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# Optical purity determination, conformer populations and $^1$H NMR spectral simplification with lanthanide shift reagents — Part IX.† A method for improved analytical precision for "DOEt", 2,5-dimethoxy-4-ethylamphetamine

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**Abstract**: The 60 MHz $^1$H NMR spectra of the potent hallucinogen 2,5-dimethoxy-4-ethylamphetamine ("DOEt"), **1**, have been studied in $CDCl_3$ at 28° with 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-(trifluoromethylhydroxymethylene)-*d*-camphorato] europium(III), **3**, and tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III), **4**. Distinct enantiomeric shift differences, $\Delta\Delta\delta$, were observed for the amphetamine $CH_3$ and the adjacent CH resonances using either **3** or **4** that permit direct optical purity determinations. A novel use of an external computing integrator as an accessory to a basic NMR is described; interfacing these instruments permits improved analytical precision for the reported optical purity determinations using nonracemic mixtures of known compositions. Relative abundances of the different conformers with respect to $C_\alpha$–$C_\beta$ bond rotation in the arylethylamine moiety is discussed based on coupling constants. Results are compared with the related hallucinogen, 3,4-methylenedioxyamphetamine.

**Keywords**: *Chiral lanthanide shift reagents; amphetamine derivative; NMR.*

## Introduction

2,5-Dimethoxy-4-ethylamphetamine ("DOEt"), **1**, is a potent "psychotomimetic" [1–3]; it is the 4-ethyl analogue of "STP", a Schedule I controlled substance (2,5-dimethoxy-4-methylamphetamine). Asymmetric synthesis of the enantiomers of **1** has been achieved and *R*-(−) and *S*-(+) absolute configurations have been assigned [4]. The *R* enantiomer was reported to have four times the potency of the *S* enantiomer in man in terms of psychedelic activity [5] and in causing contraction of sheep umbilical artery strips [6]. Some aspects of absolute configuration and psychotomimetic activity have been discussed [7]. Direct methods for optical purity determinations of **1** would be of

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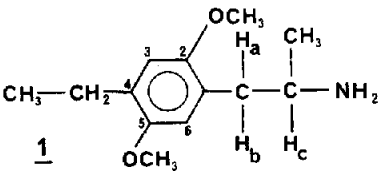


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considerable importance, particularly for forensic applications in which sample individualization bearing on the possible commonality of origin of different samples is of much concern. Derivatization of **1** to the *N*-trifluoroacetyl-*S*-prolylamide for gas chromatographic analysis of the enantiomers was reported to give variable results attributed to racemization of the reagent and use of the α-methoxy-α-trifluoromethylphenylacetamide derivative was preferred [4]. A method which required no prior derivatization would clearly be preferred. Recently, high-performance liquid chromatographic (HPLC) techniques, especially using chiral columns, have been useful for optical purity determinations. However, many such methods require prior derivatization (with an achiral reagent) for improved chromatographic behaviour and therefore are not strictly direct methods. Perhaps more important is the inability to achieve enantiomer separations in some cases, and the possibility that significant classes of compounds may not be amenable to the HPLC method [8]. It is the authors' opinion that both HPLC and the NMR technique to be discussed will continue to be important and complementary methods.

We have been pursuing studies of optical purity determinations using the method of chiral lanthanide shift reagents (LSRs). The basic theory and methodology of LSRs has been reviewed [9–18]. Chiral LSRs have been applied to a number of compounds related to **1**, including amphetamine and some mono- and dimethoxyamphetamines and analogues [19]. An achiral shift reagent such as tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), **2**, known as $Eu(fod)_3$, is commonly used to provide lanthanide-induced shifts (Δδ) for NMR spectral simplification. Δδ is defined as the chemical shift of a particular nucleus in the substrate with LSR added minus the chemical shift of the same nucleus in the absence of LSR. If chiral shift reagents are used, Δδ for a specific nucleus in the substrate may be different for each enantiomer. The enantiomeric shift difference, ΔΔδ, is defined as the magnitude of the difference in chemical shifts for a particular substrate nucleus in the two enantiomers with added shift reagent. Tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), **3**, designated as $Eu(facam)_3$ or $Eu(tfc)_3$, and tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), **4**, designated as $Eu(hfbc)_3$ or Eu(hfc), have been especially useful for optical purity determinations. The reagents **2** and **3** have been applied to the hallucinogen, 3,4-methylenedioxyamphetamine ("MDA"), **5**, [20] which is a close analogue of **1**.

