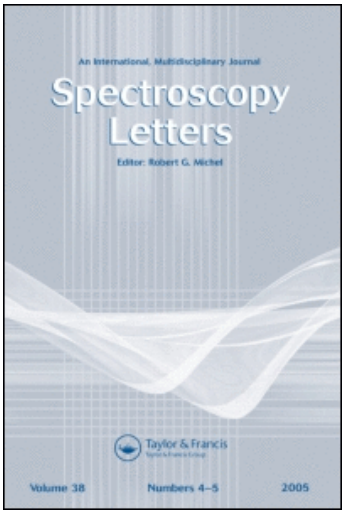

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^{1}H NMR SPECTRAL SIMPLIFICATION WITH ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS. METAPRAMINE. VARIATION OF COUPLING CONSTANTS PRODUCED BY SHIFT REAGENT.

Key Words: Metapramine, Lanthanide, NMR, Shift Reagents, Optical Purity, Enantiomers, Chiral, Conformation, Coupling Constants

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ABSTRACT

The 60 MHz ^{1}NMR spectra of racemic metapramine, 1, have been studied in $CDCl_3$ solution 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

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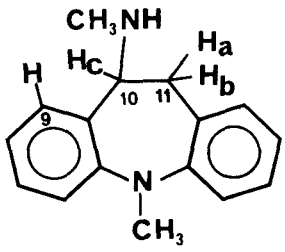
the chiral reagent, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III), 3. Reagent 2 additions resulted in changes of the apparent vicinal coupling constants within the $CH-CH_2$ moiety, as observed from the NCH methine resonance. The chiral 3 led to observable enantiomeric shift differences for the 2^o NCH_3 signal that could have potential for direct optical purity determinations of 1. Results with 2 and 3 are interpreted as consistent with major shift reagent binding at the 2^o nitrogen, with conformer equilibria changes sterically induced by this complexation.

INTRODUCTION:

Metapramine, 1, 10,11-dihydro-N,5-dimethyl-5H-dibenz[b,f]azepin-10-amine, is a member of the important pharmacological class of tricyclic antidepressants, closely related structurally to imipramine. With the introduction of the exocyclic methylamino group onto the azepine ring, metapramine becomes a substituted arylethylamine. This broad class of compounds, which includes various neurotransmitters, amphetamines and related hallucinogens, has been of considerable interest. In these laboratories, 3,4-methylenedioxyamphetamine ("MDA")[1] and 2,5-dimethoxy-4-ethylamphetamine ("DOEt")[2] have been the subjects of studies using lanthanide shift reagents (LSR) for ^1H NMR spectral sim-

plification and conformational analysis studies. In the present case of metapramine, the introduction of the 5-methylamino group creates a chiral center alpha to nitrogen, as in the arylisopropylamines or analogs reported earlier[1-8], which could then allow direct optical purity determinations for the two enantiomers by use of the chiral LSR method. Comformational analysis with respect to rotation about the C_α-C_β bond of arylisopropylamines and analogs has been of considerable interest.[1,2,9-13] The basic techniques of the LSR method for spectral simplification, optical purity determination and conformational analysis have been reviewed.[14-25] To examine the potential of shift reagents in these areas and to extend previous studies, the 60 MHz ^{1}H NMR spectra of racemic 1 in $CDCl_3$ solution at 28° have been examined with 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 racemic *l*-hydrochloride were provided by Rhone-Poulenc Sante, Centre de Recherches de Vitry, France, as no. 19 560 RP, hydrochloride, batch JLC859, with stated mp (Kofler)230° [lit mp 238-240° [26]. Chloroform-*d* (99.8 atom % D), obtained from Aldrich Chemical Corp. Milwaukee WI 53201, USA or Norell, Inc. Landisville N J 08236, USA, was dried and stored 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.

Preparation of *l*-free base: In a separatory funnel was placed *l*-HCl (306.5 mg, 1.115 mmol), 24 ml H_2O, saturated aqueous NaCl (4 ml) and 10ml (excess) 1% aqueous NaOH. The free base of *l* was extracted with CH_2Cl_2 (5 x 5 ml), and the combined organic extracts dried with anhydrous Na_2CO_3. Solvent was removed with a rotary evaporator (aspirator pressure, bath temperature 40°) to yield the free base of *l* as a light yellow oil (233.1 mg, 87.7% recovery) that was stored under N_2 and used without further purification for LSR experiments.

