mized to different structures with the lithiums coordinated to different oxygens. Clearly, the site of deprotonation is particularly important in providing the most energetically stable structure. For example, conformers 1 and 5 in Table II differ by 27 kcal, yet the basic difference between these two is the site of deprotonation; i.e., the sites of lithium coordination are the same.

Given all the labeling experiments for the 1,3-isomer and the MS/MS/MS studies, we were not initially able to postulate a mechanism for the four-carbon neutral loss with the alkoxide residing at the anomeric position. In this particular case we have used the MNDO calculations as a model for predicting the possible dissociation pathways by first determining the most likely site of metal coordination. Of course, caution is suggested when using this approach. In general, we acquire, analyze, and present both the experimental results and the theoretical calculations when proposing reaction mechanisms and sites of metal coordination.[32,36]

The positioning of the deprotonated oxygen between two lithiums as shown for both the 1,2- and 1,3-isomers is quite interesting. Indeed, many earlier studies have shown this conformation to be quite common among lithium enolates and tetrameric aggregates of lithium aldolate from pinacolone and pivaldehyde.[37,38] The Li–O coordination distances obtained in our MNDO calculations are also consistent with previously reported results for tetra- and dimeric coordination complexes.[38,39]

Although a plethora of crystallographic data exists on Lithium-ligand complexes,[37-39] very little is known about the gas-phase conformations.[40] We anticipate that further MNDO calculations of other metal-coordinated biomolecules will assist us in our future endeavors to determine both the site of metal coordination and MS/MS dissociation pathways of these complexes. (Studies are currently underway to determine the sites of lithium ion coordination for the dilithiated 1,4- and 1,6-isomers.)

Conclusions

In summary, ^{2}H- and ^{18}O-labeling studies of isomeric dilithiated disaccharides and subsequent MS/MS experiments indicate that reducing ring fragmentation occurs, and this fragmentation appears to be directly dependent on both the linkage position and the site of deprotonation. Analytically, one cannot discern the difference between the 1,2- and 1,4-linked oligomers using the dilithiated precursor. However, CID of both the mono- and dilithiated precursors provides unambiguous linkage position information for the 1,2-, 1,3-, 1,4-, and 1,6-linked isomers (the technique does not appear to discriminate between α and β conformations of the linkages).

Mechanisms of dissociation have been proposed after careful consideration of both the experimental and theoretical data, the latter being essential in determining the most likely site of deprotonation for the gas phase $(M + 2Li - H)^+$ species. Coordination of one lithium ion appears to "bridge" the two monomeric saccharides in a tetrameric configuration, while the second lithium is dicoordinate between two oxygens, one of which is deprotonated. In the gas phase, this lithium alkoxide appears to initiate rearrangement and dissociation.

Supplementary Material Available: Cartesian coordinates and Z-matrices of all conformations studied for 1,2 and 1,3 isomers, CID product ion spectra of $[M - H + 2Li]^+$ from anomeric ^{18}O-labeled sophorose, $[M - D + 2Li]^+$ from deuterated sophorose, MS/MS/MS spectrum of $[M - H + 2Li]^+$ from sophorose, CID product ion spectra of $[M - H + 2Li]^+$ from anomeric ^{18}O-labeled lactose, $[M - D + 2Li]^+$ from deuterated lactose, MS/MS/MS spectrum of $[M - H + 2Li]^+$ from lactose, CID product ion spectra of $[M - H + 2Li]^+$ from anomeric ^{18}O-labeled laminaribiose, $[M - D + 2Li]^+$ from deuterated laminaribiose, and MS/MS/MS spectrum of $[M - H + 2Li]^+$ from laminaribiose (124 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Lanthanide–Chiral Resolving Agent Mixtures as Chiral NMR Shift Reagents

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Mixtures of lanthanide complexes with soluble analogs of chiral liquid chromatographic stationary phases are shown to be useful NMR shift reagents for determining enantiomeric excess. The chiral resolution agents used in this work exhibit different association constants with enantiomeric substrates and associate weakly, if at all, with lanthanide ions. If the lanthanide associates with the substrate, the resolution observed in the spectrum of the substrate is enhanced. Enhancement occurs because the enantiomer concentrated in the bulk solution spends more time bonded to the lanthanide ion than the enantiomer with a higher association constant with the chiral resolving agent. Since the mechanism of interaction of many chiral liquid chromatographic phases is understood, or offers the potential to be understood, it should be possible to assign absolute configurations to the resolved NMR spectra. The method is applicable with donor–acceptor chiral resolving agents such *N*-(3,5-dinitrobenzoyl)-L-leucine and chiral hosts such as the cyclodextrins.

