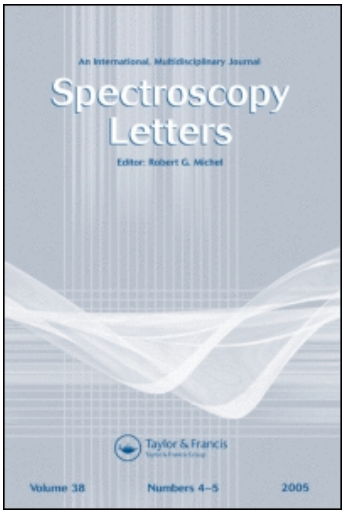


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# $^1$H NMR Spectral Simplification with Achiral and Chiral Lanthanide Shift Reagents. Lofexidine

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# $^1$H NMR SPECTRAL SIMPLIFICATION WITH ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS. LOFEXIDINE

Key Words: Lofexidine, Lanthanide, NMR Shift Reagents
Optical Purity, Enantiomers, Chiral



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ABSTRACT

The $^1$H NMR spectra of the potent anti-hypertensive drug, lofexidine, 1, have been studied in $CDCl_3$ at 60 and 300 MHz. Both the

achiral shift reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium(III), 2, and the chiral reagents, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III), 3, and tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III), 4, were employed. Substantial lanthanide induced shifts were observed with 2, 3 or 4, with the largest shifts seen for the methine at the chiral center, followed by the signal of the NH. Enantiomeric shift differences for the $CH_3$ signal of 1 were seen with 3 or 4, with 4 inducing larger values of potential analytical utility. Using a non-racemic sample of 1, the (-) enantiomer was shown to have a downfield sense of magnetic nonequivalence for the methyl resonance in the presence of added 4.



## INTRODUCTION

The compound lofexidine, 1, known as 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5-dihydro-1H-imidazole, was reported to have vasoconstrictive, spasmolytic and antihistaminic properties (1). The (-) (2)

and (+) enantiomers (3) have been prepared. Detailed structure determinations for the free base (4) and the hydrochloride salt (5) have been carried out and some $^{1}H$ and $^{13}C$ NMR data for analogs of 1 have been discussed (6). The $^{1}H$ NMR data for the hydrochloride salt of 1 in DMSO-$d_6$ were published together with data on chemical and physical properties; the striking hypotensive activity of 1 was also noted (7). Considerable stereoselectivity has been found for the two enantiomers of 1, with (-)-1 being about 20 times more potent than (+)-1 in $\alpha$-adrenoceptor activity and 30 times more potent in reducing increased heart rate evoked by electrical stimulation in pithed rats (8). Biedermann and coworkers (9) described the synthesis of the enantiomers of 1 and the resolution of racemic 1; (-)-1 was especially potent for treating hypertension and was a stereoselective $\alpha_2$-adrenoceptor agonist, about ten times more potent than (+)-1. The latter group also reported $^{1}H$ NMR data for the HCl salts of (+) and (-)-1 in $CDCl_3$.

Because of the considerable pharmaceutical interest in 1 and the dramatic activity differences between the enantiomers, we wanted to explore the possibility of direct optical purity determinations with chiral lanthanide shift reagents (LSR) as well as use of both achiral and chiral LSR for NMR spectral simplification. These LSR techniques have been extensively reviewed (10-15). We report here the NMR and LSR studies of 1.

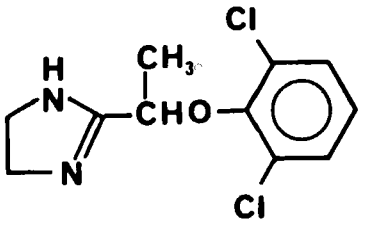


## EXPERIMENTAL

Samples of racemic 1 and the enantiomers were provided by A. Nattermann & Cie. GmbH (Chemical Research Department, Nattermannallee 1, 5000 Cologne 30 Fed. Rep. Germ.) as the HCl salts. Chloroform-d (99.8 atom % D) obtained from Aldrich Chemical Corp., Milwaukee WI 53201, or from Norell, Inc., Landisville NJ 08326, was dried over 3A molecular sieves. Shift reagents were obtained from Aldrich and stored in a desiccator over $P_2O_5$. Materials were used as supplied except as noted.

