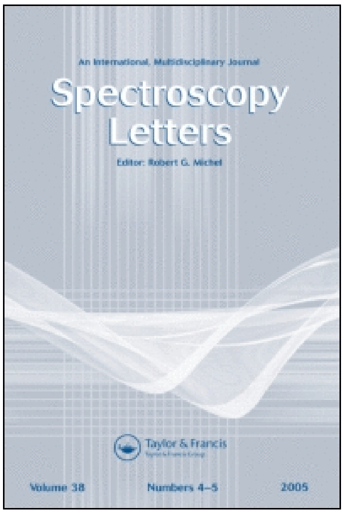

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NMR Studies of Drugs. Rimantadine. Rigorous ^{1}H and ^{13}C Assignments and Applications of Lanthanide Shift Reagents

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NMR STUDIES OF DRUGS. RIMANTADINE. RIGOROUS ^{1}H AND ^{13}C ASSIGNMENTS AND APPLICATIONS OF LANTHANIDE SHIFT REAGENTS.

Key Words: Rimantadine, Shift Reagent, Lanthanide, Carbon-13 NMR, Proton NMR, Optical Purity, Enantiomer, Chiral.

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ABSTRACT

Racemic rimantadine, 1, has been studied by NMR in $CDCl_3$ solution with the achiral shift reagent,

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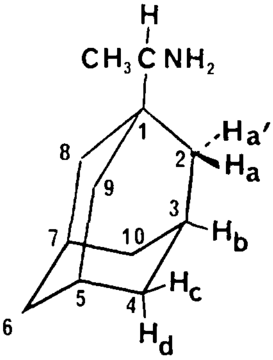
tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, and the chiral reagents, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III), 3, and tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III), 4. Substantial lanthanide induced shifts were observed for all proton signals of 1 with each reagent. Enantiomeric shift differences were seen for the CH_3 absorption using 3 or 4, with larger values for 4. Direct optical purity determinations of 1 should be possible using 4. Complete unambiguous ^1H and ^{13}C NMR assignments for unshifted rimantadine were obtained using both 1-D and 2-D techniques.

INTRODUCTION

Rimantadine, 1, α-methyltricyclo[3.3.1.$1^{3,7}$]decane-1-methanamine, is an adamantane derivative that has been studied for its antiviral and other pharmacological activity (1,2). The resolution of 1 into its enantiomers has been reported together with their specific rotation data at several wavelengths (3). Numerous derivatives of adamantane have been studied using NMR lanthanide shift reagents (LSR), since the rigidity of the ring system is particularly amenable to LSR structure determinations. A few examples of LSR studies of adamantyl derivatives by ^1H NMR include



hydroxyadamantanes and 1-adamantanemethanol (4); 1- and 2-adamantanol (5); 1-adamantylamine, 1-adamantanol, 1-adamantanemethanol, 1-adamantanemethanamine, and analogs (6); numerous 1-adamantyl derivatives (7); and some alkyl- (8) and halogen-substituted (9) adamantanones. There do not appear to have been any LSR studies on 1 itself. In particular, in view of the existence of enantiomers of 1, we were especially interested in studies with chiral LSR to explore possible direct optical purity determinations. The use of achiral and chiral LSR has been extensively reviewed (10-17).

EXPERIMENTAL

A sample of racemic rimantadine hydrochloride, 1-HCl, was provided by Hoffmann-La Roche Inc., Nutley, NJ 07110, U.S.A. as lot no. 15918-14, sample Ro 22-1859/004. Chloroform-*d*, (99.8 atom % D) obtained from

Aldrich Chemical Corp., Milwaukee WI 53201, U.S.A., or form Norell, Inc., Landisville NJ 08326, U.S.A., was dried over 3A molecular sieves. Shift reagents were obtained from Aldrich and were stored in a desiccator over P_2O_5. Materials were used as supplied except as noted.

In general, for LSR studies by 60 MHz ^{1}H NMR, an accurately weighed portion of 1, as the free base (see below), typically about 14 mg, was added to 570-630 mg $CDCl_3$ [containing about 0.5%-tetramethylsilane (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 the spectra immediately recorded.

Spectra were obtained with a Varian EM360A 60 MHz ^{1}H NMR spectrometer or a General Electric QE300 spectrometer at probe temperatures of 28° or 26° (±1°), respectively. The 60 MHz ^{1}H decoupling experiments were performed using the Varian EM-3630 lock/spin decoupler accessory. In 60 MHz 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 chiral LSR added, when enantiomeric shift differences, $\Delta\Delta\delta$, were observed, average chemical shift values for the two optical antipodes are reported here.

For all spectra obtained on the QE-300 except the long range ^{13}C-^{1}H correlation (CSCMLR) spectra, the rimantadine concentration was 0.1706 molal. For the CSCMLR experiments, a 0.836 molal solution was used. The CSCMLR experiment was that described in GE Applications Note No. 860310 (18) and uses the TANGO pulse sequence (19). Optimum sensitivity for detection of non-protonated carbons was achieved with a value of 30 msec for the delay, "D7," in this sequence. Observe frequencies of 300.15 and 75.48 MHz were used for ^{1}H and ^{13}C, respectively. Chemical shifts are referenced to internal TMS at 0.00 ppm for ^{1}H. ^{13}C chemical shifts are given relative to the center peak of $CDCl_3$ (77.0 ppm).

Preparation of Free Base of Racemic 1: Racemic 1-HCl (262.7mg, 1.217 mmol) was dissolved in 12ml H_2O and treated with ca. 8ml aq. 5% NaOH and 1.5 gm NaCl. The mixture was extracted with CH_2Cl_2 (8 ml) followed by three additional 5 ml portions of CH_2Cl_2. The combined organic extracts were dried over Na_2CO_3 (anh.) and solvent was removed on a rotary evaporator (at aspirator pressure and a bath temperature of 50°) to constant weight, to give 203.8 mg of the free base of 1, 93.4% recovery of an off-white oil which was used for NMR studies without further purification. All free base samples of 1 were routinely stored under N_2.

RESULTS AND DISCUSSION

The preliminary 60 MHz ^1H NMR spectrum of racemic 1 (0.124 molal in $CDCl_3$ at 28°) was fairly uninformative because of little useful fine structure in the signals of the adamantyl ring protons.

Because of questions of assignments of 1, extended studies were performed using 300 MHz ^1H and 75 MHz ^{13}C spectra. For 0.1706 molal 1 in $CDCl_3$ at 26°, the ^1H spectrum clearly allowed assignments of the sidechain, as follows (δ, ppm): 2.40(1H, q, ^3J=6.61 Hz, C$\underline{H}$$CH_3$); 1.04 (2H, br s, NH_2); 0.97 (3H, t, ^3J = 6.63 Hz, CH_3). See Fig. 1. The ring protons appeared as a 3H broad singlet (with shoulders) at 1.99 ppm, presumably the tertiary bridgehead methines H(3,5,7); an apparent AB quartet centered at 1.67 ppm with observed J=11.7 Hz and a separation of 14.4 Hz between the central peaks, with 6H intensity; and lastly, a 6H intensity distorted AB quartet centered at 1.51 ppm. This latter AB quartet showed the two central peaks barely separated by 1.2 Hz and low intensity outer lines with apparent J ca. 13 Hz. Thus, the 1.51 signal represents two sets of protons that are nearly isochronous, in contrast to the 1.67 multiplet which reveals greater chemical shift nonequivalence. We initially favored assignment of the protons at C(2,8,9) to the 1.51 signal, since the shift nonequivalence would reside only in the chiral sidechain inducing a difference in the diastereotopic