Introduction

Nuclear magnetic resonance spectroscopy is one of the simplest and most common methods of determining enantiomeric excess. One procedure is to synthesize a pair of diastereomers using an optically pure derivatizing reagent. The NMR spectra of the diastereomers often exhibit different chemical shifts for one or more sets of corresponding resonances. An alternative procedure is to

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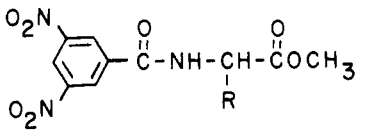
add a chiral shift reagent that associates with the optical isomers in solution. This leads to the formation of diastereomeric shift reagent–substrate complexes in which resonances of the substrates may exhibit different shifts. Chiral resolution may also occur because of different association constants between the shift reagent and the enantiomers. In this situation one enantiomer preferentially bonds to the shift reagent and exhibits greater shifts.

Lanthanide tris-β-diketonates are usually employed as the NMR chiral resolution reagent for nitrogen- and oxygen-containing compounds in organic solvents.[1,2] Chiral binuclear lanthanide–silver complexes have been developed for use with aromatics, olefins, and organic salts in organic solvents.[3-6] Water-soluble chiral lanthanide shift reagents have also been described.[7-10] These lanthanide shift reagents are widely applicable; however, the interaction between the substrate and lanthanide is not well understood. In addition, since these complexes are fluxional in solution, the likelihood of gaining an understanding of the interaction is remote. As a result, trial and error must be used in the selection of the lanthanide complex. If the spectrum is resolved, absolute configurations of the enantiomers usually cannot be assigned. Only in rare instances when similar compounds of known configurations were first tested could the absolute configuration of a new compound be assigned with any certainty.[11-13]

A second common method for enantiomeric resolution is the use of liquid chromatography. Chiral resolving agents can either be added to the mobile phase or covalently bound to the surface of the stationary phase. A number of strategies have been employed in developing bound chiral liquid chromatographic phases. Most common among them are the use of donor–acceptor phases such as those developed by Pirkle and co-workers[14,15] or chiral hosts such as cyclodextrins.[16-18] Chiral liquid chromatographic stationary phases operate by a mechanism in which the enantiomers exhibit different association constants with the chiral phase. One notable feature of the brush phases is that the interactions are often understood, or at least offer the potential to be understood, thereby enabling the prediction of retention order based on absolute configuration.

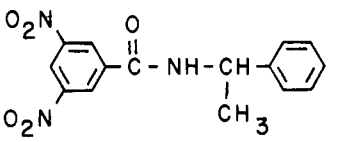
These liquid chromatographic phases offer enormous potential for enantiomeric resolution, and it is not surprising that soluble analogues of several of them have been evaluated as chiral resolving agents in NMR spectroscopy.[19-25] The enantiomeric resolution observed in the NMR spectra, however, is rather small. Pirkle and Sikkenga found that the enantiomeric resolution observed in the spectrum of a mixture of a chiral substrate with a chiral resolving agent could be improved through the addition of an appropriate achiral lanthanide species.[26,27] Furthermore, if the interaction of the chiral substrate with the resolving agent was understood, it was possible to assign absolute configurations to the resolved spectra. It is the purpose of this report to demonstrate that the improvement in enantiomeric resolution upon addition of an achiral lanthanide shift reagent appears to be a general phenomena that ought to be observed with almost all soluble analogues of donor–acceptor or host–guest chiral resolution agents.

Six chiral resolving agents (I–IV, β- and γ-cyclodextrin) were evaluated. Four of these (I–IV) are donor–acceptor

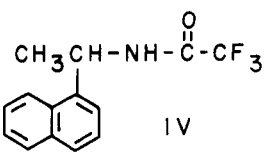


I R = $-C_6H_5$

II R = $-CH_2CH(CH_3)_2$



III



IV

compounds. The cyclodextrins function by a host–guest interaction. None of these resolving agents exhibit strong binding to the achiral lanthanide shift reagents. The method is applicable to chiral substrates that can associate with the lanthanide species.

