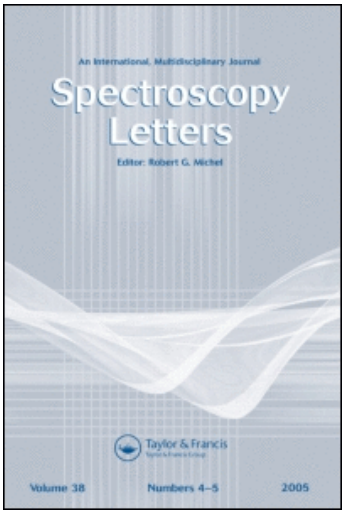

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^{1}H NMR Spectral Simplification with Chiral Solvating Agents and with Achiral and Chiral Lanthanide Shift Reagents. *Cis*-4,5-Dihydro-4-Methyl-5-Phenyl-2-Oxazolamine, "*Cis*-4-Methylaminorex," a Potent Stimulant and Anorectic

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^{1}H NMR SPECTRAL SIMPLIFICATION WITH CHIRAL SOLVATING AGENTS AND WITH ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS. CIS-4,5-DIHYDRO-4-METHYL-5-PHENYL-2-OXAZOLAMINE, "CIS-4-METHYLAMINOREX," A POTENT STIMULANT AND ANORECTIC.

Key Words: 2-Amino-4-methyl-5-phenyl-2-oxazoline, Eu(FOD)$_3$, Eu(HFC)$_3$, Europium, (R)-(-)-2,2,2-Trifluoro-1-(9-anthryl)ethanol, (R)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid, Enantiomer, Optical Purity, Analysis, Stereoisomer.

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ABSTRACT

The 60 MHz ^{1}H NMR spectra of racemic (±)-cis-4,5-dihydro-4-methyl-5-phenyl-2-oxazolamine, 1, have been

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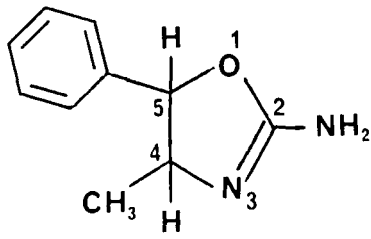
studied at 28° in $CDCl_3$ solution with the achiral lanthanide shift reagent (LSR), tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium(III), 2, and the chiral reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camphor-ato]europium(III), 3. Additional NMR studies were performed at 400 MHz in $CDCl_3$ solution at 24° using the chiral solvating agents (CSA), (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol, 4, and (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 5. Substantial enantiomeric shift differences, $\Delta\Delta\delta$, were observed for the CH_3 signal of 1 using 3 or 5, and for the ortho aryl protons using 4, which should make possible direct optical purity determinations of 1. Accurate 400 MHz data for chemical shifts and vicinal coupling constants of racemic cis-1 are presented, and compared with values for (optically active) (-)-trans-1; some differences are seen compared to previously reported data. Some additional data were obtained in C_6D_6 solution. The LSR and CSA results are compared and discussed.

INTRODUCTION

(±)-Cis-4,5-Dihydro-4-methyl-5-phenyl-2-oxazolamine, 1, known as cis-2-amino-4-methyl-5-phenyl-2-oxazoline, "cis-4-methylaminorex" or McN-822



(McNeil), had been reported as a potent anorectic and central nervous system (CNS) stimulant (1-4). For the diastereomeric trans isomer, preparation of racemic material as well as a pure enantiomer has been described (2,5,6) and the activities have been studied with respect to the stereochemistries (2,5,6). One enantiomer of the cis isomer has similarly been prepared and examined (6). A recent report (7) has suggested that 1 may become a new drug of abuse because of its CNS activity; the substance 1 is now listed in Schedule I of the Federal Controlled Substances Act. We were interested in studying the ^{1}H NMR spectra of 1 with lanthanide shift reagents, LSR, for potential spectral simplification as well as for possible direct optical purity determinations (using chiral LSR). The relatively rigid structure of the cyclic 1 and its fulfillment of general structural requirements described earlier (8) suggested that 1 would be an important model compound for us to gain further insight into the interactions of substrates with LSR. Our