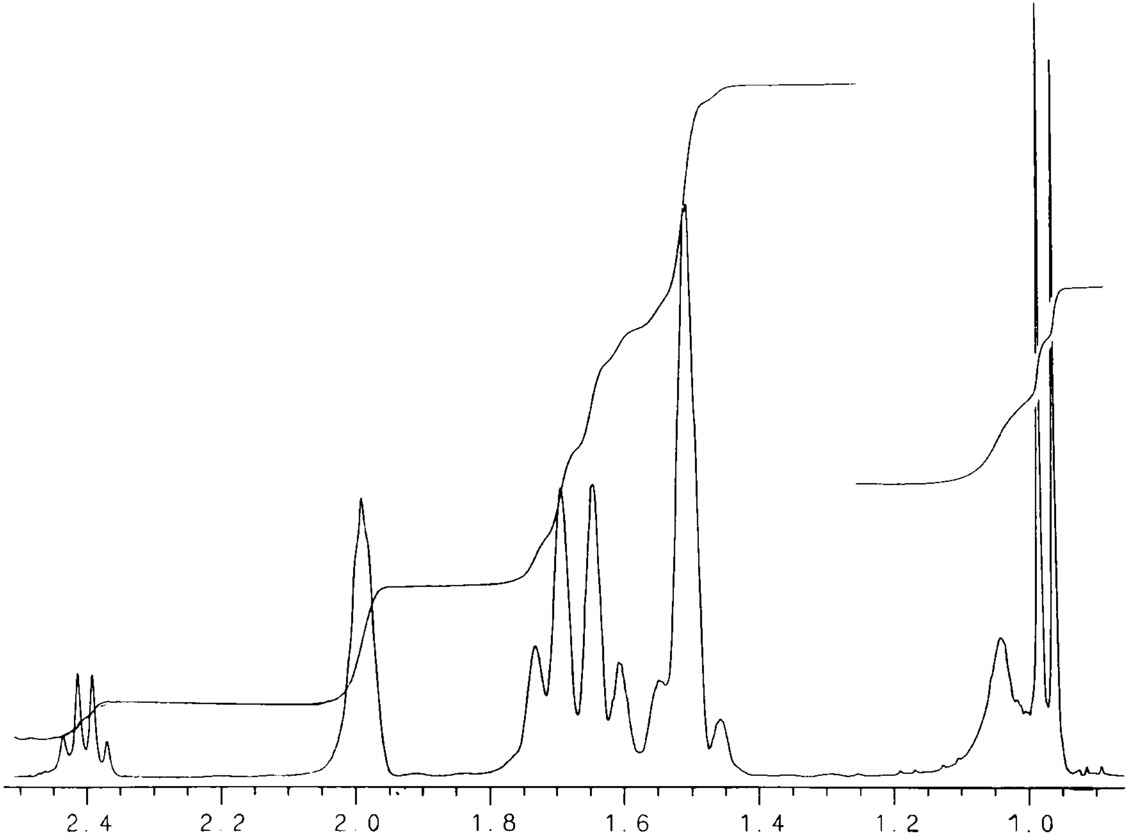


Fig. 1. The ^1H spectrum of rimantadine at 300 MHz with 8 acquisitions, 32° pulses, recycle time of 3.71 s and resolution of 0.37 Hz.

proton pair at each methylene. The protons at C(4,6,10) might differ more significantly by being <u>syn</u> or <u>anti</u> to the sidechain and could be assigned to the 1.67 AB quartet. This would leave H(3,5,7) as the broadened 1.99 signal, reflecting known small vicinal ^1H-^1H couplings of the adamantane skeleton, due to dihedral angles of about 60° (17, 20, 21).

The proton-decoupled ^{13}C spectrum, Fig. 2, showed the expected six signals at 55.85, 38.16, 37.35, 35.90, 28.54 and 16.97 ppm. Based on the downfield position of the 55.9 ppm signal, the very low intensity of the 35.9 ppm signal, and results of a series of DEPT experiments, tentative ^{13}C assignments were made as in Table 1, with the methylene assignments possibly reversed. Single frequency "on resonance" ^1H decoupling established that the carbon at 38.2 ppm was attached to the protons which absorbed at 1.51 ppm, while the carbon at 37.4 ppm was bound to the protons with signal centered at 1.67 ppm. There was some evidence in a symmetrized COSY spectrum of long range coupling between the methine at 2.40 ppm and the methylene at 1.51 ppm (circled in Fig. 3). This suggested that the 1.51 ppm signal was due to H(2,8,9) since only these protons would have potentially observable four bond coupling to the sidechain methine at 2.40 ppm.

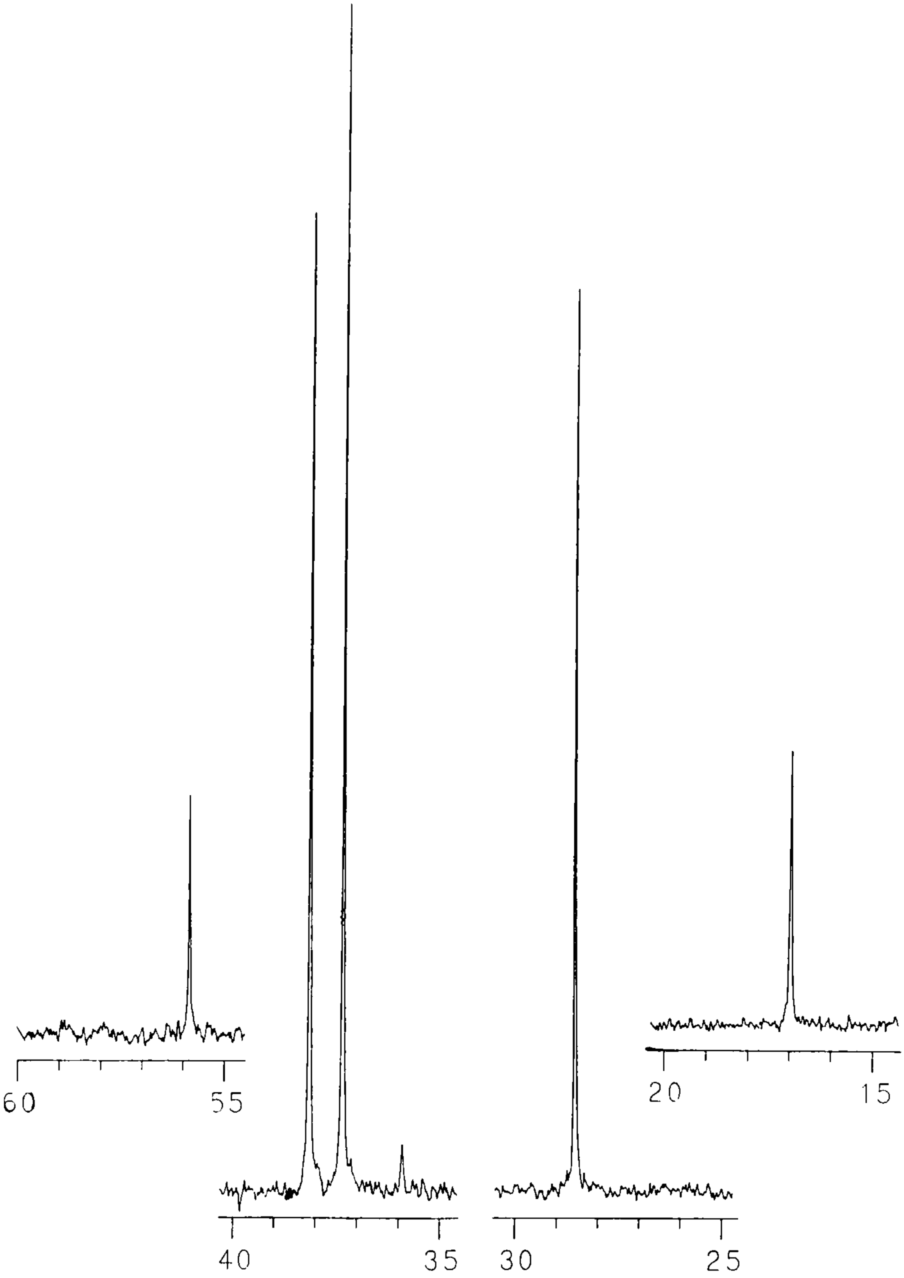


Fig. 2. The ^{13}C spectrum of 1 at 75.48 MHz, with 400 acquisitions, 48° pulses, recycle time of 2.81 s and resolution of 1.22 Hz. Processing was with an exponential line broadening of 2.00 Hz.