Theory

The mechanism by which enhanced resolution is observed in the spectrum of enantiomeric substrates in a mixture of an achiral lanthanide species and a chiral resolving agent can be represented in its simplest form by the equilibria shown in reactions 1 and 2, in which S

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$$S + CRA = CRA\text{–}S \quad (1)$$

$$S + L = L\text{–}S \quad (2)$$

represents the chiral substrate, CRA the chiral resolving agent, and L the lanthanide shift reagent.[26,27] The reactions in (1) and (2) represent the case in which the substrate binds to the achiral lanthanide species, whereas the chiral resolving agent does not. Both reactions are fast on the NMR time scale, and the spectrum of the substrate is a time average of S, CRA–S, and L–S. Association constants of the two enantiomeric forms with the lanthanide are equivalent ($K_2d = K_2l$), whereas association constants with the CRA are different ($K_1d \neq K_1l$). As a result, the ratios for the lanthanide-complexed forms of the substrate to the other forms of the substrate, as shown in equations 3 and 4, are different. Since these ratios are

$$\frac{[L\mathit{d}S]}{[CRA\text{–}\mathit{d}S] + [\mathit{d}S]} \quad (3)$$

$$\frac{[L\mathit{l}S]}{[CRA\text{–}\mathit{l}S] + [\mathit{l}S]} \quad (4)$$

not equivalent, the lanthanide ion will induce differential shifts in the spectra of the two enantiomers. The ratio in (3) and (4) will be largest for the enantiomer that is concentrated in the bulk solution (that enantiomer which has a smaller association constant with the CRA). The spectrum of the enantiomer in the bulk solution will therefore exhibit larger shifts in the presence of a lanthanide ion. The chiral resolving agents reported herein operate under the mechanism just described.

It is possible that enhanced enantiomeric resolution will be observed in the spectra of enantiomeric substrates for situations in which the chiral resolving agent exhibits strong binding with the lanthanide species. In this case reactions 5 and 6 represent the simplest set of equilibra

$$CRA + L = L\text{–}CRA \quad (5)$$

$$L\text{–}CRA + S = L\text{–}CRA\text{–}S \quad (6)$$

to describe the system. Reaction 5 describes the formation in solution of a chiral lanthanide shift reagent. Provided association of the chiral substrate with the chiral resolving agent is not inhibited by binding of the chiral resolving agent to the lanthanide, the spectrum of the enantiomer that exhibits the stronger association with the chiral resolving agent will exhibit larger shifts.

Experimental Section

Reagents. *N*-(3,5-Dinitrobenzoyl)-L-leucine, (*R*)-(–)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine, (*R*)-(–)-*N*-(3,5-dinitrobenzoyl)-α-phenylglycine, (*R*)-(+)-1-(1-naphthyl)ethylamine, and β- and γ-cyclodextrin were obtained from Aldrich Chemical Co., Milwaukee, WI.

(R)-(+)-*N*-(1-(1-Naphthyl)ethyl)trifluoroacetamide (IV) was prepared by adding trifluoroacetic anhydride (1.26 g, 0.0060 mol) to a solution of (*R*)-(+)-1-(1-naphthyl)ethylamine (1 g, 0.0058 mol) in 10 mL of ethyl acetate in a round-bottomed flask. The flask was stoppered with a drying tube and stirred at room temperature for 1 h, after which the ethyl acetate was removed by rotary evaporation. Recrystallization from ethanol afforded the product as white crystals.

The ethyl or methyl ester hydrochloride salts of (*R*)-(–)-*N*-(3,5-dinitrobenzoyl)-α-phenylglycine (I) and *N*-(3,5-dinitrobenzoyl)-L-leucine (II) were prepared by established procedures from the appropriate carboxylic acid.[22]

The benzodiazepinone derivatives 7-chloro-1,3-dihydro-3-methyl-5-phenyl-1,4(2*H*)-benzodiazepin-2-one (V) and 7-chloro-1,3-dihydro-3-isopropyl-5-phenyl-1,4(2*H*)-benzodiazepin-2-one (VI) were prepared by established procedures from 2-amino-5-chlorobenzophenone and the appropriate amino acid ethyl ester hydrochloride.[28] The products were purified by column chromatography through silica gel. Unreacted starting materials were eluted using methylene chloride, after which the product was eluted with 2-propanol.