In general, for spectral runs with *l*, an accurately weighed sample of drug (40-55mg) was added to 850-950 mg $CDCl_3$ [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. All spectra were recorded using a Varian EM-360A 60 MHz ^{1}H 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. Reported coupling constants are believed accurate to ±0.2 Hz. For runs with racemic 1 and chiral reagent 3, reported δ values for resonances displaying enantiomeric shift differences, 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.

RESULTS AND DISCUSSION:

Racemic 1, 0.260 molal in $CDCl_3$, displayed the following spectrum, in δ (ppm) units: 1.43(br s, 1H, NH); 2.48(s, 3H, 2° NCH_3); 2.8-3.6(m, 2H, CH_2); 3.37(s, 3H, 3° NCH_3); 4.17(dd [see text], 1H, NCH); 6.8 - 7.4(m, 8H, aryl H). The methine alpha to N appeared as a double doublet (apparent J= 3.7, 7.1 Hz) because of unequal vicinal coupling constants to the hydrogens of the adjacent methylene. These coupling constants could provide information concerning relative abundances of conformational isomers with respect to rotation about the C(10)-C(11) bond, i.e., CH-CH_2 bond rotation. This

corresponds to the key bond about which rotational isomerism has been examined in many amphetamines and related compounds. Examination of the C(10)H methine signal of 1 with the achiral 2 was undertaken to avoid potential line broadening complications that might result from enantiomeric shift differences, $\Delta\Delta\delta$, that could be produced by the chiral 3. The spectra of 1 were examined with added 2 up to a 2:1 molar ratio of 1.17. Substantial lanthanide induced shifts, $\Delta\delta$, were observed; $\Delta\delta$ for a given nucleus in the chemical shift in the presence of LSR minus the chemical shift of the same nucleus with no added LSR. Relative $\Delta\delta$ magnitudes were fully consistent with LSR binding to the 2^{o} N of the 10-methylamino group. This would be predicted based on steric factors (relative to the 3^{o} N) as well as electronic factors. The 3^{o} N would have decreased basicity because of electron pair delocalization into the two aromatic rings. Europium binding at the 2^{o} N would be consistent with relative $\Delta\delta$ magnitudes NH > NCH $\approx$ 2^{o} NCH_3 > CH_2 > 3^{o} NCH_3. A unique aryl proton which appeared as a doublet (1H) with much larger $\Delta\delta$ than the remaining aryl protons was assigned to C(9)H based on proximity to the 10-methylamino group. The CH_2 multiplet in the unshifted spectrum of 1 appeared as a deceptively simple doublet (apparent $J \approx 5.6$ Hz) for a 2:1 molar ratio of 0.0645 and also at a 2:1 ratio

of 0.0913 (apparent $J \approx 5.1$ Hz), becoming a more complex multiplet at higher shift reagent levels. This could suggest a "crossover" in the chemical shifts of these protons, H_a and H_b, in which the proton producing a higher field signal with unshifted 1 moves further downfield in the presence of 2. Accidentally isochronous signals for H_a and H_b at 2:1 ratios in the 0.06-0.09 range could account for the observed apparent doublet. This result may have also been observed for 3,4-methylenedioxyamphetamine.[1] Variation of the chemical shifts of 1 with 2 is summarized in Fig. 1.

With low levels of 2, the methine NCH signal was sufficiently free from lanthanide - induced line broadening and adventitious peak overlaps to allow measurement of the vicinal coupling constants to H_a and H_b. These couplings were observed to vary smoothly with 2:1 molar ratio and are summarized in Fig. 2. LSR use for conformational analysis and related studies has been particularly considered in several reviews.[14,16,17,19,21,24,25] Because of the usual Karplus relation between dihedral angle and vicinal coupling constants for HCCH couplings, these vicinal couplings have proven extremely useful in estimating conformer abundances or determining conformations with respect to rotations about the C-C bond joining the vicinal hydrogens. LSR studies have frequently been employed to help measure