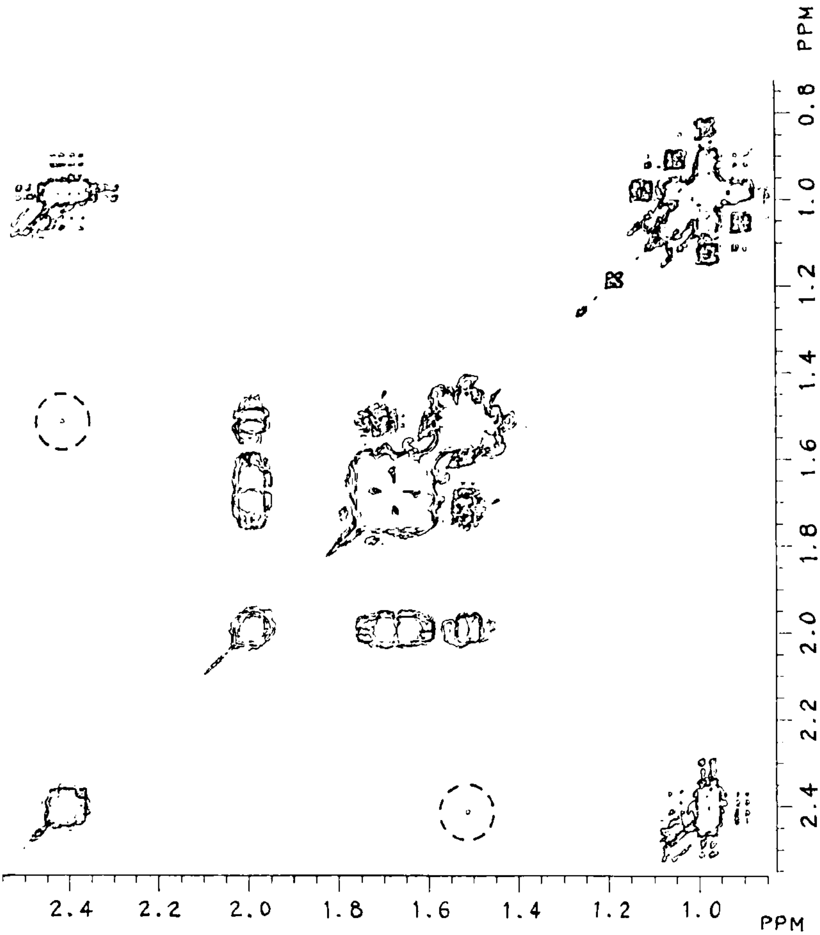


Fig. 3. The ^1H-^1H COSY spectrum of rimantadine, with 800 Hz spectral width, 640 msec acquisition time and 1.14 s recycle time. The weak crosspeak of a possible long range coupling (see text) is circled. The COSY spectra are in the magnitude mode with 8 acquisitions of 512 points for each of 128 t_1 values. Processing was with unshifted sine-bell apodization in both dimensions with zero filling once in t_1 for a final data matrix of 256x256, which was symmetrized.

This assignment was unambiguously confirmed by the long range ^{13}C-^{1}H correlation experiment, Fig. 4, which mainly shows two- and three-bond couplings, with some residual direct $^{1}J_{CH}$ couplings. A clear correlation is seen between the 55.9 ppm carbon, $H_2N\underline{C}H$, and the 1.51 ppm proton signal, allowing rigorous assignment of this as H(2,8,9) by $^{3}J_{CH}$. No such correlation is seen for the 1.67 ppm signal, thereby establishing that the 1.67 ppm signal is due to the other set of methylenes, H(4,6,10). With these ^{1}H assignments now firmly in hand, the assignments of the ^{13}C signal at 38.2 ppm to C(2,8,9) and at 37.4 ppm to C(4,6,10) can be made. All other correlations in the long range CH correlation spectrum are fully consistent with previous assignments. The utility of some of these 2-D NMR techniques for structure determination in some related systems has been reported (22-24).

Interestingly, close inspection (Fig. 4b) of these latter correlations may permit assignment of <u>syn</u> versus <u>anti</u> protons H(4,6,10) [$H_{c,d}$]. A dihedral angle of about 60° obtains for C(2)-H(4_{syn}), and the dihedral angle is near 180° for C(2)-H(4_{anti}), with a larger coupling expected for the <u>anti</u> protons. The H(4_{syn}) should have 180° dihedral angles with C(6,10) and substantial ^{3}J would be expected, in contrast to the smaller ^{3}J expected with the near 60° dihedral angles

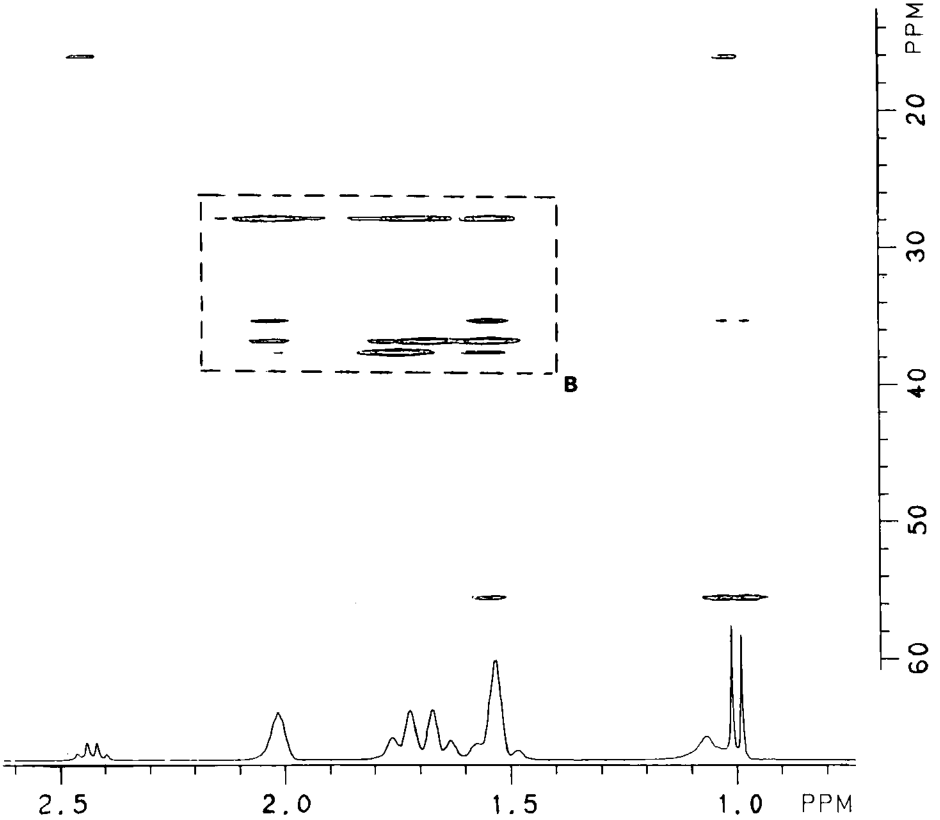


Fig. 4 (a) The "long range" ^{13}C-^{1}H correlation spectrum (GE "CSCMLR" experiment, see text) of 1, with 2 s pulse delay, and ^{13}C acquisition time of 102.4 msec. The ^{13}C spectral width was 5000 Hz with 512 real points for a resolution of 9.77 Hz. The ^{1}H spectral width was 600 Hz with 512 points (after zero filling) in the ^{1}H dimension for a resolution of 1.17 Hz. Data in both dimensions were processed with a Lorentzian-Gaussian function using a standard GE software value of DM=3. (b) Expansion of Fig. 4a.