Lanthanide chelates of fod were prepared and purified according to literature methods.[29] Lanthanide chelates of triethylenetetraaminehexaacetic acid (H_6TTHA) were prepared by dissolving H_6TTHA (1 g, 0.0020 mol) in 10 mL of water. Sodium bicarbonate (1 g, 0.0120 mol) was added and the solution warmed with stirring for 30 min to ensure evolution of carbon dioxide. A stoichiometric amount (0.0020 mol) of the appropriate lanthanide(III) nitrate hexahydrate was added, and after the solution was cooled to room temperature, the product was obtained as a viscous oil by the addition of acetone. The supernatant was decanted and the oil rinsed with acetone and dried in vacuo over phosphorus pentoxide to a crystalline mass.

Procedures. The appropriate amount of substrate and chiral resolving agent were weighed into an NMR tube and dissolved in a suitable solvent. Small portions of the appropriate solid lanthanide shift reagent were then added to the NMR tube and the spectrum recorded. The concentration of lanthanide was determined either by weight or by relative integration of lanthanide resonances to substrate or resolving agent resonances.

Apparatus. NMR spectra were recorded on a Varian EM-360L 60-MHz or General Electric QE 300-MHz instrument at ambient probe temperature, unless otherwise specified.

Results and Discussion

Compounds I–IV and the cyclodextrins were all known from previous work to function as chiral resolving agents in NMR spectroscopy.[19–25] Compounds III and IV have been used as chiral resolution agents in NMR spectroscopy with sulfoxides and phosphine oxides.[20,21] It is known from liquid chromatographic studies that I and II are capable of resolving thousands of chiral compounds including benzodiazepinones.[14,15] The solubility of I was limited in deuteriochloroform and deuteriochloroform/carbon tetrachloride mixtures, however, and was found impractical for most applications. The cyclodextrins have been applied as chiral resolution agents in NMR spectroscopy with ionic antihistaminic and analgesic agents.[23,24]

The NMR spectra of I–IV in chloroform and carbon tetrachloride/chloroform mixtures in the presence of Eu(fod)$_3$ at a variety of lanthanide–chiral resolving agent ratios were recorded. Either no or only small shifts were observed in all cases, which is indicative of weak association of these substrates with lanthanide ions. This is not surprising since all four reagents have electron-withdrawing groups near the functional group at which binding would occur. The NMR spectra of β-cyclodextrin in deuterium oxide in the presence of lanthanide(III) nitrates or Na_3[Ln(TTHA)] complexes also exhibited no shifts. Only carbohydrates with an axial–equatorial–axial arrangement of adjacent oxygen atoms, which is not present in the cyclodextrins, exhibit strong association with lanthanide ions in aqueous solution.[30] In mixtures of I–IV and the cyclodextrins with lanthanide ions the lanthanide will therefore be available to bind to the enantiomer that has the weaker association with the chiral resolving agent.

The spectra in Figures 1 and 2 support the conclusion that the lanthanide shift reagent bonds to the enantiomer concentrated in the bulk solution. These spectra are for a mixture of methyl *p*-tolyl sulfoxide and IV in which the (*R*)-enantiomer of the sulfoxide is enriched relative to the (*S*)-enantiomer. Increasing quantities of Eu(fod)$_3$ and

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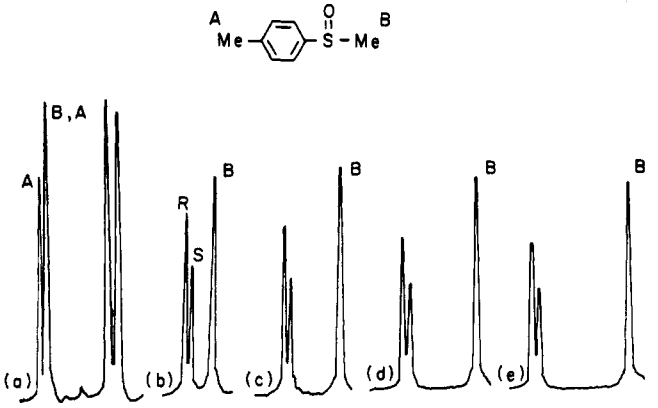


Figure 1. Proton NMR spectrum (60 MHz) of methyl *p*-tolyl sulfoxide (0.06 M (*R*)- and 0.04 M (*S*)-enantiomer) in carbon tetrachloride with IV (0.20 M) and (a) no $Eu(fod)_3$ and (b–e) increasing amounts of $Eu(fod)_3$.