studies employed the achiral reagent, tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, known as $Eu(FOD)_3$, and the chiral reagent, tris[3-(heptafluoropropylhydroxy-methylene)-d-camphorato]europium(III), 3, known as $Eu(HFC)_3$ or $Eu(HFBC)_3$. The general principles and techniques for the use of both achiral and chiral LSR have been discussed (9-16).

In addition, we examined the use of the chiral solvating agents (CSA), (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol, 4, and (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 5, as alternative methods for potential optical purity determinations of 1. We sought to compare the efficacy of the chiral LSR and CSA techniques. The complementary values of these methodologies, and of newer methods in chiral chromatography, will become increasingly important in view of the impact of new enantioselective syntheses on the preparations of pharmaceuticals. The CSA technique continues to be important (17-21); the subject has been reviewed (9, 11, 22-23).

EXPERIMENTAL

Samples of racemic 1 free base were obtained from the Research Technology Branch of the National

Institute on Drug Abuse (Rockville, MD) through the Research Triangle Institute (Research Triangle Park, NC) as batch no. 5667-1022-87, and from the R.W. Johnson Pharmaceutical Research Institute/McNeil Pharmaceutical/Janssen Research Foundation (Spring House, PA) as McN-822 notebook no. 465-135A1 lot 0789, and were used as supplied without further purification. The (-) enantiomer of trans-1 (as McN-877Z notebook no. 350-109B) had $[\alpha]_D^{20}$ = -1.6 (c=1, CH_3OH), and was also used as supplied by McNeil Pharmaceutical. Chloroform-d (99.8 atom % D) was obtained from Aldrich Chemical Corp., Milwaukee WI 53201; Norell, Inc., Landisville NJ 08326; or Cambridge Isotope Laboratory, Inc., Woburn MA 01801. The $CDCl_3$ (from Aldrich or Norell) was dried and stored over 3Å Molecular Sieves for 60 MHz studies with LSR. For 400 MHz FT work, $CDCl_3$ from freshly opened sealed ampules (Cambridge) was used directly. C_6D_6 (99.96 atom % D) was obtained from Aldrich. Lanthanide shift reagents and chiral solvating agents (CSA) were obtained from Aldrich and were stored in a desiccator over P_2O_5. Materials were used as received except as noted.

For runs with shift reagents, an accurately weighed portion of drug was added to $CDCl_3$ [containing

about 0.5% tetramethylsilane (TMS) as internal standard] in an NMR sample tube and dissolved by shaking; increments of solid shift reagent were added directly to the sample, dissolved by shaking, and the spectra immediately obtained. Drug concentrations were typically from 0.23-0.28 molal. All LSR spectra were run on a Varian EM360A 60 MHz ^1H NMR spectrometer at 28°. In runs with chiral shift reagent where enantiomeric shift differences were observed for selected resonances, reported chemical shifts are the average values for the two enantiomers. In spectra where TMS was obscured by shift reagent peaks, $CHCl_3$ (present as an impurity in the solvent) was used as an internal standard. Additional ^1H spectra were recorded on a Fourier transform Bruker AM-400NB spectrometer at 24° in $CDCl_3$ containing 0.05% v/v TMS, or in C_6D_6, operating at 400.13 MHz in the FT mode, using 5mm sample tubes. Chemical shifts are reported in δ (ppm) relative to TMS (0.00 ppm) or $CHCl_3$ (7.25 ppm). Coupling constants were determined from spectral expansions (at 60 MHz) or from peak frequency printouts (at 400 MHz); the latter are believed accurate to $\pm$ 0.01 Hz. Typical FT parameters were as follows: 3.7 μs pulse (30° flip angle) with a 2 s recycle time,

spectral width of 8064 Hz (-4 to +16 ppm), 1.016 s acquisition time, and a resolution of 0.984 Hz per point; 96 scans were stored. For typical runs with CSA, accurately weighed portions of 1 and CSA (4 or 5) were dissolved in 0.7 ml of $CDCl_3$ and the NMR spectra immediately recorded. Molar ratios of CSA (4 or 5) to 1 were in the range of 0.1 to 5.0. Drug molalities for CSA studies were varied from ca. 0.01 to 0.07, as noted in the Discussion.

