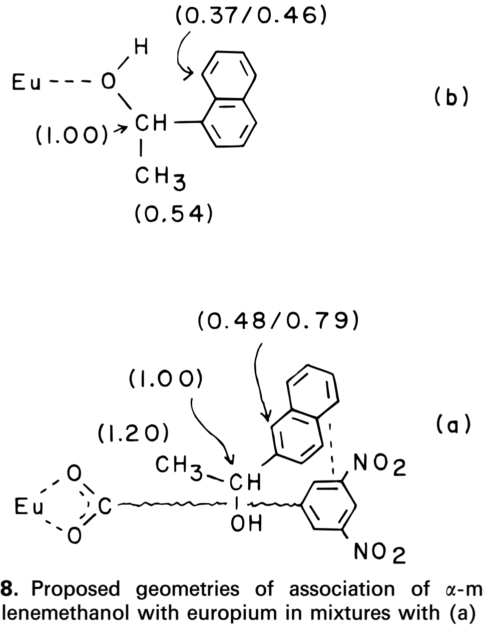


Figure 8. Proposed geometries of association of α-methyl-1-naphthalenemethanol with europium in mixtures with (a) **IIIa** and (b) **IIIb**. Numbers in parentheses are the lanthanide-induced shifts reported relative to the methine resonance.

It is expected that the naphthyl ring of α-methyl-1-naphthalenemethanol undergoes a π–π interaction with the DNB ring and that the hydroxyl group participates in hydrogen bonding with the amide portion of **IIIa** and **IIIb**. With **IIIa**, which is bound to Eu(III), the methyl group presumably points toward the Eu(III) as shown in Fig. 8(a). With **IIIb**, the substrate bonds directly to the europium [Fig. 8(b)]. Considering the general trends that would be expected by applying the dipolar shift equation, the relative shift orders $CH > CH_3 >$ aromatic with **IIIb** and $CH_3 > CH >$ aromatic with **IIIa** agrees with the proposed mechanisms for mixtures of lanthanides with these reagents.

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