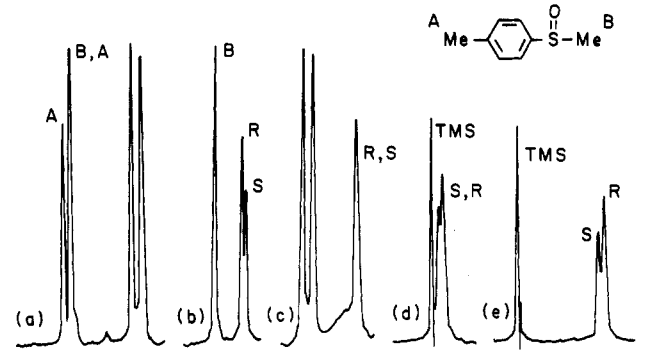


Figure 2. Proton NMR spectrum (60 MHz) of methyl *p*-tolyl sulfoxide (0.06 M (*R*)- and 0.04 M (*S*)-enantiomer) in carbon tetrachloride with IV (0.20 M) and (a) no $Pr(fod)_3$ and (b–e) increasing amounts of $Pr(fod)_3$.

$Pr(fod)_3$ are added in the two series of spectra. The signals for the (*R*)- and (*S*)-methyl group attached directly to the sulfoxide unit are resolved in the initial spectrum without any lanthanide ion; however, the resonance of the methyl group of the (*S*)-enantiomer overlaps with the unresolved *p*-tolyl methyl resonance. In the series of spectra obtained on addition of $Eu(fod)_3$ (Figure 1), a downfield shift reagent, the (*R*)-enantiomer exhibits the larger shift and the resolution is enhanced upon addition of europium. In the series of spectra obtained upon addition of $Pr(fod)_3$ (Figure 2), an upfield shift reagent, the (*R*)-enantiomer again exhibits the larger shift. This leads to an eventual crossover of the resonances for the (R)- and (*S*)-methyl groups at higher concentrations of $Pr(fod)_3$.

These spectra suggest that association of the (*S*)-enantiomer of the sulfoxide is greater than that of the (*R*)-enantiomer. Binding of the chiral resolving agent to the sulfoxide in the absence of a lanthanide shift reagent causes more shielding of the methyl group than observed for the isomer in carbon tetrachloride.

In Figure 3 is plotted the chiral resolution ($\Delta\Delta\delta$ in ppm) of the methyl group of V caused by the addition of increasing amounts of $Pr(fod)_3$ to a solution of II and V. An optimum ratio of shift reagent-to-substrate is observed, above which resolution decreases. This observation is supported by the proposed mechanism described in reactions 1 and 2. High concentrations of the lanthanide shift reagent will eventually shift equilibrium 2 to the right, thereby removing the substrate from the chiral resolving agent. Chiral resolution will then decrease. The optimum ratio of resolving agent, substrate, and lanthanide will depend on the association constants for reactions 1 and

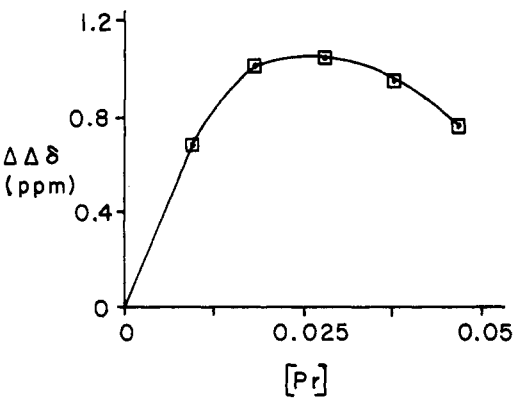


Figure 3. Plot of the chiral resolution ($\Delta\Delta\delta$) of the methyl group of V (0.05 M) in chloroform-d_1 with II (0.05 M) as a function of concentration of $Pr(fod)_3$.