RESULTS AND DISCUSSION

The 400 MHz ^{1}H spectrum for a 0.0124 molal solution of 1 in $CDCl_3$ showed signals as follows (δ, ppm): 0.74(d, 3H, ^3J=6.84 Hz, CH_3); 4.36 (approx. pentet, 1H, H_4); 5.61 (d, 1H, ^3J=8.84 Hz, H_5); 4.38 (br s, 2H, NH_2). The aromatic multiplet was tentatively assigned as: H_{meta} (approx. t, 2H, δ 7.36), H_{para} (d, 1H, δ 7.31), H_{ortho} (d, 2H, δ 7.24). At 60 MHz, the aryl region was not resolvable and appeared essentially as a singlet. When the 400 MHz spectrum was reprocessed with zero-filling to provide enhanced resolution of 0.492 Hz/pt, an eight line pattern could be seen for H_4, with the vicinal couplings of ca. 6.84 and 8.84 Hz for the double quartet. Of considerable significance is the large vicinal coupling seen for $^3J_{H(4)-H(5)}$ of 8.84 Hz, consistent with a dihedral angle near 0^0 for cis

hydrogens in a five membered ring with the constraints of the trigonal centers. The couplings measured at 60 MHz for a 0.263 molal solution of 1 were 6.75 Hz for the methyl and 8.75 Hz for H_5; the NH_2 signal appeared at 5.27 ppm reflecting the expected concentration and temperature dependence of these exchangeable protons. Eight lines were resolvable for the H_4 multiplet in the 60 MHz spectrum. Previously, coupling constants for H_5 of 10 Hz (24) or 7.9 Hz (7) had been reported. (Note that structure IV is incorrect, and structures VI and VII should be reversed, in Ref. 24). For the methyl resonance of 1, an 8 Hz coupling had been cited (24). Because of these different observed values, and the question of stereochemistry that could be posed by the trans isomer of 1, a sample of authentic trans-4,5-dihydro-4-methyl-5-phenyl-2-oxazolamine, known as trans-4-methylaminorex or trans-1, was examined at 400 MHz in $CDCl_3$ [as the (-) enantiomer, McN-877Z notebook no. 350-109B]. The authentic trans-1, as a 0.0130 molal solution, displayed signals as follows, (δ, ppm): 1.34 (d, 3H, ^3J=6.62 Hz, CH_3); 3.94 (approx. pentet, 1H, average apparent J=6.65 Hz, H_4); 4.33 (br s, 2H, NH_2); 4.93 (d, 1H, ^3J=7.23 Hz, H_5); 7.33-7.40 (mult.,5H, aryl). Thus, there is a striking difference in chemical shift for the CH_3, with cis-1 showing the

high field signal resulting from anisotropic shielding by the aryl ring, relative to trans-1. H_4 of cis-1 is at correspondingly lower field than in the trans isomer. Previously reported vicinal coupling constants of 7 Hz for both H_5 and CH_3 of racemic trans-1 (24) reflect the slightly smaller vicinal coupling expected for H_4-H_5 considering the geometric constraints of the ring, versus cis-1. Apparently some torsion about the C_4-C_5 bond results in a dihedral angle between H_4 and H_5 of trans-1 considerably different from 120°, for which a much smaller coupling would be expected. The difference in magnitudes for these couplings in cis-1 and trans-1 is ca. 1.6 Hz, close to the difference in cis versus trans vicinal coupling in the five-membered ring of 1,3-dioxolane (25), based on 7.3 and 6.0 Hz couplings in the latter case.

