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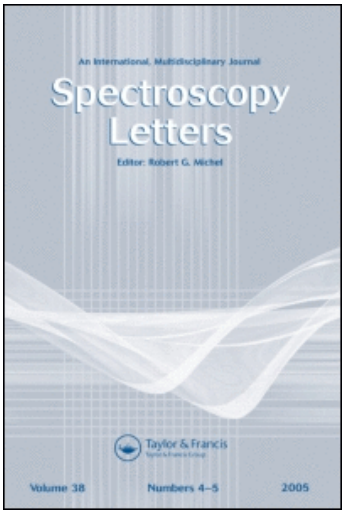

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NMR Studies of Drugs. Applications of Achiral and Chiral Wthanide Shift Reagents to Bupropion

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NMR STUDIES OF DRUGS. APPLICATIONS OF ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS TO BUPROPION.

Keywords: NMR Shift Reagents, Enantiomer, Optical Purity, $Eu(FOD)_3$, $Eu(HFC)_3$, Chiral, Bupropion, Analysis, 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone.

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ABSTRACT

The ^1H NMR spectra of racemic samples of the antidepressant drug, bupropion, 1, have been studied in $CDCl_3$ solution at 60 and 200 MHz with

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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-(heptafluoropropylhydroxymethyl-ene)-d-camphorato]europium(III), 3. Both LSR produced substantial lanthanide induced shifts consistent with ^1H assignments, but the bound complexes of 1 with 2 versus 3 may not be isostructural. With 3, substantial enantiomeric shift differences were observed for the t-butyl, CH_3CH, NCH, and the aryl H-2 and H-6 signals, which should permit potential direct determination of enantiomeric excess.

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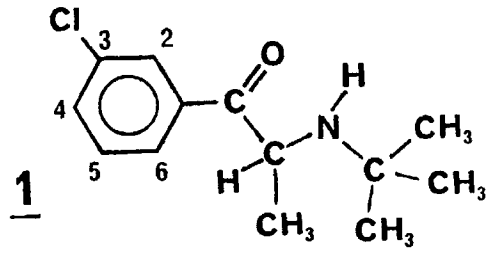
INTRODUCTION

Bupropion, 1, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone, is an antidepressant of unusual structure, and aspects of its pharmacology and clinical applications, etc., have been reviewed (1-4). We were especially interested in 1 because of the presence of a chiral center and the potential for the existence of a pair of enantiomers. Drug enantiomers may differ from each other in their physiological effects,



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potencies, toxicities, pharmacology, or legal classification. The determination of enantiomeric excess has taken on particular importance in recent years. We have previously employed diverse complementary techniques investigating potential methods for direct enantiomeric excess determination, including HPLC with a chiral stationary phase (5), and NMR using chiral solvating agents (CSA) or lanthanide shift reagents (LSR) (6,7).

The structure and partial structures of 1 bear similarities to other pharmaceutical systems where chiral LSR methods may have been applicable for enantiomeric excess determinations. Thus, 1 possesses an α-methyl-α-aminocarbonyl moiety analogous to tocainide (5,8), can be regarded as structurally related to amphetamines [aryl-C-$CHCH_3$-

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N] or clenbuterol (aryl-C-C-NH*t*-butyl) (9), and shares the *N*-*t*-butyl secondary amine structure with clenbuterol. We therefore undertook LSR studies of *1*, using 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-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), *3*, known as $Eu(HFC)_3$ or $Eu(HFBC)_3$.