Conformational analysis for rotation about the $CH_2$–CH bond of **1** was of interest in terms of implications concerning the nature of the receptor site and considerable work has been reported for related compounds [20–25]. LSRs have been used to assist in assigning benzylic proton resonances of amphetamine [26] and could permit spectral simplification to enable the determination of vicinal coupling constants within the $CH_2$–CH group in order to calculate relative conformer populations.

Previous work using chiral LSRs for optical purity determinations have sometimes been limited in accuracy or precision because of reliance on the simple "step integral"

trace provided by basic NMR spectrometers. This can be especially troublesome when relevant signal peaks are broad and incompletely resolved. Earlier work in these laboratories [20] has prompted the exploration of a possible cost-effective alternative to traditional step-integral traces that might offer better and more objective results. Potential improvements in this area would be especially important in analysing forensic samples. The results of this study are presented in the following sections.

## Experimental

Samples of racemic **1** hydrochloride (DAC Code No. 3004-1022-16), (+)-**1**·HCl (1793-1022-120) and (−)-**1**·HCl (1793-1022-119) were provided by the National Institute on Drug Abuse, Rockville MD 20857, USA, through the Research Triangle Institute, Research Triangle Park, NC 27709, USA. These samples of **1** hydrochloride had stated mp 193.5–194.5° (racemic), 224.5–225.0° (*S*-(+), lit. 225.5–226.5° [4]) and 223–224° (*R*-(−), lit. 226.5–227° [4]). Stated specific rotations were $[\alpha]_D = +16.3°$ (c 1, $H_2O$) (lit. $[\alpha]_D^{25}$ +16.0° (c 2, $H_2O$) [4]) and $[\alpha]_D = -16.8°$ (c 1, $H_2O$) (lit. $[\alpha]_D^{25}$ −16.1° (c 2, $H_2O$) [4]) for the (+) and (−) enantiomers, respectively. Chloroform-*d* (99.8 atom % D), obtained from Aldrich Chemical Corp., Milwaukee WI 53201, USA or Norell, Inc. Landisville NJ 08236, USA, was dried and stored over 3A molecular sieve. 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 runs with racemic **1**, an accurately weighed sample of drug (37–45 mg) was added to 700–800 mg of $CDCl_3$ (containing about 0.2% tetramethylsilane (TMS) as internal standard) in an NMR sample tube and dissolved by shaking; increments of shift reagent were added, dissolved by shaking, and the spectra recorded immediately. For calibrations with nonracemic mixtures of **1**, weighed portions of appropriate amounts of racemic, (+) or (−)-**1** free base were weighed directly into the NMR sample tube. Shift reagent increments were added and spectra obtained as described above.

All spectra were recorded using a Varian EM-360A 60 MHz $^1H$ NMR spectrometer at a probe temperature of 28°. Chemical shifts are reported in parts per million (δ) relative to TMS as internal standard and are believed accurate to ±0.05 ppm based on instrument limitations. For runs with racemic **1** and chiral reagents **3** or **4**, the reported δ values for resonances displaying ΔΔδ are the average values for the two enantiomers. In those spectra where the TMS signal was obscured by shift reagent peaks, $CHCl_3$, present as an impurity in the solvent, was used as internal standard.

For improved precision in the determination of optical purity of nonracemic samples of **1**, an external Shimadzu C-R3A Chromatopac computing integrator–recorder was connected to the NMR. Analogue voltage corresponding to the vertical (Y) axis signal of the EM-360A flat bed recorder was obtained from pins 7 and 8 at jack J4 on the rear of the NMR electronics control console. These pins are missing in the corresponding RS-232C connecting plug as originally supplied and must be provided. Pins 7 and 8 then provide positive and negative polarities, respectively of the input signal to the integrator; they are referred to as "Recorder Input" (or, for pin 7, "Recorder Y Monitor") in the NMR manual. A DC offset voltage was found to be present between these points even in the absence of an NMR peak signal. Critical adjustment of the NMR fine spectrum amplitude control, with the aid of a digital multimeter (200 mV scale) for monitoring this offset voltage, permitted the offset voltage to be brought within the required −1 to +5 mV window for establishment of baseline by the C-R3A. Proper amplitude for digital

integration and spectral plotting on the C-R3A were then achieved by use of the EM-360A coarse spectrum amplitude (typically 10 or 100) and the C-R3A attenuation setting (typically 5–10).