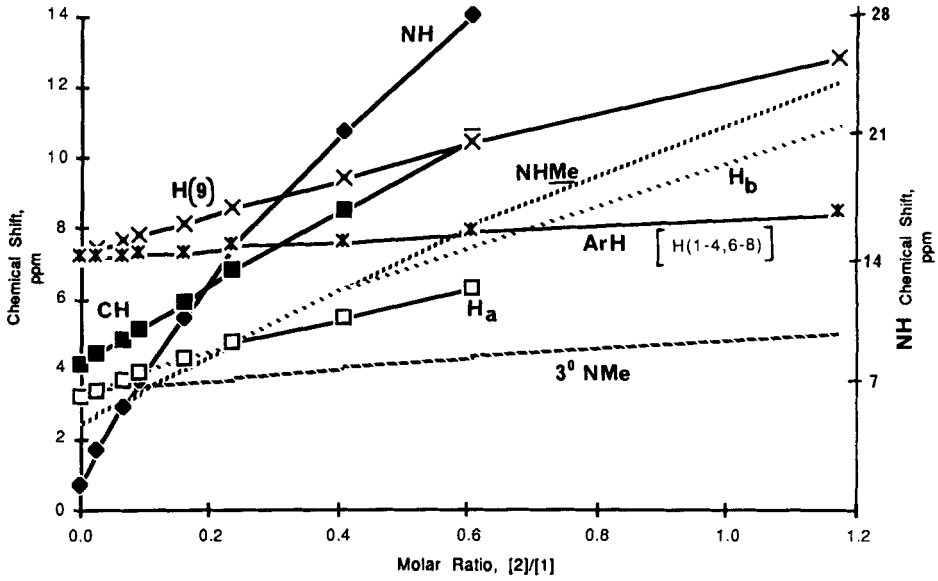

FIG. 1. Variation of chemical shift, δ (in ppm), with molar ratio of 2:1. Note: Plotted chemical shift values for H(1-4,6-8), designated as ArH, represent the approximate center of gravity for the complex broad multiplet of these nuclei. Chemical shifts for the NH proton are based on the right-hand axis.

these coupling constants by reducing the possible overlap of interfering resonance signals.

However, such application of shift reagents must be approached with caution because of (a) possible lanthanide - induced changes in coupling constants that are not directly related to conformational changes; and (b) possible erroneous structural determinations based on an actual LSR:substrate complex inappropriately extended to the conformation of unbound substrate, free

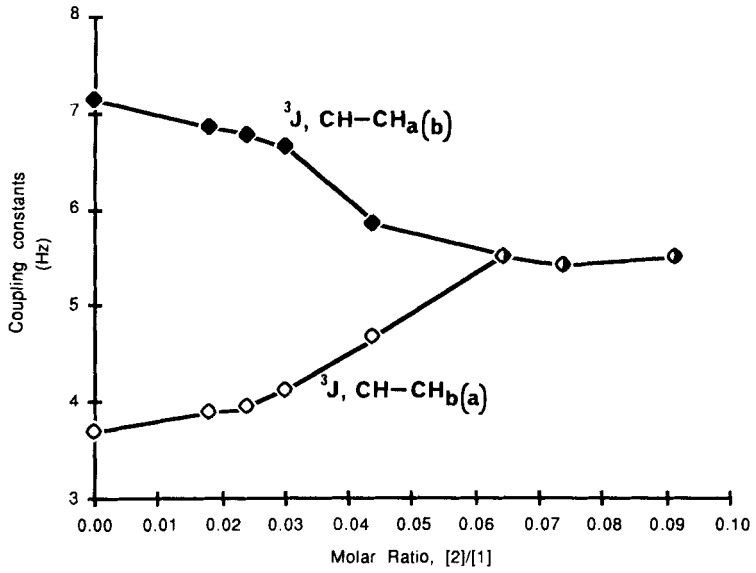

FIG. 2. Variation of observed vicinal coupling constants, ^{3}J (in Hz), within the C(10)H_c-C(11)H_aH_b moiety of 1, with molar ratio of 2:1. Reported coupling values between the methine CH (H_c) and the methylene hydrogens (H_a and H_b) are based on the C(10)H methine resonance.