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EXPERIMENTAL

Samples of the racemic hydrochloride salt of *1*, *1*-HCl, were obtained from Burroughs Wellcome Co., Research Triangle Park, NC 27709 as lot no. 90/0079-004-F. Chloroform-*d* (99.8 atom % D), obtained from Aldrich Chemical Corp., Milwaukee, WI 53201 or from Wilmad Glass Co., Buena, NJ 08310, was dried and stored over 3A Molecular Sieves. Shift reagents were obtained from Aldrich and were stored in a desiccator over anhydrous $CaSO_4$ or P_2O_5. Materials were used as received except as noted. Samples of the free base *1* were stored under N_2 upon isolation from the HCl salt. Solutions were prepared for NMR analysis and spectra were acquired

on the same day as the free base was isolated, due to the apparent instability of 1 (vide infra). Chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS) at 0.00 ppm. For typical runs with LSR, an accurately weighed portion of drug was added to $CDCl_3$ [containing a trace of TMS as internal standard] in an oven-dried thin wall 5mm 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. Studies were performed at 60 MHz on a Varian EM360A ^1H NMR spectrometer with EM3630 lock/decoupler accessory at 28° with drug concentrations from 0.327 - 0.395 molal. Reported chemical shifts from these runs are believed accurate to $\pm$ 0.05 ppm and apparent (observed) coupling constants to $\pm$0.2 Hz. In runs with chiral LSR 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, signals of $CHCl_3$ (present as an impurity in the solvent) or CH_2Cl_2

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(used in extraction of 1 free base) served as secondary internal standards.

Additional studies were performed with a Bruker AC200-F Fourier transform NMR spectrometer with ASPECT 3000 data system for a ^{1}H observe frequency of 200.13 MHz. These spectra were obtained in the FT mode at ambient probe temperature, using the dual $^{1}H/^{13}C$ probe. Chemical shifts were obtained from spectral peak tables. Coupling constants and enantiomeric shift differences were determined by subtraction from peak frequency printouts and are believed accurate to $\pm$0.1 Hz. Typical FT-NMR parameters were as follows: 4032 Hz spectral width (about -4 to +16 ppm) over 64K data points collected in the quadrature detection mode for a digital resolution of 0.123 Hz per point, pulse width 3.0 μs, 8.13 s acquisition time, 1.0 s relaxation delay; 16 FIDs were accumulated. No line broadening or resolution enhancement was applied.

Preparation of Free Base of Racemic 1:

In a typical conversion, racemic 1-HCl (681.5 mg, 2.47 mmols) was added to a mixture of 7 ml

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saturated aqueous NaCl, 5 ml H_2O and 170 mg (4.25 mmol) NaOH. The mixture was extracted with CH_2Cl_2 (5 x 5 ml), the combined organic extracts dried over anhydrous Na_2SO_4 and the solvent removed on a rotary evaporator (aspirator pressure, bath temperature 46°) to yield 562.5 mg of the free base of 1 (2.35 mmols, 95.1 % recovery) as a slightly viscous clear yellowish oil which was stored under N_2. Samples of the neat free base appeared to undergo significant decomposition after a few weeks of storage at 4° or a few days at ambient temperature as evidenced by darkening (to an orange color) and substantial formation of solid which was largely insoluble in $CDCl_3$. The NMR studies, therefore, used freshly prepared 1.

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RESULTS AND DISCUSSION

The unshifted ^1H reference spectrum of 1 was recorded at 60 MHz as a solution 0.395 m in $CDCl_3$ (with parallel studies at 200 MHz) and showed signals as follows (δ, ppm): 1.06 (9H, s, t-butyl); 1.27 (3H, d, J 7.08 Hz, CH_3); 2.55 (1H, br s, NH); 4.32 (1H, q, J 7.05 Hz, NCH). The aryl protons were not fully resolved at 60 MHz, with H-4,5

appearing as a multiplet, ca. 7.2 - 7.7 ppm, and H-2,6 overlapped around 7.8 - 8.1 ppm. The 200 MHz spectrum clearly separated the H-2,6 pair (7.98 ppm, 1H, br s, H-2), (7.89 ppm, 1H, app. d, J 7.60 Hz, H-6) with H-4 appearing as a gross doublet (one vicinal neighbor) near 7.57 ppm (observed J ca. 7.99 Hz) and H-5 as a gross triplet (two vicinal neighbors) near 7.47 ppm (observed J ca. 7.79 Hz). The approximate multiplicities are consistent with expected values of ^3J on an aromatic ring (10); observed leanings between the multiplets are in accord with the assignments. Some non-first order effects remain even at 200 MHz. Results of incremental addition of the achiral $Eu(FOD)_3$, 2, are summarized in Figure 1. H-4,5 are not resolved at 60 MHz, even with added 2, and this is reflected in Fig. 1. Relative lanthanide induced shift (LIS) magnitudes are in the sequence: NH > NCH > CH_3CH > t-butyl > H-6 > H-2 > H-4,5. The very large LIS values for NH support major lanthanide binding on the nitrogen despite expected severe hindrance from the t-butyl group (9,11,12). Of the two ortho protons, H-6 has distinctly larger LIS values than