The results of incremental additions of the achiral LSR, $Eu(FOD)_3$, 2, to 0.276 molal racemic cis-1 in $CDCl_3$ are summarized in Fig. 1. Substantial lanthanide-induced shifts, LIS ($\Delta\delta$), are observed for all nuclei of 1, with the largest induced shifts for the NH_2 signal. Larger $\Delta\delta$ magnitudes seen for H_4 versus H_5 are consistent with predominant LSR binding to N-3, closer to H_4. This binding site would be favored on both steric and electronic grounds.

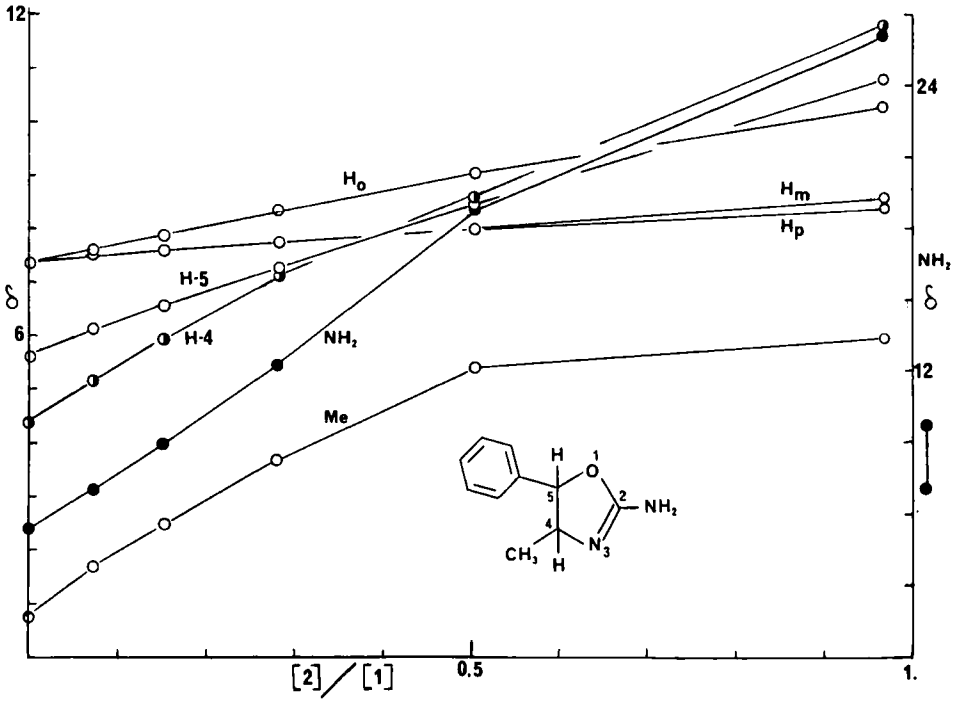


Fig. 1. Variation of chemical shift, δ (in ppm), with molar ratio of 2:1 for (±)-cis-1.

The chiral LSR, $Eu(HFC)_3$, 3, was employed to elicit enantiomeric shift differences, $\Delta\Delta\delta$, of racemic cis-1, and the results are summarized in Figs. 2 and 3. Significant $\Delta\Delta\delta$ values were clearly seen for the signals of H_5 and CH_3, with the methyl signal displaying excellent potential for direct determinations of optical purity of 1. Thus, for a 0.235 molal solution of 1 with a 3:1 molar ratio of