from complexed LSR. In the first category, possible "substitution", electronic or other changes may result from LSR binding that does not produce changes in substrate geometry but may nonetheless change some coupling constants; several examples of this situation have been reported.[27-29] In the second category, coupling constants were changed on addition of LSR to a substrate as a result of changes in substrate conformational equilibria induced by coordination with

the LSR. Examples of this are known for slow exchange conditions, where separate NMR signals can be seen for different conformers [as with secondary amides [30]] or for configurationally distinct isomers [as with benzylidene anilines [31]]. Examples are also known for fast exchange conditions; in these cases, separate signals for different conformers are not observed because the conformational isomerism is fast on the NMR time scale. The fast exchange case is the more common situation.[32,33] The observed couplings extracted from the signals in the presence of LSR reflect weighted averages of the different conformers for both free and bound substrate, since the equilibrium between free and bound substrate is usually, but not always, fast. Changes in conformational equilibria of a substrate induced by LSR are most commonly ascribed to steric requirements of the shift reagent when bound to the basic site in the substrate, but electronic factors have also been invoked. It is now considered that LSR - induced conformational changes are most likely to occur in cases of: steric repulsion; multifunctional substrates (which can coordinate the lanthanide in a multidentate fashion); strong chelation; flexible systems (especially acyclic systems) in which the LSR coordination site is directly involved in possible conformational changes. If LSR is to be used for conformational

analysis of "unbound" substrate in systems where such factors are present, it is advisable to either confirm that observed coupling constants do not change on addition of LSR (to preclude LSR - induced conformational changes) or to extrapolate coupling constants back to zero LSR concentration (if coupling constants are found to change with LSR concentration). Otherwise, conformational data determined in the presence of LSR will reflect structure of the LSR:substrate complex and not strictly the free substrate.

In the case of 1 with 2, only a single set of signals is observed, confirming fast exchange between different conformers on the NMR time scale, as well as fast exchange between free 1 and 1 bound to LSR. (It is also possible that only one conformer is present in detectable levels.) We favor a change in conformer equilibria for the LSR:1 complex with respect to torsion about the C(10)-C(11) bond resulting from steric interaction of the LSR, probably involving the aryl C(9)H based on the large $\Delta\delta$ for this proton. As the 2:1 molar ratio was increased to 0.07 - 0.09, the NCH resonance became a triplet, $J \approx 5.4$ Hz, requiring equal vicinal coupling constants for the $CH-CH_2$ unit. Line broadening at higher LSR levels prevented coupling constant measurements beyond this point.

Spectra of 1 with added chiral 3 were also recorded up to a 3:1 molar ratio of 1.107. Substantial

enantiomeric shift differences, $\Delta\Delta\delta$, were observed for the 2^{o} NCH_3 and for the signal assigned to C(9)H. For analytical purposes in potential optical purity determinations of 1, the 2^{o} NCH_3 resonance should be the preferred signal because of its lower multiplicity (singlet rather than doublet) and greater intensity and peak height. Low 3:1 ratios should be employed if this methyl signal is used in order to avoid overlaps of the 2^{o} NCH_3 with the 3^{o} NCH_3 signal or with the CH_2 signal at higher levels of 3. Thus, a 3:1 ratio of 0.0444 for a 0.227 molal solution of 1 leads to the 2^{o} NCH_3 peak free from overlap (upfield of the 3^{o} NCH_3 peak) with a valley height between the two peaks of the enantiomers of about 60% of the peak heights and $\Delta\Delta\delta$ of 4.1 Hz. A 3:1 ratio of 0.0674 increases $\Delta\Delta\delta$ and reduces the corresponding valley height to about 50% with slight overlap of the 3^{o} NCH_3 signal; $\Delta\Delta\delta$ was 6.3 Hz. At 3:1 levels near 0.12, the 2^{o} NCH_3 signal has moved downfield past the 3^{o} NCH_3 and resolution between the enantiomer signals has improved by the valley criteria; overlaps with adjacent peaks make this less useful, however. A 3:1 ratio in the range 0.05 - 0.065 should be optimal, although a higher field NMR would clearly be desirable to increase dispersion and reduce overlaps of peaks. Results of 3 with 1 are summarized in Figs. 3 and 4.