In general, an accurately weighed portion of 1 as the free base (see below), typically 16-27 mg, was added to 600-750 mg $CDCl_3$ [containing about

0.5% tetramethylisilane (TMS) as internal standard] in an oven-dried NMR sample tube and dissolved by shaking; increments of shift reagent were added, dissolved by shaking (and gentle warming in a water bath, if required) and the spectra immediately recorded.






Spectra were obtained at 28° with a Varian EM360A 60MHz $^{1}H$ NMR spectrometer equipped with the Varian EM-3630 lock/spin decoupler accessory. The 300 MHz spectral data were acquired using a General Electric QE300 spectrometer at 27 ± 1° with a 3.0 μs (32°) pulsewidth, 2.72s acquisition time, 3.71 s recycle time, with 8 scans acquired with 6024 Hz spectral width. The deuterium resonance of the solvent was used as the internal lock signal. Chemical shifts are reported in parts

in parts per million ($\delta$) relative to TMS and are believed accurate to $\pm 0.05$ ppm. In spectra where TMS was obscured by shift reagent peaks, $CHCl_3$ (present as an impurity in the solvent) was used as internal standard. For samples with added chiral 3 or 4, when enantiomeric shift differences, $\Delta\Delta\delta$, were observed, average chemical shift values for the two optical antipodes are reported.



Preparation of Free Base of Racemic 1: The sample of racemic 1.HCl had mp. 235-236° (uncorr.) with some darkening above 225°, [lit. mp. 221-223° (1), 230-231°(7)]. The salt (309.5 mg, 1.047 mmol) was dissolved in 4 ml $H_2O$, to which was added 5 ml 5% aq. NaOH and 1 gm NaCl. The free base of 1 was extracted four times with a total of 25 ml $CH_2Cl_2$, and the combined extracts dried with anhyd. $Na_2CO_3$. Solvent was removed on a rotary evaporator (aspirator pressure, bath temperature 50°) to constant weight, to yield 253.6 mg of 1 (0.9787 mmol, 93.5% recovery) as a white solid, mp 126-127° (uncorr.) [lit. mp. 129° (7)]. All samples of

lofexidine free base were routinely stored under $N_2$.

Preparation of Free Base of (-)-1.HCl: A portion of the (-)-1.HCl salt (152.5 mg, 0.5158 mmol) in 2.5 ml $H_2O$, was treated with NaOH, NaCl and $CH_2Cl_2$ as described above. After drying and solvent removal, 128.2 mg (0.4947 mmol, 95.9% recovery) of (-)-1 free base was obtained as a white solid, mp. 107-108° (uncorr.), which was stored under $N_2$.



## RESULTS AND DISCUSSION

A $^1H$ NMR spectrum of 1 at 300 MHz as a solution 0.0993 molal in $CDCl_3$ showed signals as follows, with shifts reported in ppm ($\delta$) from internal TMS: 7.31 (d, 2H, $^3J$=8.1 Hz, $H_{meta}$); 7.00 (t, 1H, $^3J$=8.1 Hz, $H_{para}$); 5.27 (br s, 1H, NH); 5.15 (q, 1H, $^3J$=6.6 Hz, $\underline{CH}CH_3$); 3.83 (br s, 2H, $\underline{CH_2}NH$ or $\underline{CH_2}N{=}C$); 3.51 (br s, 2H, $\underline{CH_2}N{=}C$ or $\underline{CH_2}NH$); 1.58(d, 3H, $^3J$=6.7Hz, $CH_3$). At 60 MHz, the aromatic signals are a complex multiplet, and the NH and $\underline{CH}CH_3$ absorptions extensively overlap. In principle, all four hydrogens of the $CH_2CH_2$ moiety are unique because the two faces of the imidazoline ring are