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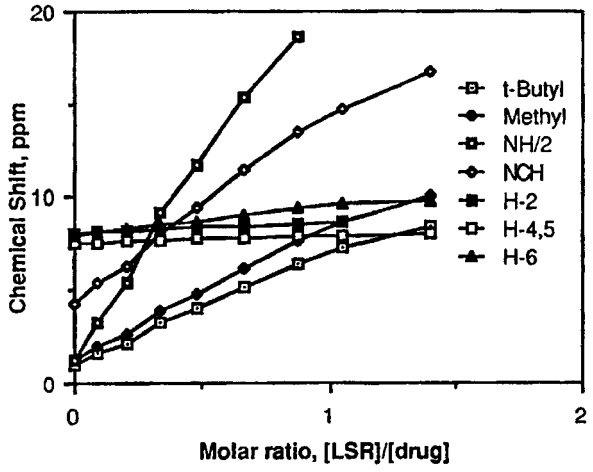

Fig. 1. Variation of chemical shift, δ (in ppm), with molar ratio of 2:1, based on 60 MHz data. Note: Actual chemical shifts for the NH signal have been divided by two for plotting in this Figure to remain onscale. Thus, the legend denotes these points as NH/2.

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H-2. We attribute this to a favored conformation in which the large chlorine atom and H-2 are proximal to the carbonyl oxygen and distal with respect to the very bulky t-butylamino alkyl sidechain. H-6 could then be closer to lanthanide bound on nitrogen. Very slightly larger LIS values for H-5 versus H-4 are consistent with H-5 being nearer to the lanthanide binding site (13). The above discussion has referred to LSR as primarily

bound to nitrogen, but we do not rule out the possibility of contributions from species with a lanthanide being chelated to the carbonyl oxygen and to the nitrogen via a favorable five-membered ring. Such examples of bidentate chelation have been considered in similar cases (8,9,14). Contributions from complexes in which LSR is bound solely to the nitrogen or to the carbonyl may also be present, in rapid equilibrium. Ordinarily, LSR is expected to bind much more strongly to an amine than to a ketone (11,12,15). For multifunctional substrates like 1, there may well be numerous bound complexes present.

The chiral LSR, $Eu(HFC)_3$, 3, was employed to elicit enantiomeric shift differences, $\Delta\Delta\delta$, of racemic 1, summarized in Figures 2 and 3, reflecting results for a series of increments of 3 added to 0.336 m 1, based on 60 MHz data. Additional studies were subsequently performed at 200 MHz using a different concentration of 1 and a different batch of 3, to further establish the robustness of this technique for potential direct enantiomeric excess determinations of 1. At 60

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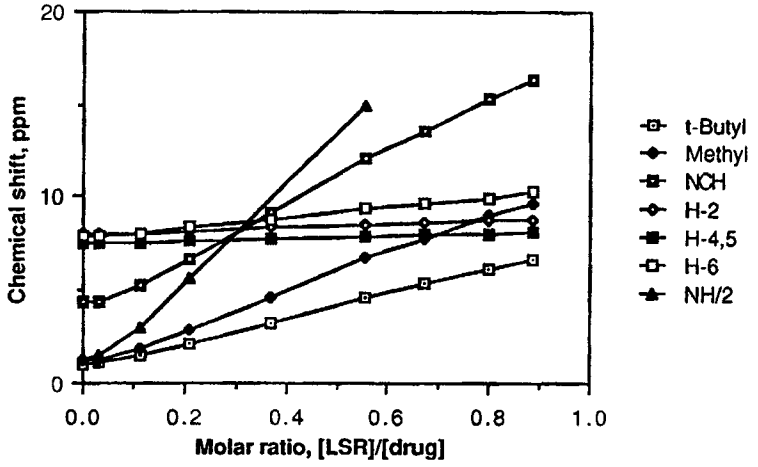