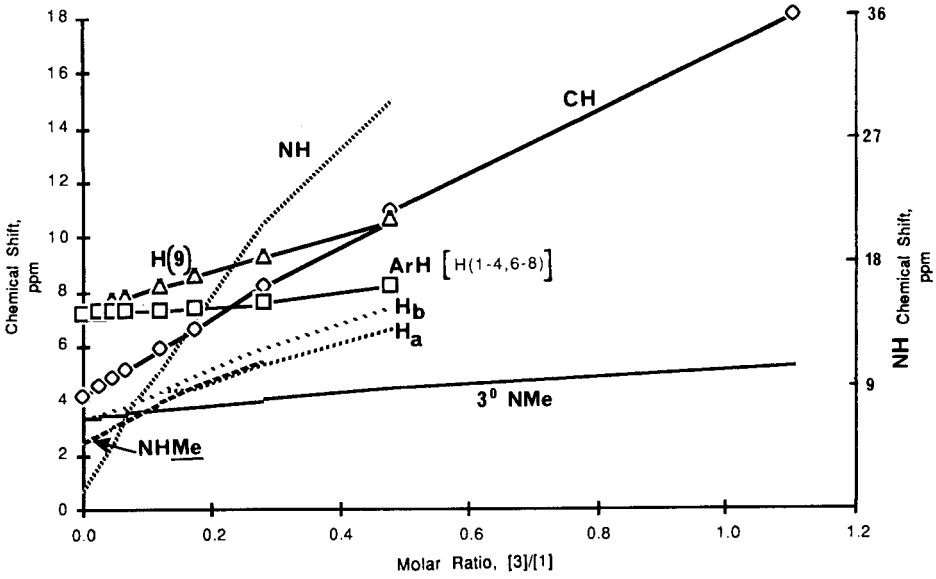

FIG. 3. Variation of chemical shift, δ (in ppm), with molar ratio of 3:1. Where enantiomeric shift differences occur, the average chemical shift for the two antipodes is plotted. See Note for Figure 1.

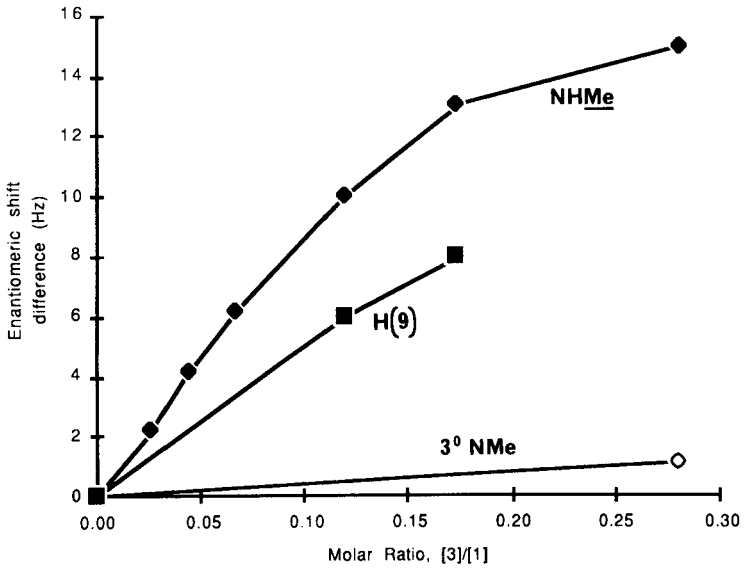

FIG. 4. Variation of enantiomeric shift difference, ΔΔδ (in Hz), with molar ratio of 3:1.

In conclusion, we have shown the use of achiral $Eu(FOD)_3$ for spectral simplification of 1, and the use of chiral $Eu(HFC)_3$ for potential direct optical purity determinations of 1. With both shift reagents, results are consistent with LSR complexation on the nitrogen of the $NHCH_3$ group. Runs with 2 demonstrated clear variation of ^3J vicinal coupling constants within the $CHCH_2$ moiety as LSR concentration was increased, interpreted as a changed conformer equilibrium with respect to torsion about this bond, resulting from steric repulsions in the complex of 1 bound to LSR. The structure and conformation of diverse pharmaceuticals in the class of tricyclic antidepressants and tranquilizers (such as 1) is considered to have enormous importance concerning properties and actions of these drugs.[34] Our findings regarding possible conformational changes in metapramine induced by a Lewis acid shift reagent (and reflected in coupling constant variations) have special significance which may bear upon the actual conformation of a drug at its receptor site.

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