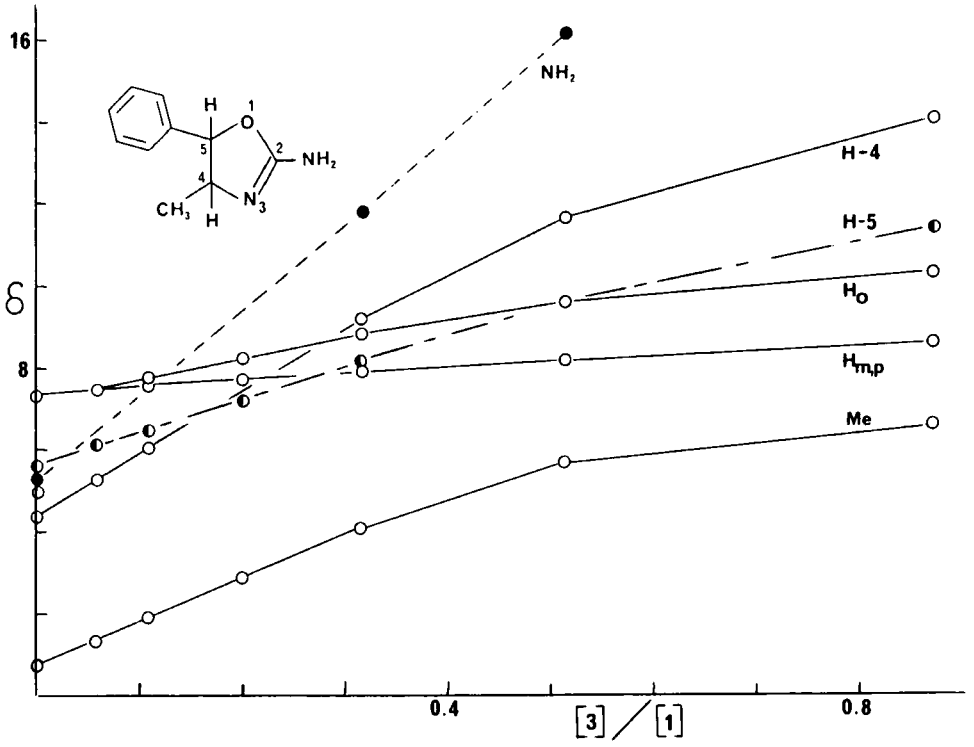


Fig. 2. Variation of chemical shift, δ (in ppm), with molar ratio of 3:1 for (±)-cis-1. Note: Where enantiomeric shift differences occur, average chemical shifts are presented.

0.314, the doublet methyl signals for each enantiomer are well separated with $\Delta\Delta\delta$ of ca. 40 Hz (at 60 MHz). The valley height between the doublets was only 8.5% of the average doublet peak heights, indicating good resolution between the enantiomer signals. Detection of less than 5% of a minor enantiomer should