*Preparation of free base*

The HCl salts of **1** were converted to the free base as illustrated by the following example. To 156.0 mg (0.60 mmol) of (−)-**1**·HCl was added 39.0 mg (1.95 mmol) NaOH dissolved in 2 ml saturated aqueous NaCl, and the liberated free base extracted at once with 5 × 5 ml $CH_2Cl_2$. The combined washings were dried with anhydrous $Na_2CO_3$; solvent was removed with a rotary evaporator at aspirator pressure at 40° (bath temperature) to constant weight, 100.7 mg (74.6% recovery) of (−)-**1**, mp 73.0–75.0°. Melting point ranges for (+) and racemic free bases were 72.5–74.0° and 58.0–61.0°, respectively. Recoveries were 82.4% (+) and 94.4% (racemic). All samples of the free base were routinely stored under $N_2$.

## Results and Discussion

The NMR spectrum of **1** does not appear to have been previously reported. For a 0.250 molal solution of racemic **1** in $CDCl_3$, assignments were as follows, in δ(ppm) units: 6.70 and 6.67 (singlets, aryl $H_3$ and $H_6$, assignments may be reversed); 3.78 (s, 6H, aryl 2-$OCH_3$ and 5-$OCH_3$); 3.17 (br m, 1H, methine $\underline{C}\underline{H}CH_3$, $H_c$); 2.83–2.40 (m, 4H, benzylic protons); 1.18 (t, 3H, $\underline{C}\underline{H}_3CH_2$); 1.13 (d, 3H, $\underline{C}\underline{H}_3CH$); 1.12 (br m, 2H, $NH_2$). First order coupling constants were obtained from spectra with added **2** to eliminate coincidental overlaps; the values given here are averages for the different branches of a specific multiplet as observed at several **2**:**1** molar ratios. Consistent variations in these couplings with respect to the **2**:**1** ratio were not seen and are assumed to be relatively unaffected by the added shift reagents. Vicinal coupling constants were 7.6 Hz ($CH_3CH_2$), 6.4 Hz ($CH_3CH$), 7.6 Hz ($\underline{C}\underline{H}_a\underline{H}_b\underline{C}\underline{H}_c$) and 4.3 Hz ($CH_a\underline{H}_b\underline{C}\underline{H}_c$). The benzylic protons $H_a$ and $H_b$ refer to the protons giving absorptions at lower and higher field, respectively, with added shift reagent. The vicinal couplings $J_{ac}$ and $J_{bc}$ were obtained by first order approximation from spectra with added **2** so that the $H_a$ and $H_b$ signals were well separated. The geminal coupling, $J_{ab}$, was 12.9 Hz. Reported values for the analogue MDA were estimated as 7.7, 5.7 and 13.6 Hz for $J_{ac}$, $J_{bc}$ and $J_{ab}$, respectively [20]. The accuracy measurement of the coupling constants is ±0.4 Hz. Lanthanide-induced peak broadening for the $\underline{C}\underline{H}_3CH$ of **1** with added **2** was considerable. Greater line broadening was seen for aryl $H_6$ versus $H_3$ consistent with expected distances from the complexed lanthanide. The achiral reagent, **2**, was employed for spectral simplification of **1**. Some difficulty was presented in the analysis of **1** compared to **5** because of adventitious overlaps from the ethyl group of **1**. The molar ratio of **2**:**1** is critical to provide windows through which the resonances of the diastereotopic benzylic protons of the $\underline{C}\underline{H}_2CH$ group of **1** can be observed free from interferences. Enhanced dispersion of these benzylic signals facilitates determination of the crucial vicinal coupling constants in order to estimate relative rotamer populations (*vide infra*). Downfield shifts induced in the resonances of **1** by added increments of **2** enable the 2-$OCH_3$ and aryl H-6 to be distinguished from the 5-$OCH_3$ and H-3 based on the presumed europium complexation at a nitrogen atom. The former protons show greater Δδ values, consistent with greater proximity to the lanthanide complexation site. Results with **2** are summarized in Fig. 1.