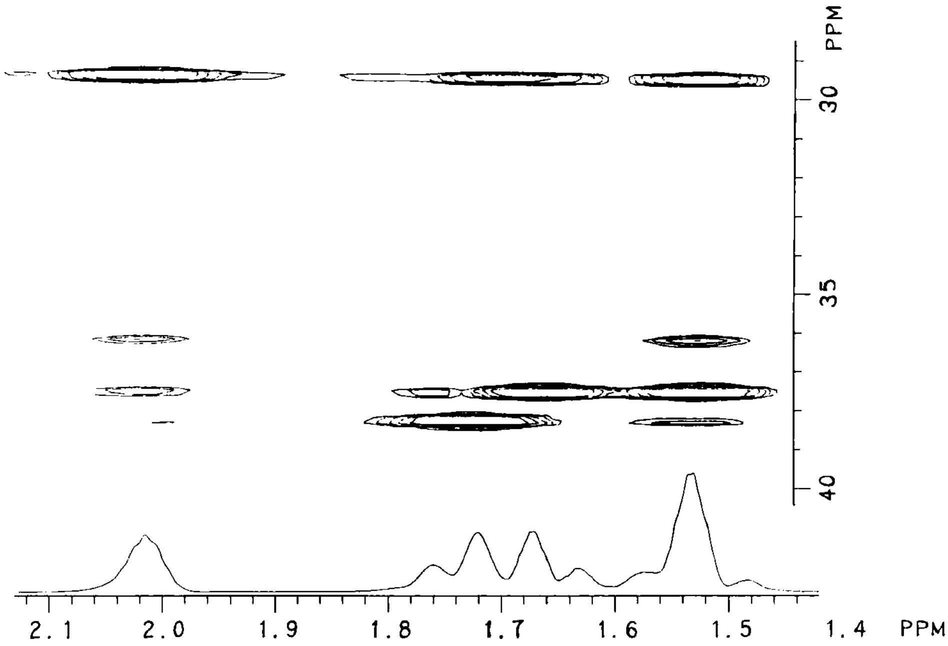


Fig. 4 continued

of H(4_{anti}) to C(6,10). Thus, C(2,8,9) should be more strongly coupled, with larger ^3J, to the <u>anti</u> H(4,6,10) and C(4,6,10) more strongly coupled to the <u>syn</u> H(4,6,10). In Fig. 4b, more intense crosspeaks are seen with the downfield portion of the ^1H AB quartet centered at 1.67 ppm and the carbon resonance at 38.2; the carbon signal at 37.4 more strongly correlates with the upfield portion of this AB quartet (and with the proton signal at 1.51 ppm). If the larger crosspeaks in Fig. 4b correspond to larger coupling constant magnitudes, then the ^{1}H and ^{13}C methylene assignments discussed above may be extended, with the long range CH correlation spectrum permitting assignment of syn and anti H(4,6,10). Since C(2,8,9) should be more strongly coupled to anti H(4,6,10) because of a 180° dihedral angle, the strong crosspeaks for the downfield half of the 1.67 ppm proton AB quartet indicate this half to be the anti protons. The upfield half is strongly correlated to C(4,6,10), consistent with appreciable ^3J for the syn protons and a dihedral angle near 180°. The assignments are summarized in Table 1.

Since the basic NH_2 is known to efficiently bind LSR, it was expected that complexation should occur at this site in 1. Variation of chemical shifts observed upon incremental addition of the achiral reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, is shown in Figure 5. The lanthanide induced shift, $\Delta\delta$, is defined as the chemical shift of a nucleus in the presence of LSR minus the chemical shift of the same nucleus with no added LSR. As expected, because of proximity to the binding site, extremely large $\Delta\delta$ values were seen for the NH_2. The sidechain CH and CH_3 resonances were also substantially shifted by added 2. Interestingly, some variations in the relative slopes in the plots of

Table 1. ^1H and ^{13}C chemical shifts (δ, ppm) of rimantadine

Proton	Shift	Carbon	Shift
2,8,9	1.51[a]	2,8,9	38.16
3,5,7	1.99	3,5,7	28.55
4,6,10 (syn)	1.63[b]	4,6,10	37.35
4,6,10 (anti)	1.71[b]	1	35.90
α-CH	2.40	α-CH	55.85
CH_3	0.97	CH_3	16.97
NH_2	1.04		

[a] Approximate AB quartet; average shift given for diastereotopic pairs.

[b] Half of approximate AB quartet centered at 1.67 ppm; observed J_{gem} = 11.7 Hz.

chemical shift versus 2:1 ratio were noted for the sidechain CH and CH_3. At 2:1 ratios below ca. 0.5, the methyl signal had greater slope (and larger induced shifts) but the methine had greater slope at higher ratios, suggesting a possible change in bound complex geometry or stoichiometries. Assignments for the adamantane skeleton protons are fully consistent with those of Table 1. Vicinal couplings in this system are known to be small, ca. 2.6 Hz, since HCCH dihedral

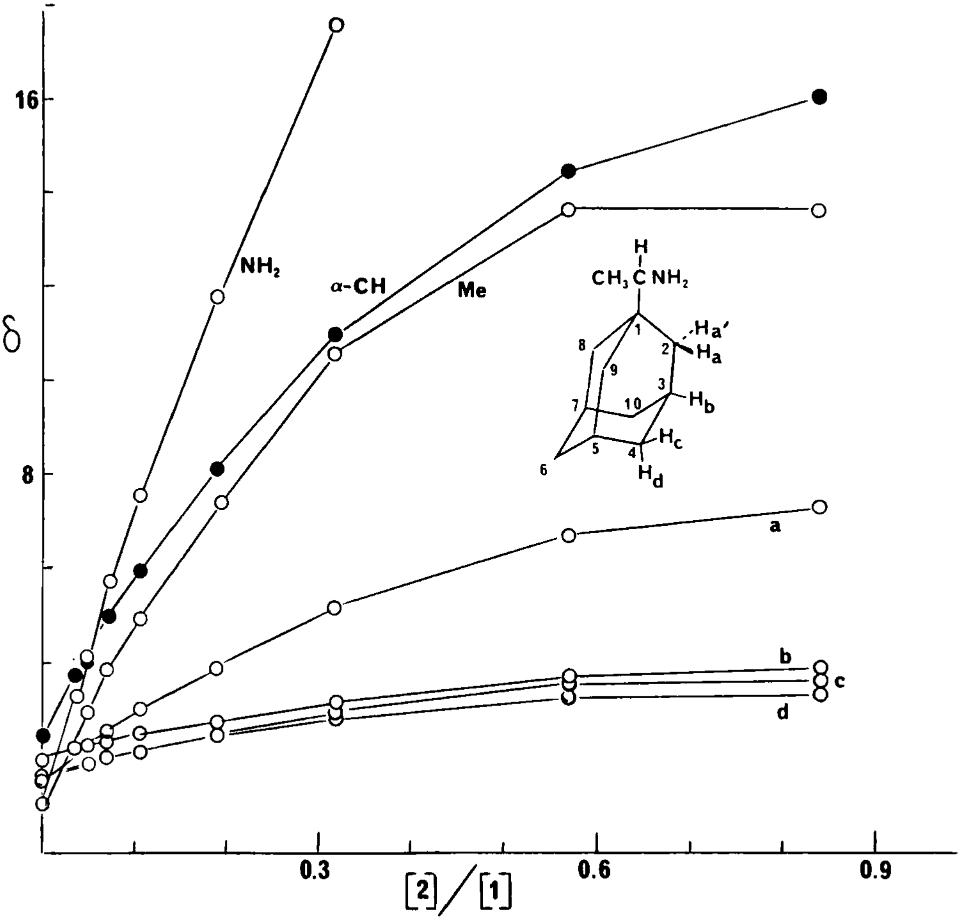


Fig. 5. Variation of ^{1}H chemical shifts of 1, in ppm, with molar ratio of 2:1.