Fig. 2. Variation of chemical shift, δ (in ppm), with molar ratio of 3:1, based on 60 MHz data. See Note in caption for Fig. 1.

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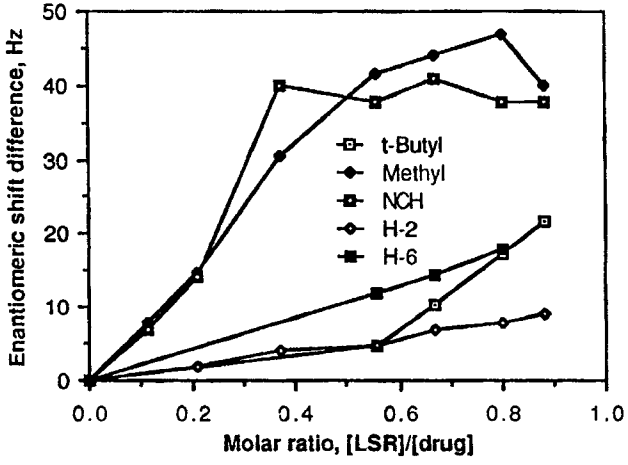

Fig. 3. Variation of enantiomeric shift differences (in Hz, at 60 MHz) with molar ratio of 3:1.

MHz, $\Delta\Delta\delta$ was clearly seen for the signals of the t-butyl, $\underline{CH_3}CH$, NCH, and aromatic H-2 and H-6 for 3:1 molar ratios of 0.558 or more. At the 3:1 ratio of 0.558, the methyl doublet signals of each enantiomer, while displaying some lanthanide-induced broadening, are essentially baseline resolved, although slightly overlapping the residual $CHCl_3$ signal. The methine proton signal, NCH, exhibits comparable $\Delta\Delta\delta$ magnitude to that of the $\underline{CH_3}CH$, but broadening is worse for the methine, and its multiplicity results in poor signal to noise ratios versus the methyl. Best analytical potential at 60 MHz is obtained for the t-butyl signal with a 3:1 molar ratio of 0.884. As seen in Figure 4, use of the t-butyl as the analytical marker signal with this level of LSR avoids overlapping interferences and provides optimal signal to noise ratio, with valley height between each enantiomer's signal only 9.4% (of the average peak heights). Less than 3% of the minor enantiomer should be detectable under these conditions.

To verify the applicability of the LSR method under different conditions, 3 (different batch than