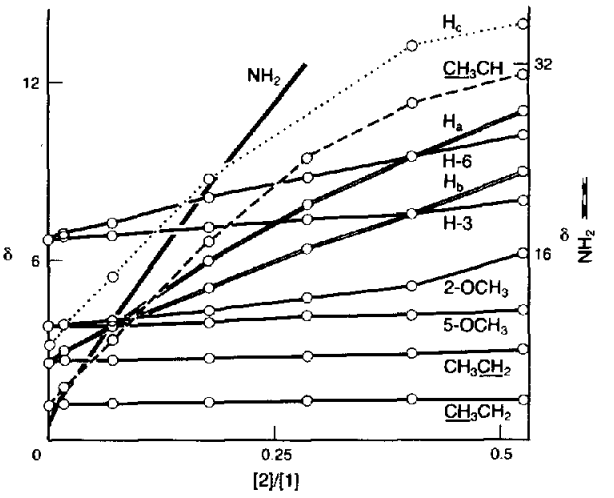


**Figure 1**
Variation of chemical shift, δ, with molar ratio of Eu(fod)$_3$:**1**. Chemical shifts for the $NH_2$ protons are presented according to the right-hand axis.

The chiral shift reagents **3** and **4** each effectively induced enantiomeric shift differences, ΔΔδ, for selected resonances of **1**. For analytical purposes, the $\underline{C}\underline{H}_3CH$ and methine resonances can be used for optical purity determinations. The smaller ΔΔδ value observed for the aryl 2-$OCH_3$ is not analytically useful. The presence of the ethyl group in **1** results in coincidental overlaps with the signals which would be used for measuring optical purity except within specific "windows" of molar ratios of **3**:**1** or **4**:**1**. Thus, with the low **3**:**1** ratio of 0.0462 and 0.249 molal **1**, the $\underline{C}\underline{H}_3CH$ doublet is clearly doubled, ΔΔδ = 2.9 Hz. Less line broadening for this methyl signal was observed with **3** than with **2**. The ΔΔδ was 12.9 Hz at a **3**:**1** ratio of 0.263. Using a **3**:**1** ratio near 0.25 places the $\underline{C}\underline{H}_3CH$ resonances just upfield of the $H_{a,b}$ signals and just downfield of the methoxy groups, a useful condition for analysing optical purity. With **3**:**1** ratios above about 0.4, the methine signal is shifted downfield past those of the aryl protons. Although broadened by extensive coupling to vicinal protons, the methine resonance displays large ΔΔδ values with well resolved signals for each enantiomer and could be the preferred analytical signal. At a **3**:**1** ratio of 0.832, the valley height was only 15.6% of the average peak heights for the methine signal of each enantiomer. However, the sensitivity using the methine will not be as good as with the $\underline{C}\underline{H}_3CH$ group because of signal peak height. At this same **3**:**1** ratio, distinct ΔΔδ is seen for the downfield methoxy absorption, assigned to the 2-$OCH_3$. This signal is very sharp and intense and could be useful for rough optical purity measurements in cases of limited sample availability. Although **3**:**1** ratios as high as 2.29 were examined, analytical utility was not improved.

For a 0.217 molal sample of **1**, distinct doubling of the $\underline{C}\underline{H}_3CH$ peaks is observed with a **4**:**1** ratio of 0.0175 (ΔΔδ = 2.85 Hz) with the methyl signal free from overlaps. Despite the substantial ΔΔδ at higher **4**:**1** ratios and little line broadening of these peaks, it is experimentally difficult to obtain the $\underline{C}\underline{H}_3CH$ in a region free from interfering peaks to obtain optical purity measurements. As with **3**, it is easier to examine the methine signal, despite the broadness and low intensity of the latter; for at **4**:**1** ratios as