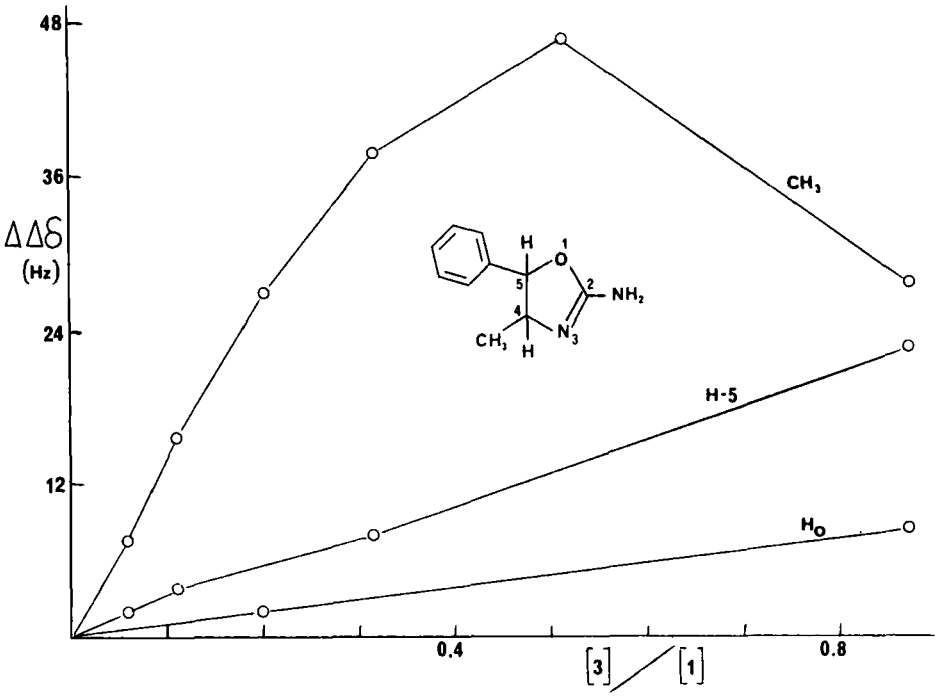


Fig. 3. Variation of enantiomeric shift difference (in Hz at 60 MHz) with molar ratio of 3:1 for (±)-cis-1.

be possible. In addition, analysis conditions based on the CH_3 signal should be rather non-critical. Resolution by the valley height criterion for the methyl resonance was 12.2% and 14.3% at 3:1 molar ratios of 0.198 and 0.510, respectively, with no interfering peaks. The downfield methyl doublet was consistently broader and lower in height than the

upfield doublet, presumably the result of differential lanthanide-induced broadening. Quantitative studies of enantiomeric excess should therefore be based on peak areas (integrals) rather than on peak heights. The general trends for LIS values with 3 were similar to those seen with 2.

Parallel studies were performed on cis-1 using chiral solvating agents, CSA, with a 400 MHz spectrometer. The CSA, (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol, 4, was added incrementally to solutions of cis-1 in $CDCl_3$ to give 4:1 molar ratios from 0.143-5.01. Molalities of 1 ranged from 0.0146-0.0676. Observed enantiomeric shift differences with 4 were strikingly different than with LSR 3. With 4, large $\Delta\Delta\delta$ was seen for the ortho aryl hydrogens, with full baseline separation of the signals of each enantiomer for 4:1 ratios from 1.0-5.01. The $\Delta\Delta\delta$ for these ortho hydrogens reached 35.5 Hz (at 400 MHz) for 0.0146 molal 1 and a 4:1 ratio of 5.01. The H_5 signal appeared as a triplet, i.e., $\Delta\Delta\delta \approx {}^3J$ at the highest 4:1 ratios examined. No observable $\Delta\Delta\delta$ was seen for the methyl signal. Small $\Delta\Delta\delta$ was noted for H_4 which, because of extensive multiplicity, would not be analytically useful. These results are shown in Fig. 4. Generally, small upfield complexation shifts for