distinguishable (due to the chiral center) and each $CH_2$ differs by proximity either to NH or to N=C. Only two broad signals are observed at 3.83 and 3.51 ppm; we would tentatively assign the downfield absorption to $CH_2N=C$ but these assignments are not certain. Proton exchange between N(1) and N(3) combined with fast rotation about the C(2)-CH single bond would render both nitrogens equivalent and all four protons of the $CH_2CH_2$ equivalent. The broadening and absence of fine structure in the $CH_2CH_2$ signals are consistent with the rate processes being in between the slow exchange and fast exchange limits. The 60 MHz $^1H$ NMR spectra of 1 as 0.0894 molal solution at 28° were studied as increments of the achiral LSR, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, known as $Eu(FOD)_3$, were added. At the lowest molar ratio of 2:1 examined (0.0326), the two broad singlets of the $CH_2CH_2$ group coalesced and sharpened dramatically. Considerable broadening of the CH quartet resulted in essentially complete loss of fine structure, such that distinguishing this CH and the broad NH

signals became problematic (see below). At higher 2:1 ratios, considerable lanthanide-induced shifts ($\Delta\delta$) were seen for all absorptions except for the aryl signals. These results are summarized in Figure 1. The $\Delta\delta$ value for a nucleus is defined as the chemical shift in the presence of LSR minus the chemical shift with no LSR present. Substantial lanthanide-induced broadening was seen for the NH and $\underline{CH}CH_3$, and for the $CH_3$ and $CH_2CH_2$ as well (at higher molar ratios). Thus, the $CH_2CH_2$ absorptions, which initially coalesced and sharpened at low 2:1 levels, gradually became a broad singlet, and even the $CH_3$ doublet structure was lost. We suggest that even traces of the LSR appear to catalyze the proton exchange between the nitrogen sites, effectively averaging out gross differences of the $CH_2CH_2$ group resonances. LSR binding to the $sp^2$ lone pair of the doubly bonded nitrogen is expected. Although bidentate chelation of lanthanide to this nitrogen and the oxygen to form a five-membered ring would ordinarily be considered favorable, and might be consistent with the high degree of line broadening, we feel that