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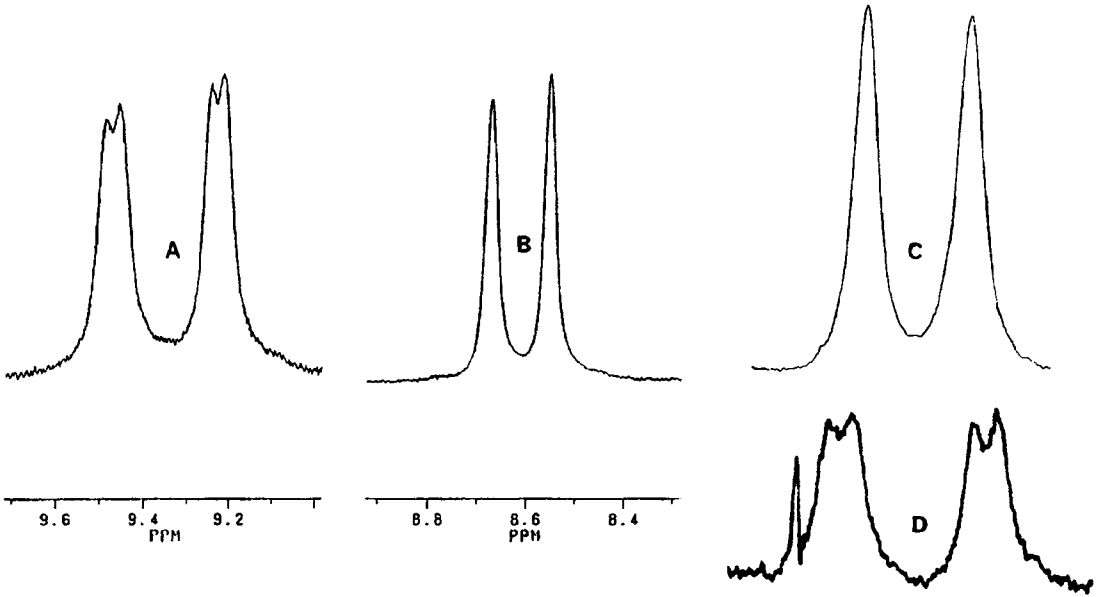

Fig. 4. Spectral expansions showing enantiomeric shift differences for selected protons in 1 with added 3, under specified conditions: spectrometer frequency, observed nucleus, nominal drug molality, average chemical shift in ppm [enantiomeric shift difference in Hz at the specified spectrometer frequency]: a) 200 MHz, H-6, 0.118m, 9.33 ppm [48.3 Hz]; b) 200 MHz, H-2, 0.118m, 8.61 ppm [24.0 Hz]; c) 60 MHz, t-butyl, 0.336m, 6.67 ppm [21.6 Hz], 3:1 ratio ca. 0.884; d) 60 MHz, CH_3CH, 0.336 m, 6.79 ppm [40.0 Hz], 3:1 ratio ca. 0.558. See Discussion regarding molar ratios of 3:1.

for the above 60 MHz runs) was added to 0.118 m 1 to bring the chemical shift of H-6 to ca. 9.33 ppm and the H-2 signal to ca. 8.60 ppm, using the 200 MHz spectrometer. The results (Fig. 4) show excellent analytical potential, with the valley height 11.9% of the average peak heights for each enantiomer for the H-6 signal, and only 8.3% for the H-2 signal. The H-2 resonance is analytically superior also because of its higher signal to noise ratio, since the H-6 signal is appreciably split into gross doublets by the vicinal H-5. Interestingly, using the 200 MHz NMR at this and a higher 3:1 level did not provide acceptable results based on the t-butyl, CH_3CH or NCH signals, due to very severe lanthanide induced broadening. Despite greater $\Delta\Delta\delta$ magnitudes (in Hz) by a factor of 200/60 with the higher field NMR, actual resolution of the signals of each enantiomer by the valley height criterion was much poorer for the t-butyl, CH_3CH and NCH. In contrast, resolution of the H-2 and H-6 signals was dramatically improved at 200 MHz. The main point is that the higher field NMR may not be assumed a priori to give superior

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results for the signal of a specific nucleus, and the prediction of actual signal resolution as a function of NMR field strength may be non-trivial. There may be numerous mechanisms considered for lanthanide induced broadening, such as electron spin relaxation or electron-proton dipole-dipole interactions (16-18), reduced spin lattice relaxation time (19), fast-exchange NMR line broadening with dependence upon bound complex lifetime (20), and chemical exchange (rather than shortened T_1 values, with reduced tumbling rates in the bound complex more important than the lanthanide paramagnetism) (21). It has been pointed out that the line broadening magnitude could be proportional to the square of the spectrometer field strength (20, 21, 22). The worsening of resolution of enantiomer signals with chiral LSR on going to higher spectrometer field was in one case ascribed to chemical exchange of free versus bound substrate (23). The particularly severe line broadening seen for substrates that chelate LSRs has been noted (20, 21, 24).