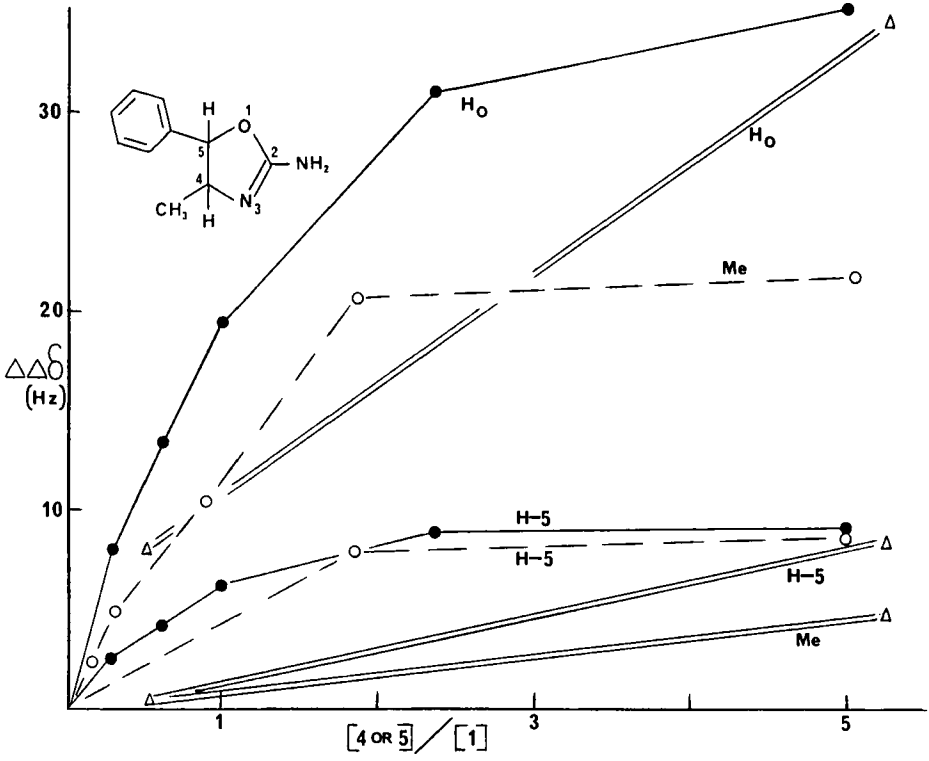


Fig. 4. Variation of enantiomeric shift difference (in Hz at 400 MHz) for (±)-cis-1 with added 4 (solid lines, filled circles) or 5 (broken lines, open circles) in $CDCl_3$. Small $\Delta\Delta\delta$ values for H_4 are not indicated. Values for 4 in C_6D_6 are also shown (double lines, triangles).

the signals of 1, ca. 0.2-0.3 ppm, were noted with high levels of 4.

These results were extended by use of another CSA, (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 5, in $CDCl_3$ solutions at 400 MHz. Using

concentrations of 1 from 0.0124-0.0822 molal, 5:1 molar ratios from 0.178-5.05 were examined. With 5, largest $\Delta\Delta\delta$ were seen for the methyl signal, ca. 21-22 Hz (at 400 MHz) for 5:1 ratios of 1.86-5.05, providing near baseline resolution of each enantiomer's doublet signal. The H_5 signal of 1 appeared as a triplet at the highest 5:1 ratios. Results are summarized in Fig. 4. Added 5 induced downfield shifts with the aliphatic signals of 1 (but interfered with observation of aryl meta and para signals). These downfield shifts were typically 0.1-0.3 ppm for carbon-bound protons and were several ppm for the NH_2 signal. These shifts would be consistent with protonation of 1 and resulting delocalized positive charge expected with use of the acidic CSA, 5. The relative $\Delta\Delta\delta$ magnitudes for 1 with added LSR 3 or CSA 5 suggests that each reagent coordinates or protonates at the same site, presumably N-3.

CSA 4 was also employed with cis-1 in C_6D_6 to examine possible effects of an aromatic solvent. Some differences were noted relative to results in $CDCl_3$. For 0.0203 molal 1 in C_6D_6 and a 4:1 ratio of 5.25, excellent baseline resolution was again seen for the ortho protons ($\Delta\Delta\delta$ 34.6 Hz), with modest $\Delta\Delta\delta$ for H_5 of 8.33 Hz resulting in an apparent triplet signal.

However, the methyl displayed definite $\Delta\Delta\delta$ of 4.82 Hz, appearing as overlapping doublets. Thus, the C_6D_6 appears to somewhat mediate the solvation of 4 with 1, but does not significantly enhance or change the analytical utility based on the ortho proton signal.