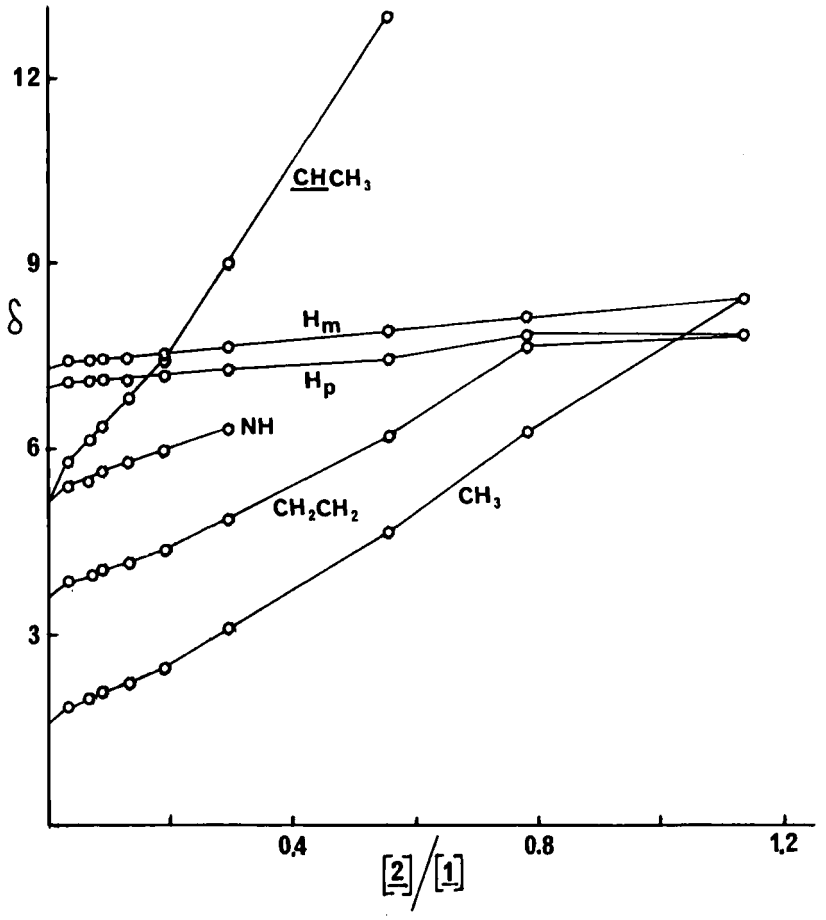



Figure 1. Variation of chemical shift, $\delta$ (in ppm), with molar ratio of 2:1.

this is unlikely in the present case. The oxygen is present as an aryl ether, severely hindered by the ortho chlorines, and would not be expected to significantly bind LSR. The large $\Delta\delta$ magnitudes for the methine could be explained by LSR binding

to the doubly bonded nitrogen with a favored conformation in which this nitrogen and the CH were essentially syn coplanar. Indeed, the single crystal diffractometry studies of the free base of 1 (4) reported dihedral angles for $NHC_a—C_bO$ of $-75^\circ$ and for $NHC_a—C_bCH_3$ of $44^\circ$ so that the dihedral angle $N=C_a—C_bH$ should be close to $16^\circ$ if $C_b$ were tetrahedral and $C_a$ planar. This latter dihedral angle was certainly quite small for the crystalline solid. This is a sterically favorable arrangement which would place the CH very close to the LSR. However, such geometric interpretations exclusively based on assumptions of pseudocontact shifts (16) may be an oversimplification here. Several workers (17, 18) have shown the possibility of appreciable contact contributions for hydrogens alpha to a carbonyl at which LSR is bound, especially with 2. Binding of LSR to 1 may similarly introduce such complexities.

Since our primary interest was the use of chiral LSR for potential direct optical purity determinations, we undertook studies of 1 in the

presence of the chiral LSR, tris[3-heptafluoropropylhydroxymethylene)-d-camphorato]europium-(III), 3, known as Eu(HFBC)$_3$ or Eu(HFC)$_3$, and also 4, tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III), known as Eu(FACAM)$_3$ or Eu(TFC)$_3$. With 3 added to 0.0955 molal 1, induced shifts, line broadenings, and coalescence of the $CH_2CH_2$ signals in the presence of even low levels of LSR, all closely paralleled results with 2. The $CH_3$ signal showed no sign of enantiomeric shift difference, $\Delta\Delta\delta$, at a 3:1 ratio of 0.475. (The $\Delta\Delta\delta$ value is the difference in chemical shifts for corresponding nuclei in two enantiomers in the presence of a chiral shift reagent.) At very high 3:1 ratios (1.21 to 1.56) the signal assigned to the $CH_3$ of 1 appeared as a triplet, suggesting $\Delta\Delta\delta$ comparable to the vicinal coupling constant. Analytical utility would be limited by only modest $\Delta\Delta\delta$ and appreciable line broadening. The results with 3 are shown in figures 2 and 3. In an attempt to improve the separation between the overlapped $CH_3$ doublets from the two enantiomers, a sample of 0.0918 molal 1 with a 3:1