angles are close to 60° (17, 20, 21). At 60 MHz, with lanthanide induced line broadening, clean multiplets to permit assignments are generally not seen. At a 2:1 ratio of 0.841 (the highest ratio examined here) splitting fine structure was no longer observable in the signals of the $CHCH_3$ moiety. Because of the chiral center, the two hydrogens of each CH_2 group [$H_{a,a'}$] at C(2,8,9) are diastereotopic. Evidence for their nonequivalence is seen in their appearance as an AB quartet with very small outer lines, reflecting substantial geminal ^2J coupling of ca. 12 Hz. In contrast, the protons of the CH_2 groups at C(4,6,10) ($H_{c,d}$) are diastereotopic by virtue of being <u>syn</u> or <u>anti</u> with respect to the sidechain (and to added LSR), and these exhibit separate signals at <u>2</u>:<u>1</u> ratios above 0.3. Larger $\Delta\delta$ is seen for the <u>syn</u> relative to <u>anti</u> as expected based on distance from the lanthanide binding site. The <u>syn</u> protons H_c are upfield of H_d in unshifted <u>1</u> and move downfield past H_d as LSR is added.

It is especially striking that H(2,8,9), at higher field than H(4,6,10) in unshifted <u>1</u>, displays substantially greater induced shift magnitudes. With a <u>2</u>:<u>1</u> molar ratio near 0.016, the chemical shifts of both sets of methylenes are nearly identical; H(2,8,9) has moved to lower field than H(4,6,10) with a <u>2</u>:<u>1</u> ratio of 0.356. With a <u>2</u>:<u>1</u> ratio near 0.05, H(2,8,9) coincides with H(3,5,7). Anisochronicity of <u>syn</u> and <u>anti</u> H(4,6,10) has essentially disappeared as the <u>syn</u> protons move past the <u>anti</u>; their signal appears as a broad singlet with no sign of AB quartet splitting. With <u>2</u>:<u>1</u> ratios above 0.1, the <u>syn</u> protons are further downfield than the anti, and AB quartet fine structure is again apparent, becoming especially obvious at 2:1 ratios above 0.3.

Our results appear consistent with some previous reports. In an earlier study of 1-adamantanemethanol with tris(dipivalomethanato)europium(III), Eu(DPM)$_3$, Cockerill and Rackham (4) observed slightly greater slopes for the syn 2° hydrogens [corresponding to H_c at C(4,6,10) of 1] than for the 3° hydrogens [corresponding to H_b at C(3,5,7) of 1] in plots of chemical shift versus molar ratio of LSR to substrate. However, these slope values were the same within the authors' experimental error. Using some geometric assumptions regarding the LSR binding, the syn hydrogens were estimated as 0.25± 0.06 Å closer to the Eu than were the 3° methines. For the 1-adamantanemethanol, larger induced shifts were seen for H(2,8,9) and smallest for anti H(4,6,10), H_d. The $\underline{CH}_2$OH had the largest $\Delta\delta$ of any of the carbon-bound hydrogens. For the homologous 1-(2-hydroxyethyl)-adamantane, the 3° methine signal was further downfield than the 2° H (corresponding to $H_{a,a'}$ of 1) in the absence of LSR, although the 2° H were shifted further downfield when LSR was added. Wahl and Peterson (5), using 1-adamantanol and Eu(DPM)$_3$ in CDCl$_3$, observed slightly greater induced shifts for the syn-H(4,6,10) than for the tertiary H(3,5,7). Their geometric approximations suggested that the former would be about 0.21 Å closer to the bound Eu. We note that an early NMR study of 1-bromoadamantane assigned the 6H intensity signal at lowest field to the 2° protons, H(2,8,9), with the 3° protons at slightly higher field (25). This apparent contrast with our analysis of 1 can be explained by the greater expected inductive and field deshielding effects expected for bromoadamantane. In 1, the electronegative atom is one bond further from the ring, and the dominant effect reflects greater deshielding of 3° versus 2° hydrogens [as was seen for 1-(2-hydroxyethyladamantane)].

Increments of the chiral reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III), 3, known as Eu(HFBC)$_3$, were added to a 0.136 molal solution of 1 in $CDCl_3$ to produce the chemical shifts shown in Figure 6. Enantiomeric shift differences, $\Delta\Delta\delta$, defined as the difference in chemical shift between corresponding nuclei of enantiomeric molecules in the presence of chiral LSR, were seen for the CH_3 signal of 1 at 3:1 molar ratios of 0.22 or higher. The CH_3 signal appeared as a slightly broadened triplet (due to the overlap of the doublet signals from each enantiomer) for 3:1 ratios of ca. 0.33-0.50, indicating $\Delta\Delta\delta$

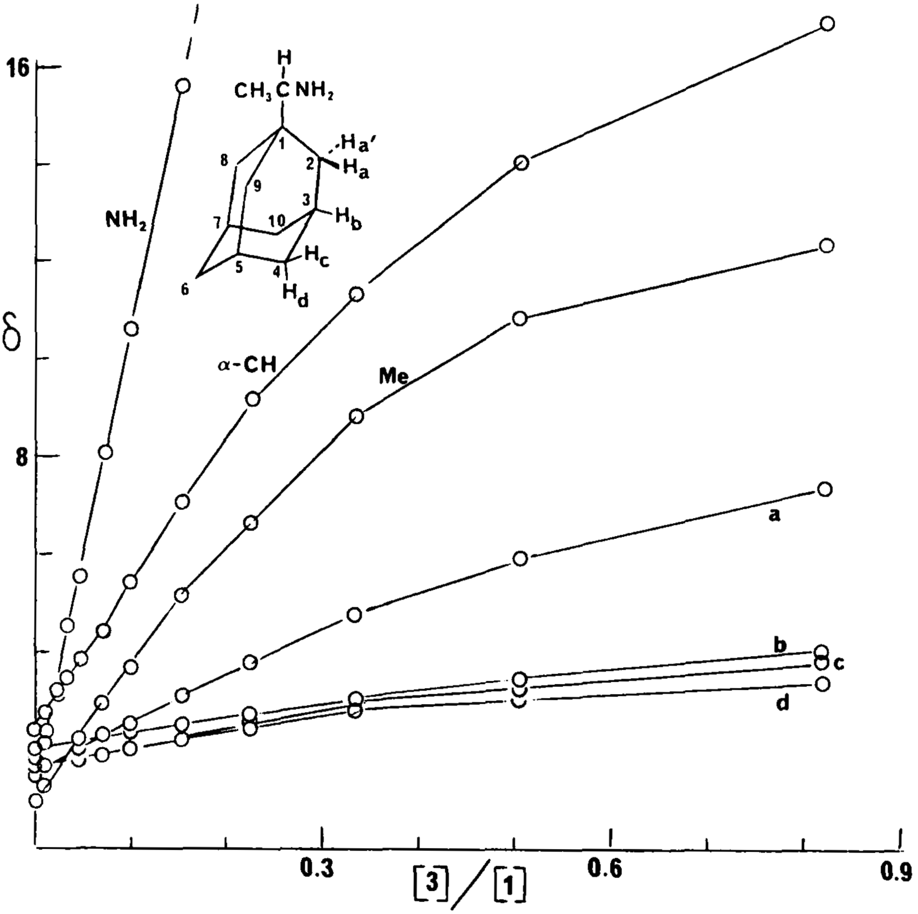


Fig. 6. Variation of ^{1}H chemical shifts of 1, in ppm, with molar ratio of 3:1. Note: Where enantiomeric shift differences occur, average chemical shift values for the optical antipodes are presented.