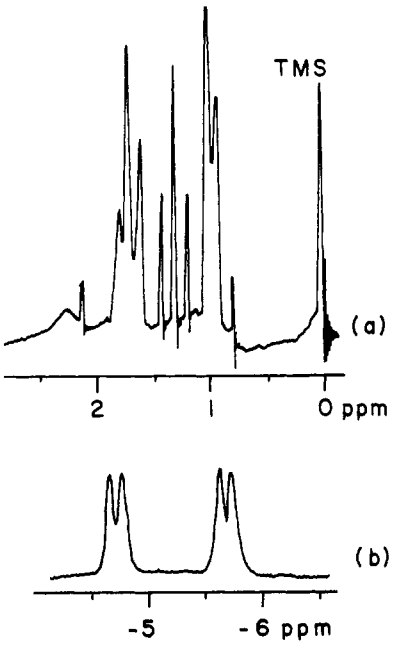
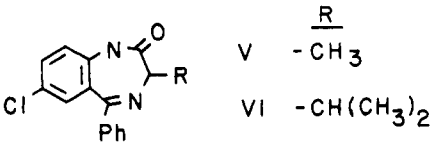


Figure 4. Proton NMR spectrum (60 MHz) of V (0.05 M) in chloroform-d_1 with II (0.05 M) and (a) no $Pr(fod)_3$ and (b) $Pr(fod)_3$ (0.03 M).

2. We typically found it was best to employ resolving agent–substrate ratios of 2:1 or 1:1. Small amounts of the solid lanthanide shift reagent were then added to the NMR tube and the spectra recorded.

The spectra in Figures 4 and 5 illustrate the practical benefits of adding lanthanide shift reagents to mixtures of chiral resolving agents and chiral substrates. The substrates shown in these figures are benzodiazepinones (V and VI). No observable resolution is noted in the



methyl resonance in the spectrum of V (0.05 M) with II (0.05 M) (Figure 4a). Addition of $Pr(fod)_3$ (0.03 M) (Figure 4b), an upfield shift reagent, causes enantiomeric resolution of the methyl resonance of slightly more than 1 ppm. Enantiomeric resolution on the order of a few hertz is usually considered acceptable, so that resolution of almost 1 ppm is noteworthy.

No observable enantiomeric resolution is noted in the methyl resonances of VI (0.05 M) in the presence of II (0.05

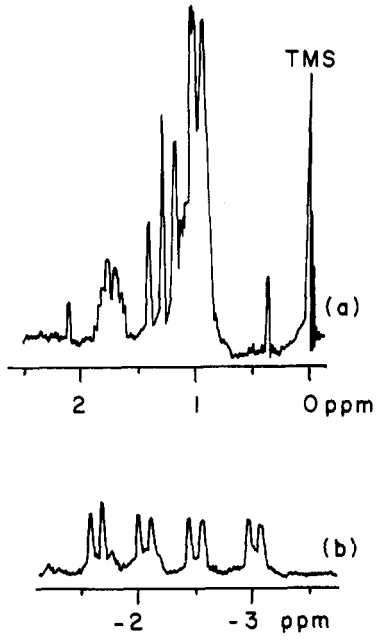


Figure 5. Proton NMR spectrum (60 MHz) of VI (0.05 M) in chloroform-d_1 with II (0.05 M) and (a) no $Pr(fod)_3$ and (b) $Pr(fod)_3$ (0.01 M).

M) (Figure 5a). Four methyl doublets, which result because the methyl groups of the isopropyl unit of VI are diastereotopic, are observed in the spectrum with $Pr(fod)_3$ (0.01 M) (Figure 5b). Assignment of absolute configurations for V and VI can be made on the basis of prior liquid chromatographic data.[31] It was shown in this earlier work that the (*R*)-enantiomer of V and VI associated more strongly with the chiral stationary phase. The (*S*)-enantiomer should therefore be concentrated in the bulk solution and be available to bond with the lanthanide. The spectrum of the (*S*)-enantiomer is expected to exhibit the larger shift in the presence of a lanthanide shift reagent.

Initial attempts at using lanthanide complexes with I–IV in organic solvents on a 300-MHz instrument resulted in unacceptable levels of broadening in the ^1H spectra. It has been shown that the broadening with lanthanide shift reagents on high-field instruments is caused by slow exchange on the NMR time scale.[32] There are examples from previous work with chiral lanthanide tris-β-diketonates in which warming the sample was sufficient to remove the exchange broadening, while still maintaining the association necessary for enantiomeric resolution.[33,34] Figure 6 provides an example of the effect of elevated temperatures on the enantiomeric resolution in the spectrum of methyl phenyl sulfoxide (0.10 M) with IV (0.10 M) and $Eu(fod)_3$ (0.025 M). At ambient probe temperatures (Figure 6a), the broadening precludes the observation of enantiomeric resolution of the methyl resonance. At 40 °C (Figure 6b), two singlets corresponding to the methyl groups of the two enantiomers are apparent.