low as 0.308 this signal has been shifted downfield of the aryl proton absorptions and is free from overlap with other proton signals. Valley height between the CH absorptions of the two enantiomers was only 22.1% of the average peak heights and $\Delta\Delta\delta$ was 39.2 Hz. With **4**:**1** ratios between about 0.66 and 0.91, slight $\Delta\Delta\delta$ is seen for the 2-$OCH_3$ which, unfortunately, is partly overlapped by absorptions of **4**. However, with a **4**:**1** ratio near 1.22, the $\underline{C}H_3CH$ signal has moved free of overlaps with other resonances. With $\Delta\Delta\delta$ of 18.0 Hz, good analytical conditions result that are particularly suitable for limited amounts of **1** because of the good peak intensity. Valley height between each doublet for the racemic material was 56.7% of the average peak heights. Under these conditions, $H_a$ and $H_b$ are well separated from each other and from other signals; enantiomeric shift differences for the signal of each proton are clearly evident but of limited analytical use because of extensive splitting and low intensity. With the $H_a$ and $H_b$ signals appearing roughly as broadened triplets, $\Delta\Delta\delta$ values close to 13 Hz are estimated for each. At a higher **4**:**1** ratio of 1.59, decreased $\Delta\Delta\delta$ and increased line broadening resulted in no observable valley between the signals for each enantiomer, either for the methine or $\underline{C}H_3CH$ resonances. Results with **3** and **4** are summarized in Figs 2–4.

Studies were performed with the chiral reagents **3** and **4** using samples of **1** with both relatively high (optical purity about 70%) and low (optical purity about 30%) enantiomeric excess. These nonracemic samples of **1** were enriched with either the (+) or (−) isomer and were quantitatively based on digital electronic peak area measurements using the external integrator for either the methine or the $\underline{C}H_3CH$ resonances. In some cases, peak heights were employed for analysis. The viability of the method was therefore demonstrated over a broad range of conditions. Since resonance signals for the two enantiomers of a substrate with added chiral LSR may have undergone lanthanide-induced line broadening to different extents, a reliance on peak areas rather than peak heights is recommended, although the present analyses using peak heights were satisfactory for the cases reported here. NMR spectrometer RF power and sweep rates were selected to avoid saturation of the signals from one or both of the enantiomers. The biggest virtue of using the external integrator for forensic and related applications is

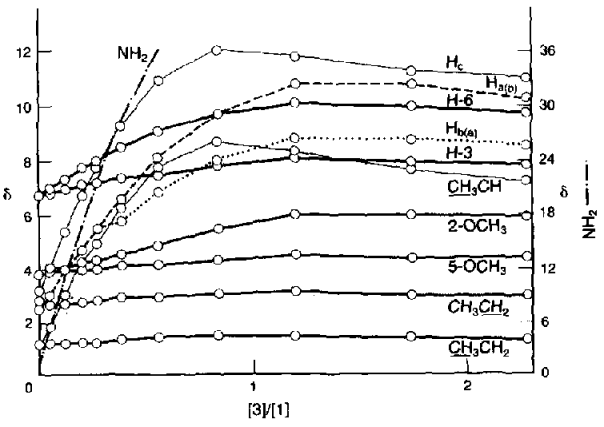


**Figure 2**
Variation of chemical shift, δ, with molar ratio of $Eu(facam)_3$:**1**. Chemical shifts for the $NH_2$ protons are presented according to the right-hand axis. Average values are used in the plots when antipodal differences occur.

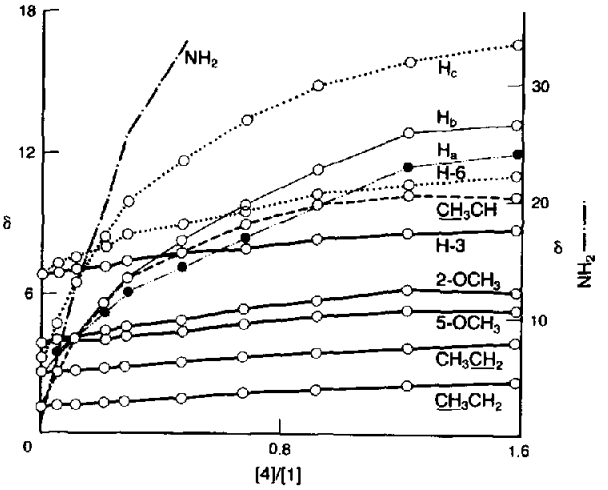


**Figure 3**
Variation of chemical shift, δ, with molar ratio of Eu(hfbc)$_3$:**1**. Chemical shifts for the $NH_2$ protons are presented according to the right-hand axis. Average values are used in the plots when antipodal differences occur.