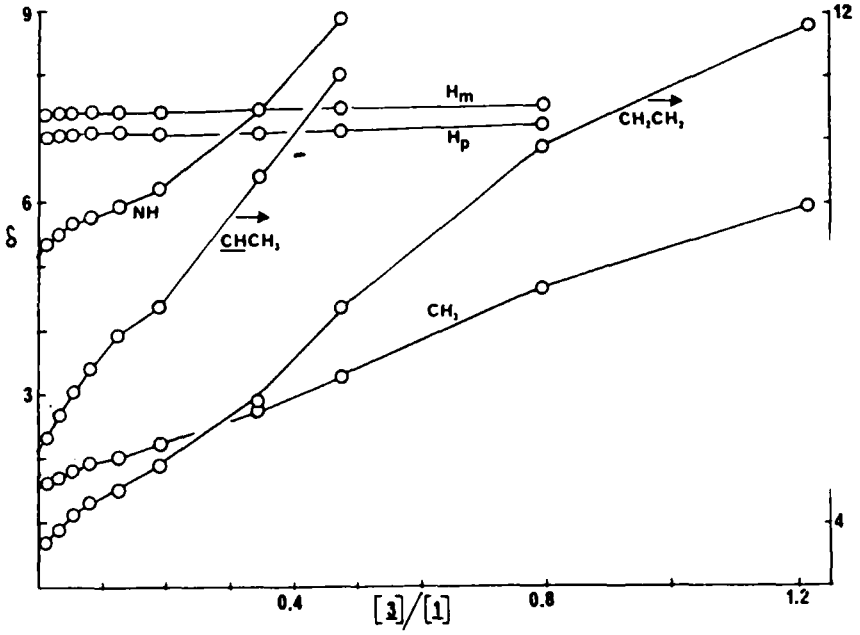



Figure 2. Variation of chemical shift, $\delta$ (in ppm), with molar ratio of 3:1.



ratio of 1.094 was examined at 300 MHz. The methyl signal, which had appeared as a triplet at 60 MHz, appeared only as a broad singlet at 300 MHz, with no trace of $\Delta\Delta\delta$. Perhaps the rate of LSR binding and dissociation to 1 is such that at 300 MHz the fast exchange limit for the methyl signal is not achieved and severe broadening

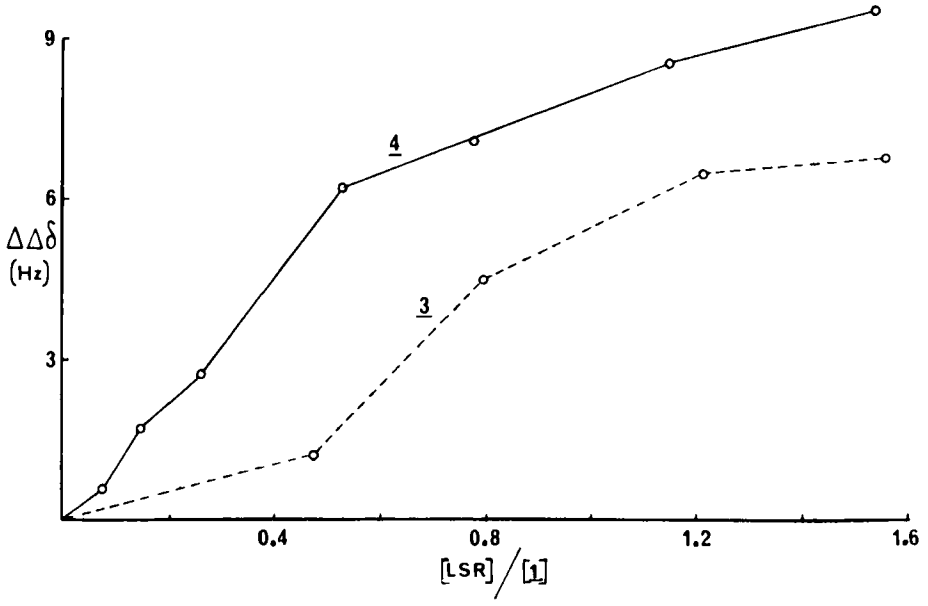



Figure 3. Variation of enantiomeric shift difference, $\Delta\Delta\delta$ (in Hz), with molar ratio of 3:1 (broken line), and of 4:1 (solid line).