approximately equal to the vicinal coupling. At the highest 3:1 level examined, 0.824, lanthanide induced broadening became more severe and the triplet (resulting from overlap of the doublet CH_3 signals for each enantiomer) was more poorly resolved. These

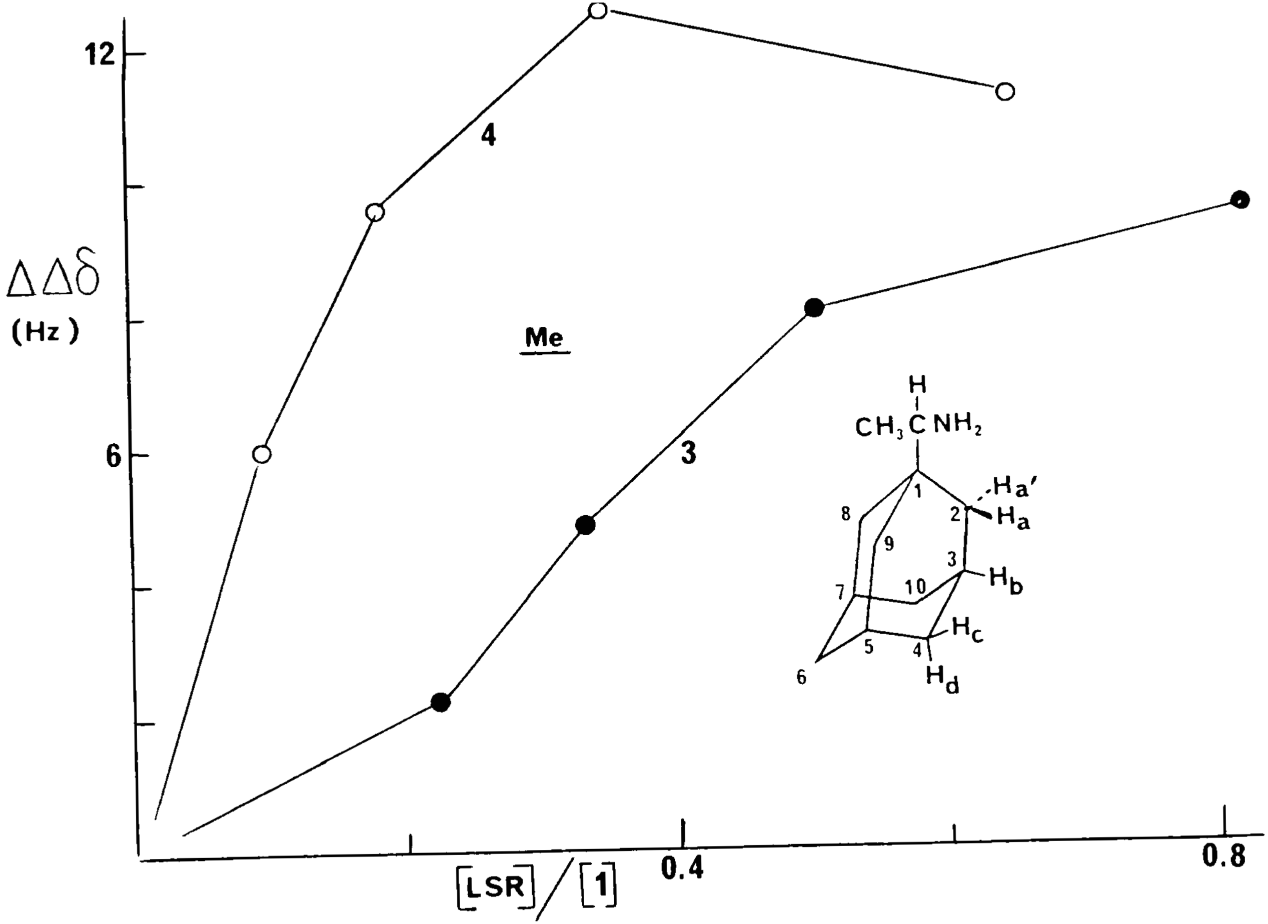


Fig. 7. Variation of enantiomeric shift differences, ΔΔδ (in Hz), with molar ratios of 3:1 and 4:1.

results are shown in Figure 7. The induced shifts were similar to those seen with 2. Since the magnitudes of $\Delta\Delta\delta$ obtained with 3 were somewhat limited, a different chiral LSR was examined.

In order to examine the possibility of obtaining more analytically useful $\Delta\Delta\delta$ magnitudes, 1 was examined as a 0.136 molal solution with added increments of tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III), 4, known as $Eu(TFC)_3$ or $Eu(FACAM)_3$. Results were considerably improved compared with $\Delta\Delta\delta$ values seen with 3, although at comparable molar ratios of LSR:substrate the lanthanide induced shifts for the CH_3 signal were less with 4 than with 3. For example, with a 3:1 ratio of 0.0998, the methyl resonance of 1 appeared as a clean doublet, with no sign of $\Delta\Delta\delta$, at 3.70 ppm. With a 4:1 molar ratio of 0.0961, the methyl resonance is a sharp triplet at 2.63 ppm (due to overlap of the CH_3 doublet signals from each enantiomer) i.e., $\Delta\Delta\delta$ is equal to the vicinal CH_3CH coupling of about 6.2 Hz. The finely resolved triplet is characterized by average valley heights between the three peaks of only 11.9% of the central peak height, as measured to a baseline joining the noise floor on either side of the triplet. Interestingly, the signal of the methine at the chiral center appears simply as a broadened quartet, indicating smaller $\Delta\Delta\delta$ even though this methine is directly attached to the chiral center and one bond closer than the CH_3 to the LSR binding site on nitrogen. With a 4:1 ratio of 0.349, the CH_3 appears as four lines of nearly equal intensity (double doublet) and almost equal spacing, since $\Delta\Delta\delta$ is 12.6 Hz (about twice the vicinal coupling constant of 6.45 Hz at this molar ratio). The valley separating the two doublets was approximately 46% of the average peak heights, so that direct optical purity determinations of samples of 1 should be possible under these conditions. Higher 4:1 ratios resulted in decreasing $\Delta\Delta\delta$. These results with 4 are shown in Figures 7 and 8. The observed small coupling constant variations for the sidechain as LSR:substrate ratio is changed are not unusual and probably reflect slight hybridization changes as the LSR (a Lewis acid) binds to the amino group. We observed an average ^3J for CH_3CH of unshifted 1 of 6.61 Hz and the slight changes are close to expected experimental error.