Similar results were obtained with mixtures of V, II, and $Eu(fod)_3$. The enantiomeric resolution of the methyl resonance was apparent at ambient probe temperatures; however, the broadening made assignment difficult without prior knowledge of the location of the methyl resonances in the resolved spectrum. The spectrum of the sample

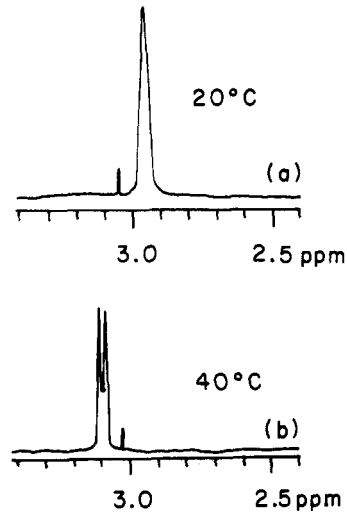


Figure 6. Proton NMR spectrum (300 MHz) of methyl phenyl sulfoxide (0.10 M) in chloroform-d_1 with IV (0.10 M) and $Eu(fod)_3$ (0.025 M) at (a) 20 °C and (b) 40 °C.

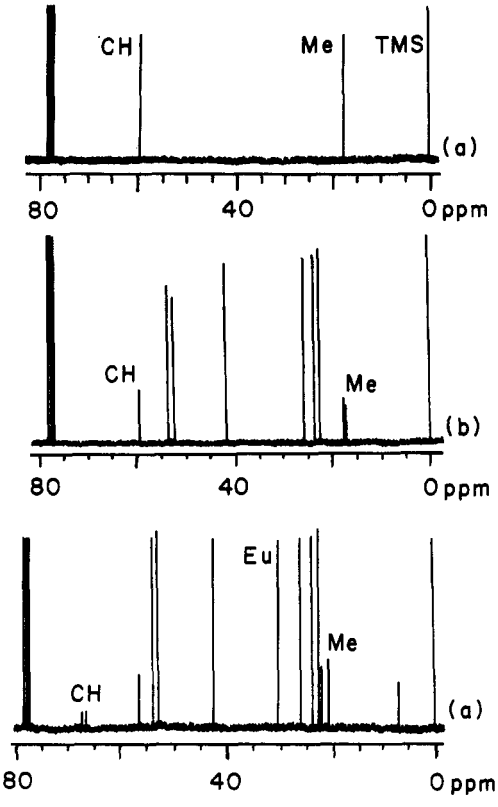


Figure 7. Carbon-13 NMR spectrum (75.6 MHz) in chloroform-d_1 of (a) V (0.05 M), (b) V (0.05 M) and II (0.05 M), and (c) V (0.05 M), II (0.05 M), and $Eu(fod)_3$ (0.05 M).

warmed to 50 °C still exhibited significant enantiomeric resolution, yet the resonances showed fine structure that enabled assignment.

An alternative to warming the sample is to record the spectrum of a nucleus for which broadening should not be as severe. Figure 7 shows a comparison of the ^{13}C spectrum of V with II (Figure 7b) to the spectrum of V with II and $Eu(fod)_3$ (Figure 7c). Only slight enantiomeric resolution of the methyl carbon of V is observed in the presence of II. Addition of $Eu(fod)_3$ enhances this resolution considerably and also causes observable resolution of the methine resonance.

Cyclodextrins have been employed as chiral resolution agents for water-soluble cationic substrates.[23,24] The resolution in these spectra is generally quite small. Lan-

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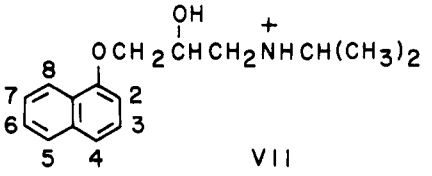
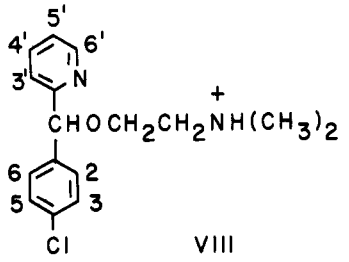
thanide shift reagents for cations have been described,[35] although most applications of these have been with metal ions of physiological importance such as sodium, potassium, calcium, and magnesium. It is generally noted that lanthanide complexes of tripolyphosphate or triethylenetetraaminehexaacetic acid [Ln(TTHA)$^{3-}$] are the best shift reagents for cations.[35] The spectra of propranolol hydrochloride (VII) and carbinoxamine maleate (VIII) exhibited shifts in the presence of lanthanide complexes of TTHA.