results. At 60 MHz, the fast exchange limit results in relatively sharp averaged doublets for the two enantiomers' methyl resonances. These results emphasize the potential for increased line broadening and resulting decreased utility when LSR are employed at higher fields. Some aspects of exchange reactions and the resulting potential field or temperature dependence of NMR line

broadening have been summarized (19). Specific contributions to line broadening with LSR and to influences on $\Delta\Delta\delta$ have also been discussed (20). The heterocyclic ring of 1 should be expected to bind LSR tightly based on the very high association constant reported by Rackham for N-methylimidazole with tris(dipivalomethanato)-europium(III), $Eu(DPM)_3$, (21). Since $Eu(DPM)_3$ is considered a weaker Lewis acid than any of the fluorinated LSR, 2, 3 or 4, corresponding binding or association constants should be even greater with the latter group of reagents. A particularly high association constant for 1 with LSR might result in line broadening effects sometimes seen with substrates that strongly bind LSR through chelation.



When the chiral LSR 4 was employed with 0.1015 molal 1, distinct $\Delta\Delta\delta$ was seen for the $CH_3$ resonance with a 4:1 ratio as low as 0.148, and a sharp triplet was seen at a ratio of 0.527 ($\Delta\Delta\delta$ ca. 6.7 Hz). Slightly larger $\Delta\Delta\delta$ values could be achieved at increased 4:1 ratios but at the cost of more broadening. The results with 4 are