Further improvement in analytical utility for optical purity determinations of 1 with 4 could be achieved by means of homonuclear double resonance, irradiating the sidechain methine signal to collapse the methyl doublets (from each enantiomer) to two singlets, as illustrated in Figure 9. Improved

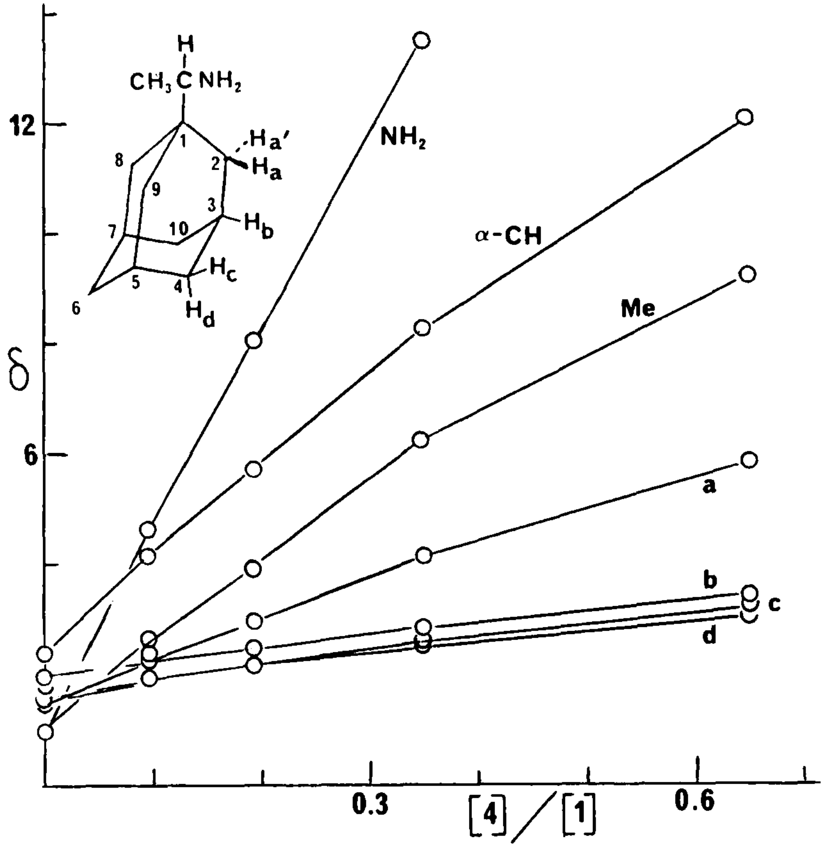


Fig. 8. Variation of ^1H chemical shifts of 1, in ppm, with molar ratio of 4:1. See Note for Fig. 6 caption.

resolution of the signals of each enantiomer, with valley heights as low as 25% of the average peak heights for the two CH_3 singlets, was readily obtained. About 7% of a minor enantiomer should be detectable under these conditions.

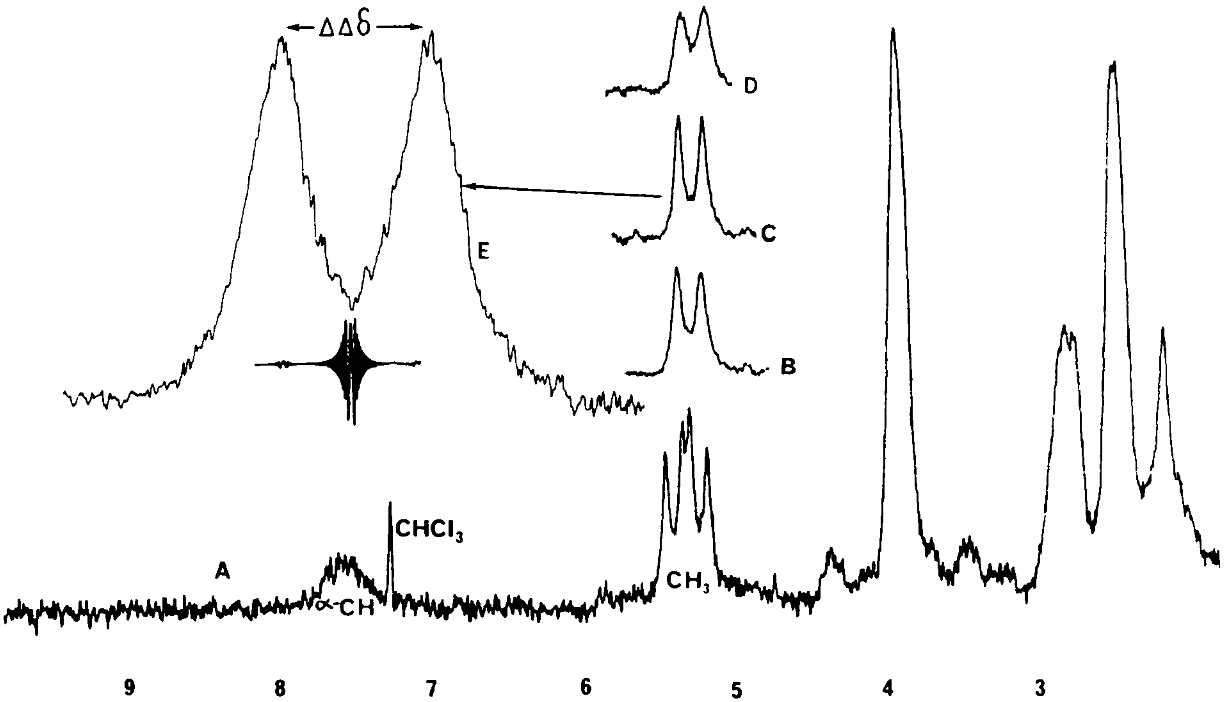


Fig. 9. a) Partial 60 MHz ^1H NMR spectrum of 0.1031 molal 1 in presence of added 4. The 4:1 molar ratio is 0.3645. b,c,d) Irradiation of sidechain $C\underline{H}NH_2$ at ca. 2,3 and 4 mG, respectively, collapses the methyl signal to two singlets separated by $\Delta\Delta\delta$ of 9.3 Hz. e) Expansion of methyl signal from c, sweep width 1 ppm, sweep time 1 min.

Perhaps most significant is the improved $\Delta\Delta\delta$ observed for the CH_3 signal of 1 with 4 versus 3, especially in light of the larger $\Delta\Delta\delta$ values occurring at smaller induced shifts. This suggests that there is a greater sense of nonequivalence between the enantiomers of 1 when they bind to 4 than to 3. The observed increase in $\Delta\Delta\delta$ with 4 is not simply a result of greater binding constant, since the induced shifts are smaller (than with 3 at comparable molar ratios) but must suggest different geometries in the corresponding bound complexes. Evidently relatively small changes in LSR structure are important, since 3 and 4 differ only by a CF_2CF_2 moiety. Two factors which may be crucial are: (a) steric hindrance in 3 versus 4 because of the longer ligand chains, and (b) increased Lewis acid strength in 3 versus 4. We have seen that the stronger acid, 3, may generally be preferred with less basic substrates, e.g., amides, and the weaker acid, 4, may be superior with strongly complexing substrates such as 1, a primary alkyl amine.

The ^{13}C NMR assignments presented here for unshifted 1 are of interest in relation to extensive ^{13}C NMR studies of adamantane derivatives and analogs (22-37, and references cited therein). Assignments in some of these earlier reports have employed shift reagents (26,28,31,32,34-36), SFORD (26-30, 36) and selective decoupling (27,29) as well as relative intensities (by inverse gated decoupling with broad band ^{1}H decoupling and nOe suppression) (27) and ancillary methods.

SUMMARY

We have reported results of achiral and chiral LSR, 2, 3 and 4, on the ^{1}H NMR spectra of 1. Differences were found between the three LSR in the observed relative magnitudes of induced shifts, and between the chiral LSR 3 and 4 in terms of inducing enantiomeric shift differences for the CH_3 signal of 1. Reagent 4 showed considerable potential for use in direct optical purity determinations of 1 at 4:1 molar ratios from 0.1-0.5, with ratios near 0.35 being optimal. ^{1}H and ^{13}C chemical shifts for 1 were obtained using techniques which allowed strictly rigorous assignments that can permit further consideration of 1 on the basis of various substituent chemical shift rules.