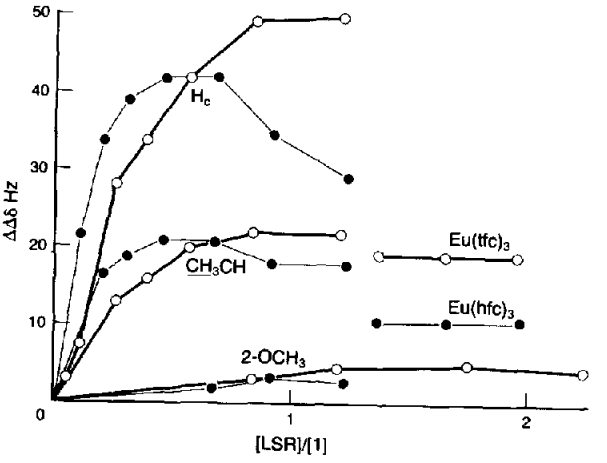


**Figure 4**
Variation of enantiomeric shift difference, ΔΔδ (in Hz), with molar ratios of Eu(facam)$_3$, [**3**:**1**], or Eu(hfbc)$_3$, [**4**:**1**].

likely to be the objectivity of the analyses. Representative results are summarized in Table 1. About 5% of the minor enantiomer should be detectable.

With both **3** and **4**, the $\underline{CH_3}CH$ and methine resonances were further downfield for (−)-**1** than for the antipode under the conditions used, but the 2-$OCH_3$ displayed the opposite sense of non-equivalence. For the benzylic protons $H_{a,b}$, although substantial ΔΔδ values were observed at high molar ratios of **3**:**1** or **4**:**1**, the sense of non-equivalence was unambiguously confirmed in only one case. For a 0.217 molal sample of

**Table 1**
Summary of analytical results using external electronic integrator

| Enantiomeric composition Actual %* | Found % (standard deviation) | N† | Shift reagent | [LSR]/[1] | Molality of 1 | Resonance signal used | Method |
|---|---|---|---|---|---|---|---|
| (+) 35.9<br>(−) 64.1 | 40.6 (1.61)<br>59.4 (1.43) | 5 | **3** | 0.0462 | 0.341 | $CH_3$ | area |
| (+) 35.9<br>(−) 64.1 | 36.9 (1.25)<br>63.1 (1.25) | 4 | **3** | 0.765 | 0.341 | CH | area |
| (+) 85.1<br>(−) 14.9 | 83.7 (1.50)<br>16.3 (1.50) | 5 | **3** | 0.756 | 0.311 | CH | area |
| (+) 85.1<br>(−) 14.9 | 84.4 (0.76)<br>15.6 (0.76) | 5 | **3** | 0.756 | 0.311 | CH | height |
| (+) 66.4<br>(−) 33.6 | 66.5 (1.37)<br>33.5 (1.37) | 5 | **4** | 0.0175 | 0.277 | $CH_3$ | area |
| (+) 66.4<br>(−) 33.6 | 66.1 (1.19)<br>33.9 (1.19) | 7 | **4** | 1.024 | 0.277 | CH | area |
| (+) 66.4<br>(−) 33.6 | 65.9 (1.98)<br>34.1 (1.98) | 7 | **4** | 1.024 | 0.277 | CH | height |
| (+) 13.7<br>(−) 86.3 | 16.3 (1.94)<br>83.7 (1.94) | 8 | **4** | 1.287 | 0.217 | $CH_3$ | area |
| (+) 13.7<br>(−) 86.3 | 16.1 (2.14)<br>83.9 (2.14) | 4 | **4** | 1.287 | 0.217 | $CH_3$ | height |
| (+) 13.7<br>(−) 86.3 | 15.1 (0.99)<br>84.9 (0.99) | 5 | **4** | 1.287 | 0.217 | CH | area |

*Calculated percentages based on actual weights of enantiomers.
†Number of analytical scans used for calculation.