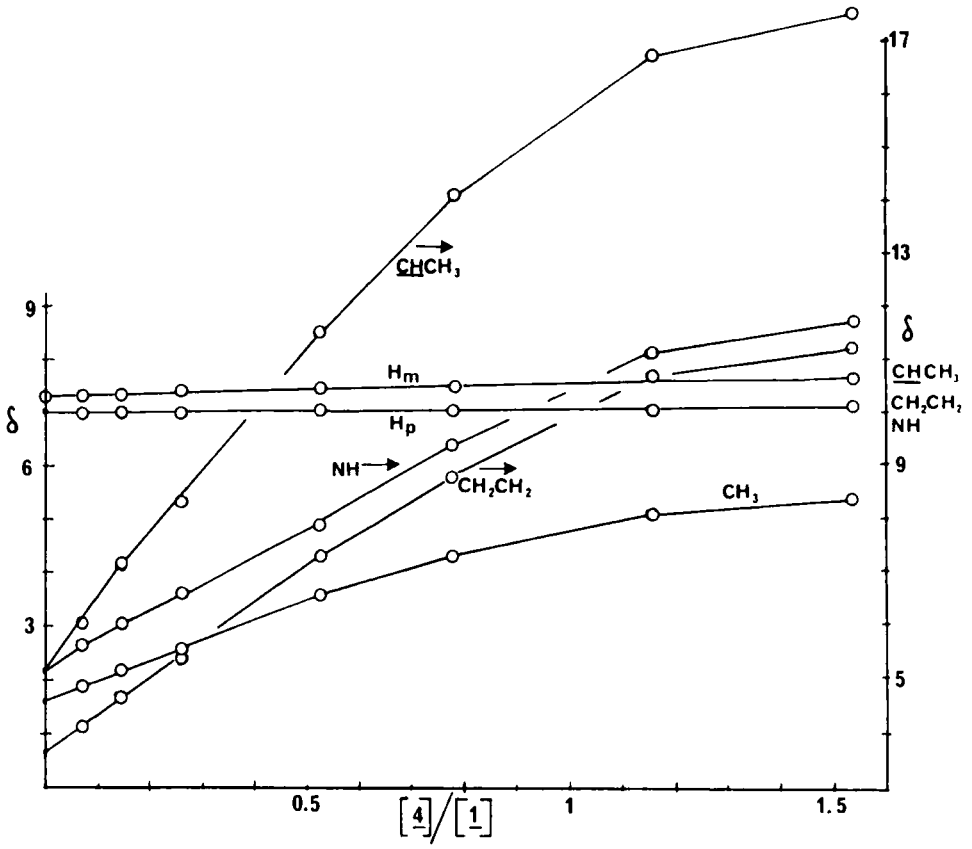



Figure 4. Variation of chemical shift, δ (in ppm), with molar ratio of 4:1.

summarized in Figures 3 and 4. The optimal conditions for optical purity determinations of 1 appear to be with a 4:1 ratio near 0.5.

Several homonuclear decoupling experiments were performed. The assignment of the methine (versus

the NH) remained unclear because of loss of quartet structure due to LSR-induced broadening, even at the lowest levels of added LSR. Selective irradiations of the two CH and NH signals and of the $CH_3$ resonance for 1 with added 4 were carried out, using several different 4:1 molar ratios. Using a solution 0.143 molal in 1 and a low 4:1 molar ratio of 0.0693 to just separate the NH and CH signals, irradiation of $CH_3$ was found to selectively sharpen the downfield absorption tentatively establishing the methine as the downfield signal with this level of added 4. By way of confirmation, irradiation of the downfield signal (assigned to the methine) resulted in collapse of the $CH_3$ doublet to a singlet with decoupling powers as low as 1 mG. In contrast, irradiation of the signal at higher field (assigned to NH) still left a distinct doublet for the $CH_3$ signal with 2 mG decoupler power, and a noticeable shoulder remained with 3 mG applied. Using a 4:1 ratio of 0.268, the CH and NH signals are separated by about 2.0 ppm. Again, irradiation of the downfield (CH) signal near 8.6

ppm led to considerable sharpening of the $CH_3$ signal; irradiation at the (NH) signal at 6.6 ppm did not. Finally, irradiation of the downfield (CH) signal near 11.7 ppm using a 4:1 ratio of 0.520 collapses the $CH_3$ triplet (because of $\Delta\Delta\delta$) to a well defined doublet, i.e., two singlets for the two enantiomers of 1. Irradiation at the NH did not appreciably collapse the $CH_3$ signal. Thus the assignments for CH and NH with added LSR are confirmed: the methine has much greater $\Delta\delta$ magnitudes and is further downfield. See Figure 5.



To confirm analytical utility and to determine the actual sense of magnetic nonequivalence of 1 with 4, a "spiking" experiment was performed. A mixture of 17.0 mg of racemic 1 and 9.3 mg of (-)-1 was dissolved in $CDCl_3$ to give a solution 0.157 molal in total 1, with enantiomer ratio of (-)-1:(+)-1 of 67.7:32.3, or 2.11:1.00. With a 4:1 ratio of 0.547, the $CH_3$ signal appeared as an unsymmetrical triplet, the downfield branch more intense than the upfield branch. The average ratio of peak heights measured to a sloping