VII



VIII

Broadening in these spectra was minimal at 300 MHz, indicating that the association between the shift reagent and substrate were fast on the NMR time scale. Improvements in the ability to measure enantiomeric resolution in the spectra of these two compounds with either β- or γ-cyclodextrin were realized on adding complexes of the formula Ln(TTHA)$^{3-}$.

Enantiomeric resolution in the spectrum of propranolol hydrochloride is better with γ-cyclodextrin than β-cyclodextrin.[23] The slight resolution of H_8 and H_2 observed in solutions of γ-cyclodextrin (0.030 M) and propranolol hydrochloride (0.030 M) was enhanced on addition of Pr(TTHA)$^{3-}$ (0.0075 M). The complicated aromatic portion of the spectrum from 7.3 to 7.6 ppm containing the resonances for H_3, H_4, H_6, and H_7 was altered as the concentration of Pr(TTHA)$^{3-}$ was raised from 0.0075 to 0.0900 M. At the higher value of shift reagent, the resonance corresponding to H_7 was resolved from the other signals and seen to exhibit enantiomeric resolution of 8.2 Hz.

Enantiomeric resolution has been observed for several resonances in the spectrum of carbinoxamine maleate with β-cyclodextrin.[24] The resolution was better, however, when γ-cyclodextrin was employed as the resolving agent. In solutions of carbinoxamine maleate (0.025 M) and γ-cyclodextrin (0.025 M), the resonance of the benzylic hydrogen changed from one to two singlets, with enantiomeric resolution of 7.1 Hz. Enantiomeric resolution was also evident in the resonances for H_3' (2.7 Hz), $H_{3,5}$ (2.8 Hz), and $H_{2,6}$ (2.8 Hz). Addition of Yb(TTHA)$^{3-}$ (0.025 M) improved the enantiomeric resolution of $H_{3,5}$ and $H_{2,6}$ to 3.8 Hz. Addition of Pr(III)nitrate caused slight shifts in the spectrum of carbinoxamine maleate, perhaps through chelate association of Pr(III) at the pyridyl nitrogen and ether oxygen atoms. The enantiomeric resolution of the resonance of the benzylic hydrogen was enhanced by 1 Hz.

Provided one can identify a suitable achiral lanthanide shift reagent for a substrate, addition of a lanthanide species to mixtures of substrates with chiral resolution agents seems to generally improve enantiomeric resolution. This method is expected to work effectively with soluble analogues of the wide variety of chiral donor–acceptor and cavity liquid chromatographic stationary phases that have been described in the literature.

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Registry No. I, 69632-50-4; II, 86091-69-2; III, 69632-32-2; IV, 66964-32-7; (*R*)-V, 50691-97-9; (*S*)-V, 39200-48-1; (*R*)-VI, 51990-97-7; (*S*)-VI, 50691-96-8; (*R*)-methyl *p*-tolyl sulfoxide, 1519-39-7; (*S*)-methyl *p*-tolyl sulfoxide, 5056-07-5; (*R*)-methyl phenyl sulfoxide, 4850-71-9; (*S*)-methyl phenyl sulfoxide, 18453-46-8; β-cyclodextrin, 7585-39-9; γ-cyclodextrin, 17465-86-0.

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Enantioselective Formation of *cis*-3,5-Dimethylcyclohexanone Lithium Enolate and Stereoselective Aldol Reaction with Benzaldehyde

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Deprotonation of *cis*-3,5-dimethylcyclohexanone (**6**) with chiral lithium amide bases **10–12** has been investigated. The resulting lithium enolates **7a,b** react with benzaldehyde, acetic anhydride, or trimethylsilyl chloride to yield, respectively, the aldols **8** and **9**, the acetates **13a,b**, and the enol ethers **14a,b** as nonracemic mixtures in high yields and up to 79% ee. Effects of solvents and additives on the selectivity of these reactions have been studied. A model based on the hypothesis that the deprotonation of **6** with lithium amides proceeds via a pericyclic transition state involving a dimer of the base is proposed.

Deprotonation of a ketone followed by a reaction of the resulting enolate with an electrophile is one of the fundamental reaction sequences in organic synthesis. In the last decade this process has been the focus of vigorous investigations by several groups, and many of its salient features are now firmly established.[1] Complexation be-

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