Table 1 presents the values of the slopes of the plots of chemical shift versus molar ratio of

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Table 1. Slopes[a] of Lanthanide-Induced Shifts (LIS) versus Molar Ratios of [LSR]/[Drug] for Nuclei of Bupropion, 1.

	[b]Eu(FOD)$_3$ data		[c]Eu(HFC)$_3$ data	
Nucleus	Unnormalized	Normalized, Note(d)	Unnormalized	Normalized, Note(d)
t-Bu	6.233	0.844	7.056	0.656
Me	7.384	1.0	10.758	1.0
NH	42.663	5.778	53.801	5.001
NCH	10.728	1.453	15.085	1.402
H2	0.673 (R = 0.99)	0.091	1.080	0.100
H4,5	0.406 (R = 0.98)	0.055	0.792	0.074
H6	1.704	0.231	2.764	0.257

Notes: a) Slopes based on least-squares line fitting, with R=1.00 unless shown. See text for discussion of range of molar ratios included.
b) Slope values based on six experimental points.
c) Slope values based on five experimental points, except for NH (three points) and H-2 (four points).
d) Normalized values based on a value of 1.0 for the methyl, CH_3CH, for each LSR.

LSR:drug for the different protons of 1, based on a least-squares line fitting. These values were determined for the linear portions of the plots using the 60 MHz data of Figs. 1-3. Using $Eu(FOD)_3$, these plots appeared quite linear even at low 2:1 molar ratios, and the tabulated values cover 2:1 ratios from zero (unshifted 1) up through a 2:1 ratio of 0.668. Some non-linearities (leveling off) occurred at higher molar ratios. With $Eu(HFC)_3$, anomalous low slopes were seen for the lowest 3:1 ratios used, and experimental points covering the range of 3:1 molar ratios from 0.113 through 0.671 were employed. [For H-2 with $Eu(HFC)_3$, some flattening of the plot was seen even at 0.671 3:1 ratio, so slope was calculated from 0.113 through 0.558 molar ratio of 3:1.] It has previously been suggested that a relatively flat portion of the plots at low LSR levels may reflect traces of H_2O, which competes with the drug substrate for binding of LSR (25). The generally higher slope values seen in Table 1 using 3 could be consistent with a higher binding constant between 1 and 3 than between 1 and 2, and may

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reflect greater Lewis acidity of 3 than 2. When the slope values determined with each LSR are normalized to the value of the alpha methyl, $\underline{CH_3}CH$, modest differences (greater than 10%) are seen for the normalized value of the t-butyl group. These latter protons are separated from the nitrogen by three bonds (as is also true for the $\underline{CH_3}CH$) and should not be subject to significant contact shifts (26,27). The observed differences in the normalized slopes suggests that the bound complexes of 1 with 2 versus 1 with 3 may not be isostructural, and different substrate conformations may be favored with the different LSRs (28,29). In particular, the lower value for t-butyl seen with 3 than for 2 may suggest a conformation of the complex with 3 in which the bulky t-butyl is more remote from the lanthanide, potentially due to greater steric interactions with $Eu(HFC)_3$ than with $Eu(FOD)_3$.

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CONCLUSIONS

The ^1H NMR spectra of bupropion, 1, have been studied with both achiral and chiral LSR. Using the chiral $Eu(HFC)_3$, 3, enantiomeric shift

differences are seen for the signals of t-butyl, CH_3CH, NCH, H-2 and H-6. Analytical utility for potential direct determination of enantiomeric excess of 1 appears practical based on the CH_3CH or (better) the t-butyl signal, with a 60 MHz spectrometer. With a 200 MHz NMR, the H-2 signal, followed by the H-6 signal, are the best "marker" or "reporter" nuclei. Comparative studies of lanthanide induced shift magnitudes for the achiral $Eu(FOD)_3$, 2, were also performed. Evidence is presented that the bound complexes with 1 may not be isostructural for the two LSRs. Results are interpreted in terms of predominant lanthanide binding at nitrogen, possibly with bidentate chelation to the carbonyl of 1.

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