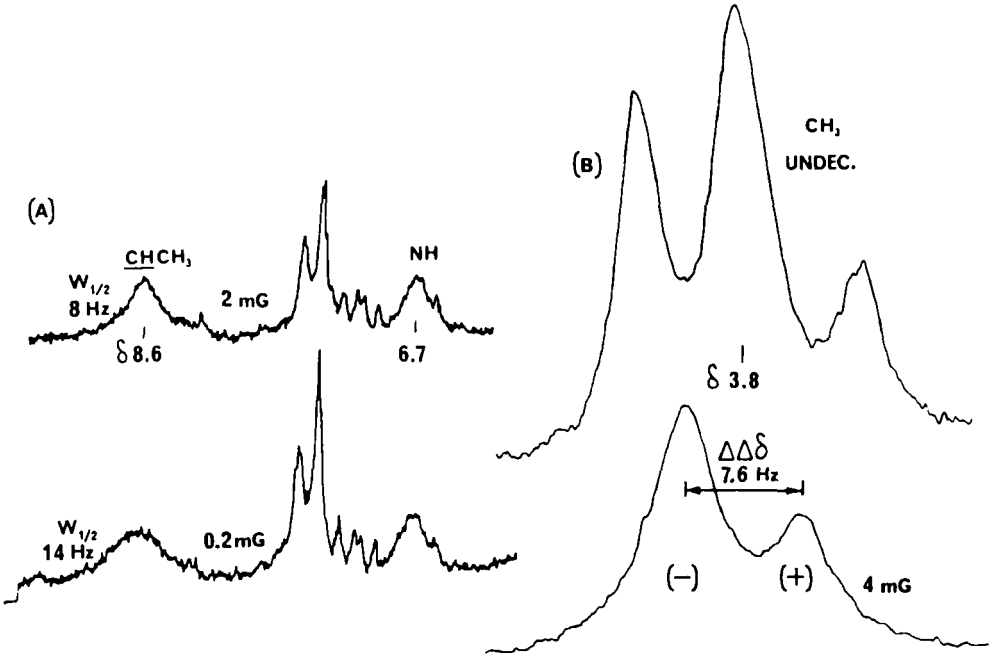



Figure 5. (a) Observation of NH and $\underline{CH}CH_3$ signals of 0.143 molal 1 with irradiation of $CH_3$ at indicated decoupler powers (mG) with a 4:1 ratio of 0.268. (b) $CH_3$ signal for a solution 0.157 molal in total 1, with a ratio of (−)-1:(+)-1 of 67.7:32.3 and a 4:1 ratio of 0.547 both without (upper trace) and with (lower trace) decoupling of $\underline{CH}CH_3$ at 4 mG decoupler power. Measured peak height ratios and $\Delta\Delta\delta$ (in Hz) are shown. Sweep width was 10 ppm for (a) and 1 ppm for (b).

valley-to-valley baseline of the triplet for the downfield versus the upfield branch was 1.98 (N=2, std. dev. = 0.177). When the downfield methine signal was irradiated at powers from 4-8 mG, the methyl signal collapsed to an unequal doublet,

with an average of downfield to upfield branch heights of 1.90 (N=4, std. dev. = 0.0311). The downfield $CH_3$ signal for 1 with added 4 must be assigned to the (-) enantiomer. The observed percentages of (-)-1:(+)-1 based on outer peak height ratios of the $CH_3$ triplet are 66.4:33.6, and based on peak height ratios of the $CH_3$ signals with methine decoupling, 65.5:34.5. These results are in good agreement with actual values based on weights of racemic and (-)-1 used, assuming 100% enantiomeric purity for the sample of (-)-1, and indicate the potential analytical value of the method. The results are illustrated in Figure 5(b).



In conclusion, we have presented 60 and 300 MHz $^1H$ NMR data for 1, both unshifted and in the presence of achiral LSR, 2, $Eu(FOD)_3$, and the chiral LSR, 3, $Eu(HFC)_3$, or 4, $Eu(FACAM)_3$. Evidence is presented for LSR catalysis of the proton exchange process which, together with rotation of the imidazoline ring, interconverts and averages all four hydrogens of the $CH_2CH_2$ moiety. Spin decoupling experiments confirmed the

assignments of NH and $\underline{CH}CH_3$ signals for 1 with added LSR. Direct optical purity determinations for samples of 1 were demonstrated using a nonracemic sample of 1 with 4; for optimal results, a 4:1 molar ratio of 0.5-0.55 is recommended. The (-) enantiomer of 1 displayed a downfield sense of magnetic nonequivalence for the $CH_3$ resonance under these conditions.



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