In C_6D_6 solution, cis-1 showed the following NMR (δ, ppm): 0.75 (d, 3H, ^3J=6.63 Hz, CH_3); 4.19 (m, six lines, 1H, average apparent J=5.82 Hz, H_4); 5.05 (v br, 2H, NH_2); 5.23(d, 2H, ^3J=8.82 Hz, H_5); 7.02-7.11 (m, 5H, C_6H_5), for a 0.0239 molal solution. These values reflect appreciable aromatic solvent-induced shifts, ASIS, relative to values in $CDCl_3$. Thus, H_4 and H_5 appear at higher field in C_6D_6 by ca. 0.2-0.4 ppm; the aryl protons of 1 are at higher field than the 7.15 ppm signal of the residual C_6D_5H in the solvent, and are not as well separated as in $CDCl_3$. A small decrease in ^3J for the methyl signal is also noted. The larger ASIS magnitude is seen for the benzylic H_5.

Direct optical purity determinations of cis-1 should be readily accessible using any of the chiral reagents examined here, either the LSR, 3, or the CSA, 4 or 5. The preferred choice of conditions may depend upon available instrumentation. If a higher field NMR spectrometer is available (400 MHz), the CSA 4 may be most effective with the ortho aryl signals of 1 serving

as analytical markers, either in $CDCl_3$ or C_6D_6, since the signals for each enantiomer are fully baseline resolved at high 4:1 ratios. Alternatively, CSA 5 would allow use of the CH_3 resonance of 1 as the analytical signal, albeit with somewhat less resolution. With a low field NMR (60 MHz), the chiral LSR 3 offers usable results based on the methyl signal. The distinction reflects the difference in spectrometer dispersions, with $\Delta\Delta\delta$ of about 0.66 ppm for a 3:1 ratio of 0.314 (with 0.235 molal 1) versus $\Delta\Delta\delta$ of only 0.09 ppm for a 4:1 ratio near 5.0 (and 0.0146 molal 1). The superiority of the CSA at high field in part reflects the virtual absence of line-broadening with the CSA, in contrast to the lanthanide-induced line broadening with LSR.

While both the LSRs 2 and 3, and CSA 5 display relative $\Delta\delta$ or $\Delta\Delta\delta$ magnitudes which seem generally consistent with predominant binding or protonation at the endocyclic N-3, the diastereomeric solvates formed with 4 may reflect contributions from different interactions. With 4, much larger $\Delta\Delta\delta$ values were seen for the ortho aryl protons than for H_4, H_5 or the CH_3, despite the proximity of H_4 or CH_3 to N-3. Indeed, observable $\Delta\Delta\delta$ for the methyl signal was seen only when 4 was used in C_6D_6. One might expect that if pi-

pi aryl interactions were significant in accounting for the large $\Delta\Delta\delta$ of the ortho protons (when 4 is added to 1), that use of the aromatic solvent, C_6D_6, should compete with the anthryl group of 4. In fact, the large $\Delta\Delta\delta$ magnitudes for these nuclei do not change appreciably on going from $CDCl_3$ to C_6D_6 solvent, although the CH_3 shows much greater $\Delta\Delta\delta$ in the latter solvent.

CONCLUSIONS

The 60 and 400 MHz ^1H spectra of racemic cis-1 have been examined. The 400 MHz chemical shift and coupling constant data were obtained in $CDCl_3$ and C_6D_6 and compared to earlier reported values. For reference, 400 MHz data are also presented for optically active (-)-trans-1. Some differences were noted from the literature values. The achiral LSR 2 and the chiral LSR 3 were used with cis-1 at 60 MHz in $CDCl_3$ and the $\Delta\delta$ and $\Delta\Delta\delta$ values are presented. At 400 MHz, CSA 4 and 5 were added to solutions of cis-1 in $CDCl_3$ to induce enantiomeric shift differences for selected nuclei; 4 was also studied in C_6D_6. Substantial $\Delta\Delta\delta$ values for the ortho aryl hydrogens of cis-1 (with 4) and for the CH_3 (with 3 or 5) should have considerable potential for direct determinations of enantiomeric excess. Because of recent reports of

the abuse potential of 1, improved methods for characterization appear quite relevant (7,26).

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