(−)-**1**, 73% enantiomeric excess, with a **4**:**1** ratio of 1.29, the downfield benzylic resonance clearly showed the opposite sense of non-equivalence as the $\underline{CH_3}CH$ and methine resonances. Interestingly, the $H_b$ resonance was downfield of the $H_a$ resonance for this sample, based on a smaller vicinal coupling constant for $H_b$. In other runs with **3** or **4**, line broadening, peak overlaps and enantiomeric shift differences did not permit clear observation of $J_{ac}$ or $J_{bc}$ so that assignments of $H_{a,b}$ may be reversed. It appears that for racemic **1** with **2**, the downfield resonance has the greater vicinal coupling constant. For the run with **4** noted above, the opposite result is observed. Apparently, subtle differences in complex geometry with different shift reagents can result in greater $\Delta\delta$ for either of these benzylic protons, $H_a$ or $H_b$. These different assignments for **2** and **4** are indicated in Figs 1 and 3. While the reagent **3** might well resemble **4** in complexes with **1**, the assignments here are uncertain (Fig. 2). The conformer population calculations have been based on the unequivocal results with **2**.

Determination of conformer populations with respect to rotation about the $C_\alpha$–$C_\beta$ bond of **1** was of interest since substrate structure is often suggestive of the nature of receptors at the active sites in organisms for which a substrate has pharmacological

activity. Such evaluations have been reported for a series of dimethoxyamphetamine analogues by Bailey [24]. Because of overlaps of resonances of the benzylic protons of the ethyl group of **1** with those of $H_a$ and $H_b$, it was not possible to unambiguously assign $H_a$ or $H_b$ for the *unshifted* spectra. With shift reagent **2** added, the $H_a$ and $H_b$ signals of **1** become well separated with the downfield signal displaying the greater vicinal coupling. The possibility that these signals "cross over" at relatively low levels of shift reagent cannot be ruled out, in which case the proton with higher vicinal coupling constant for *unshifted* **1** would have an absorption at higher field; this would be consistent with Bailey's reported values and with related studies [23, 26]. We have used Bailey's procedure and suggested values of $^3J$ = 12 and 2 Hz for *anti* and *gauche* protons, respectively, to permit direct comparisons with his results. The applicability of coupling constants obtained by first order approximations from spectra with added shift reagents has been discussed [20]. Using the present values for **1** of 7.6 and 4.3 Hz, calculated relative populations of the three rotamers are 0.56 for A, 0.23 for B, and 0.21 for C (Fig. 5). These conformer populations are probably subject to errors of about 10% [23, 25]. Populations of A and B may be reversed because of assignment uncertainties for the vicinal couplings of $H_a$ and $H_b$ as shown in Fig. 5. The substantial difference in $\Delta\delta$ for $H_a$ and $H_b$ of **1** with reagents **2**, **3** or **4**, is consistent with a significant difference in their average distance from the complexed europium. Conformer A would provide $H_a$ and $H_b$ with environments that differ with respect to distance from the assumed complexation site on the nitrogen atom. In addition, conformer A indicates that the proton with a signal that is further downfield with added shift reagent (because of greater proximity to the amino group) should display the larger vicinal coupling constant, $J_{ac}$, because of the dihedral angle of about 180° between $H_a$ and $H_c$. $H_b$, with a dihedral angle of about 60° relative to $H_c$ (in A) should have the smaller "gauche" vicinal coupling. This is consistent with reported results for **5**. The potential steric hindrance or intramolecular hydrogen bonding interactions of the 2-$OCH_3$ group of **1** with the isopropylamine sidechain appears to have only a modest effect on the conformer populations, compared to **5**. Bailey's data for 2,5-dimethoxyamphetamine (obtained at 40°) included coupling constant magnitudes of 12.5 Hz (geminal) and 4.4 and 8.4 Hz (vicinal) using an ABX calculation. Conformer ratios calculated for **5** were 0.57: 0.37: 0.06 [20] and for 2,5-dimethoxyamphetamine they were 0.64: 0.24: 0.12 [24].