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REFERENCES

1. Zlydnikov D.M., Kubar O.I., Kovaleva T.P., Kamforin L.E. Study of rimantadine in the U.S.S.R.: a review of the literature. Rev. Infect. Dis. 1981; 3(3): 408-421.

2. Oxford J.S. Anti influenza virus activity of amantadine, rimantadine and analogs. NATO ASI Ser., Ser. A 1984; 73: 159-176.

3. Aldrich P.E., Hermann E.C., Meier W.E., Paulshock M., Prichard W.W., Snyder J.A., Watts J.C. J. Med. Chem. 1971; 14(6): 535-543.

4. Cockerill A.F., Rackham D.M. Quantitation of the chemical shifts induced by tris-(dipivalomethanato)europium(III) in the PMR spectra of hydroxyadamantanes and cyclopentanol. Tetrahedron Lett. 1970; (59): 5149-5152

5. Wahl, Jr. G.H., Peterson, Jr. M.R. Mechanism of deshielding of the tris(dipivalomethanato)europium nuclear magnetic resonance shift reagent. J. Chem. Soc. D, Chem. Commun. 1970; (18): 1167-1168.

6. Rackham D.M. Lanthanide shift reagents. XIII. The influence of phenyl, 1-adamantyl and tert-butyl substituents on equilibrium constants. Spectrosc. Lett. 1979; 12(7-8): 603-607.

7. Raber D.J., Johnston, Jr. M.D., Campbell C.M., Guida A., Jackson, III G.F., Janks C.M., Perry J.W., Propeck G.J., Raber N.K., Schwalke M.A.,

Sutton P.M. Structure elucidation with lanthanide-induced shifts. 5. Evaluation of the binding ability of various functional groups. Monatsh. Chem. 1980; 111(1): 43-52.

8. Raber D.J., Janks C.M. Eu(FOD)$_3$ induced shifts of alkyl substituted adamantanones and molecular geometries of the adducts. Tetrahedron 1986; 42(15): 4347-4354.

9. Hájek M., Horská A., Trška P., Vodička L., Raber D.J., Podlogar B.L., Peters J.A. Halogen substituted adamantanones. Structural studies with lanthanide shift reagents. Coll. Czech. Chem. Commun. 1988; 53: 97-109.

10. Fraser, R.R. Nuclear magnetic resonance analysis using chiral shift reagents. Asymmetric Synth. 1983; 1: 173-196.

11. Rinaldi P.L. The determination of absolute configuration using nuclear magnetic resonance techniques. Progr. Nucl. Magn. Reson. Spectrosc. 1982; 15: 291-352.

12. Cockerill A.F., Davies G.L.O., Harden R.C., Rackham D.M. Lanthanide shift reagents for nuclear magnetic resonance spectroscopy. Chem. Rev. 1973; 73(6): 553-588.

13. Sullivan G.R. Chiral lanthanide shift reagents. In: Eliel E.L., Allinger N.L. eds. Topics in Stereochemistry, vol. 10, New York: John Wiley - Interscience 1978: 287-329.

14. Kutal C. Chiral shift reagents. In: Sievers R.E., ed. Nuclear Magnetic Resonance Shift Reagents, New York: Academic Press 1973: 87-98.

15. Morrill T.C. ed. Lanthanide Shift Reagents in Stereochemical Analysis. New York: VCH, 1986.

16. Wenzel T.J. NMR Shift Reagents. Boca Raton FL: CRC Press, 1987.

17. Peterson Jr. M.R., Wahl Jr. G.H. Lanthanide NMR Shift Reagents. J. Chem. Educ. 1972; 49(12): 790-793.

18. G.E. Applications Note No. 860310. CSCMLR - Long range ^{13}C-^{1}H chemical shift correlation via polarization transfer. GE NMR Instruments, Fremont CA 94539 (March 10, 1986).

19. Wimperis S., Freeman R. An excitation sequence which discriminates between direct and long range CH coupling. J. Magn. Reson. 1984; 58(2): 348-353.

20. Fort Jr. R.C., Schleyer P. von R. Adamantane: Consequences of the diamondoid structure. Chem. Rev. 1964; 64: 277-300.

21. Fort Jr. R.C., Adamantane, The Chemistry of Diamond Molecules. New York: Marcel Dekker, 1976.

22. Duddeck H., Kaiser M., Rosenbaum D. Sequence of δ-carbon signals in 2-substituted adamantanes determined by two-dimensional correlated NMR spectroscopy. Tetrahedron Lett. 1986; 27(4): 473-476.

23. Duddeck H., Elgamal M.H.A., Hanna A.G., Kaiser M. Isomeric diadamantylphosphinic acid chlorides. Tetrahedron 1985; 41(18): 3763-3770.

24. Duddeck H., Brosch D. Rearrangements of oxahomoadamantane derivatives in acidic media. 2. J. Org. Chem. 1985; 50(25): 5401-5403.

25. Stetter H., Schwarz M., Hirschhorn A. Compounds with Urotropine structure. XII. Monofunctional adamantane derivatives. Chem. Ber. 1959; 92: 1629-1635.

26. Beierbeck H., Saunders J.K. Substituent effects on the ^{13}C chemical shifts of monosubstituted twistanes. Can. J. Chem. 1977; 55(17): 3161-3165.

27. Dheu M.-L., Gagnaire D., Duddeck H., Hollowood F., McKervey M.A. ^{13}C Nuclear magnetic resonance spectra. Part 9. Strain effects on ^{13}C chemical shifts of triamantane. J. Chem. Soc., Perkin Trans. II. 1979; (3): 357-359.

28. Duddeck H., Hollowood F., Karim A., McKervey M.A. ^{13}C Nuclear magnetic resonance spectra. Part 10. Substitutent effects on the ^{13}C chemical shifts of adamantanes, diamantanes and triamantanes. J. Chem. Soc., Perkin Trans. II. 1979; (3): 360-365.

29. Majerski Z., Mlinarić-Majerski K., Meić Z. Carbon-13 chemical shifts of inverted carbon atoms. Tetrahedron Lett. 1980; 21(42): 4117-4118.

30. Majerski Z., Vinković V., Meić Z. Substituent effects on carbon-13 chemical shifts in 2,6-disubstituted adamantanes. Org. Magn. Reson. 1981; 17(3): 169-171.

31. Duddeck H., Dietrich W. Lanthanide induced shifts on the carbon-13 chemical shifts of 2-adamantanol and 2-adamantanethiol. Tetrahedron Lett. 1975; (33): 2925-2928.

32. Duddeck H. Carbon-13 nuclear magnetic resonance spectra. I. Monosubstituted adamantanes and adamantanones. Org. Magn.Reson. 1975; 7: 151-153.

33. Duddeck H., Wolff P. Carbon-13 nuclear magnetic resonance spectra. III- 2-Heteroadamantanes. Org. Magn. Reson. 1976; 8: 593-600.

34. Duddeck H., Wiskamp V. Carbon-13 nuclear magnetic resonance spectra. XVI - Lanthanide induced signal shifts of diastereotopic ^{13}C nuclei as a probe for a conformational equilibrium. Org. Magn. Reson. 1981; 15(4): 361-362.

35. Duddeck H., Wiskamp V., Rosenbaum D. Rearrangements of oxahomoadamantane derivatives in acidic media. J. Org. Chem. 1981; 46(26): 5332-5336.

36. Duddeck H. Steric repulsion and intramolecular interaction of substituents in 4-substituted adamantan-2,6-diones. Tetrahedron 1983; 39(8): 1365-1369.

37. Duddeck H., Islam Md. R. ^{2}H and ^{13}C NMR spectra of deuterated adamantan-2-ols. Org. Magn. Reson. 1983; 21(2): 140-142.

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