In conclusion, the use of an external computing integrator for objective quantitation of optical purity of nonracemic samples of **1** over a broad range of substrate concentrations, optical purities and LSR: substrate molar ratios has been demonstrated. For sample-limited cases, **3** or **4** can be used at low levels and the $\underline{CH_3}CH$ resonance can be examined. Alternatively, higher LSR levels permit quantitation of the methine

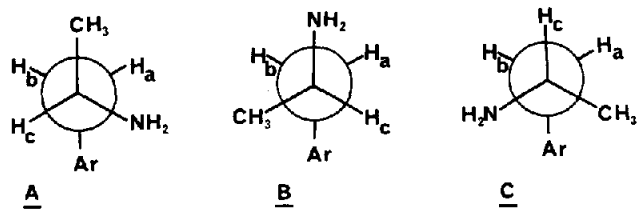


**Figure 5**
Different staggered conformations of **1**. Only one set of enantiomers is shown. See text for assignments of $H_a$ and $H_b$.

resonance under conditions in which the signal of each enantiomer is well separated and free from overlap with other proton signals. Conformer populations have been determined based on vicinal couplings in the $CH_2CH$ moiety. Senses of nonequivalence of several proton signals of **1** with **3** or **4** were established. Some unexpected differences in $\Delta\delta$ values for the benzylic protons of the $CH_2CH$ group with the shift reagents **2** and **4** were observed, suggesting subtle geometry changes in the LSR–substrate complex. Examples of the potential for optical purity determinations of **1** with **3** or **4** at various LSR levels are shown in Fig. 6.

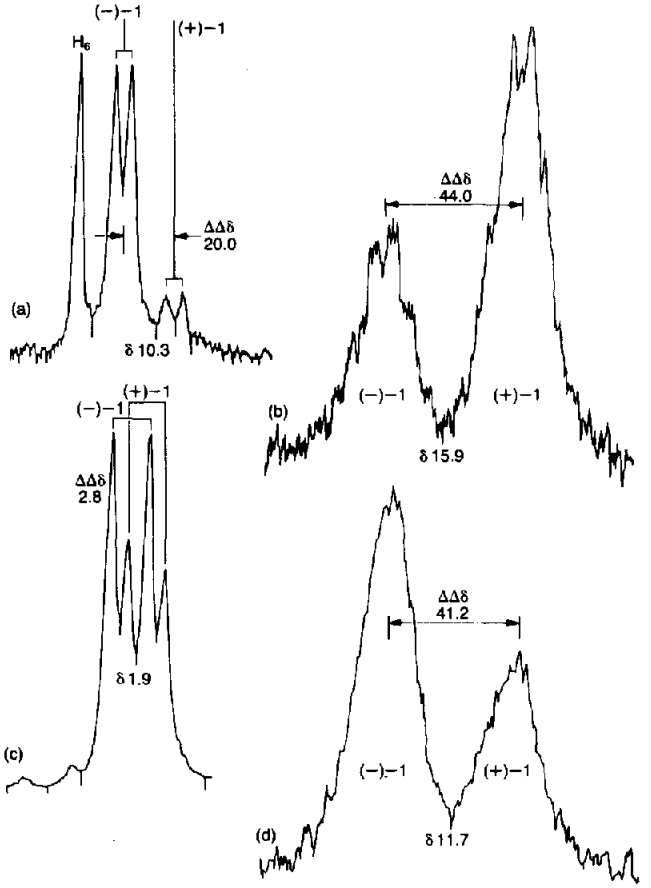


**Figure 6**
Representative spectral traces of $CH_3CH$ or methine resonance region for nonracemic standard solutions of **1** with added chiral shift reagent. Emphasis has been added to peak detection marks, when shown. Note that sweep widths, spectral amplitudes and chart speeds may differ between the traces. For each trace, enantiomeric shift difference (in Hz), chemical shift (in ppm) and assignment of the specific enantiomer are shown. The enantiomeric ratios of (+)-**1** to (−)-**1**, the molar ratios of [LSR]:[total **1**], and the observed nuclei are as follows: (a) ratio of (+)-**1** to (−)-**1** is 13.7:86.3, ratio of **4**:**1** is 1.29, $CH_3CH$ resonance (note peak detection marks provided by external integrator); (b) ratio of (+)-**1** to (−)-**1** is 66.4:33.6, ratio of **4**:**1** is 1.02, CH resonance; (c) ratio of (+)-**1** to (−)-**1** is 35.9:64.1, ratio of **3**:**1** is 0.0462, $CH_3CH$ resonance (note peak detection marks provided by external integrator); (d) ratio of (+)-**1** to (−)-**1** is 35.9:64.1, ratio of **3**:**1** is 0.765, CH resonance.

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