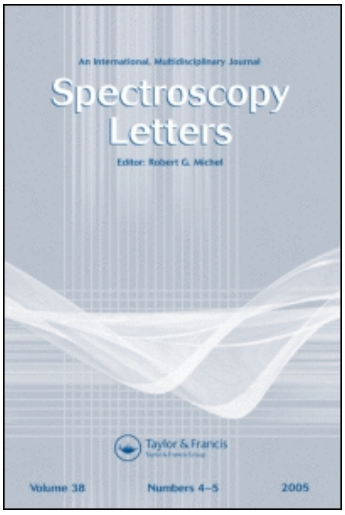

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NMR Studies of Drugs. Application of Achiral and Chiral Lanthanide Shift Reagents to α-Ethyl-α-Phenylsuccinimide

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NMR STUDIES OF DRUGS. APPLICATION OF ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS TO α-ETHYL-α-PHENYLSUCCINIMIDE.

Key Words: 3-Ethyl-3-phenylpyrrolidine-2,5-dione, Optical Purity, Europium, Stereoisomer, Enantiomer, Anticonvulsant, LSR, NMR, Analysis.

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ABSTRACT

The 60 MHz ^1H NMR spectra of 3-ethyl-3-phenylpyrrolidine-2,5-dione, 1, were studied in $CDCl_3$ at 28° using the achiral lanthanide shift reagent (LSR) tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), $Eu(FOD)_3$, 2, for spectral simplification, and the chiral LSR, tris[3-

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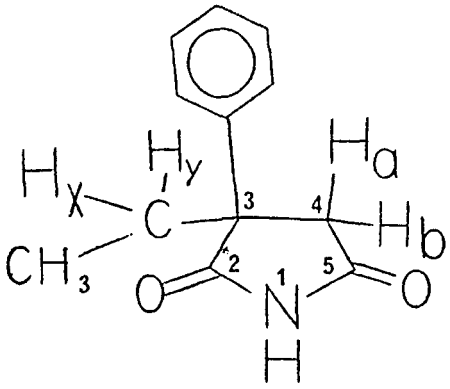
heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III), $Eu(HFC)_3$, 3, to induce enantiomeric shift differences ($\Delta\Delta\delta$) for several nuclei. A non-racemic sample of 1 was treated with 3 to determine the sense of magnetic nonequivalence of selected nuclei. Significant $\Delta\Delta\delta$ is seen for the signals of the methyl and aryl ortho protons. Modest $\Delta\Delta\delta$ can also be seen for the NH signal and for one of the H-4 protons, although LSR-induced broadening for the two latter signals is severe. The (-) enantiomer appeared to exhibit an upfield sense of magnetic nonequivalence (3:1 molar ratio ca. 0.15-0.35) for the methyl signal but a downfield sense for H_{ortho} (3:1 ratio ca. 0.6).

INTRODUCTION

Determination of enantiomeric excess (e.e.) has become increasingly important in recent years. With advances in enantioselective synthesis, and growing concerns over stereoisomer effects, the quantitation of optical antipodes of pharmaceuticals and substances of forensic interest is quite significant. One technique for e.e. determination is based on chiral lanthanide shift reagents (LSR) with NMR. Achiral LSRs can provide NMR spectral simplification. The basic LSR techniques have been reviewed (1-4).



We have been especially interested in achiral and chiral LSR studies of drugs and analogs with structures based on mono- and dicarbonyl five- and six-membered ring heterocycles (5-14). This class of compounds is especially rich in pharmaceutically or forensically important compounds. For this current study, we selected α-ethyl-α-phenylsuccinimide, 1, also known as 3-ethyl-3-phenylpyrrolidine-2,5-dione. The enantiomers of compound 1 and several analogs have been synthesized from chiral precursors (15) and the absolute configuration of 1 assigned as (R)-(+) and (S)-(-) based on ORD and CD studies and chemical correlation to a chiral substituted cyanoacetic acid (16). α-Ethyl-α-phenylsuccinimide has been studied as an anticonvulsant (17,18). In one study (18), it was the second most potent compound of 41

succinimides tested for protection against electrically-induced convulsions, and was in the highest class of activity against metrazol-induced convulsions. Compound 1 has been included in studies dealing with anticonvulsant stereochemistry (19) and isoenzyme inhibition with respect to absolute configuration of succinimides (20). (S)-(-)-1 exhibited greater inhibition of the human brain aldehyde reductase, H4.2, than its enantiomer (20). Recently, in a study of a chiral stationary phase bonded to silica for HPLC, no chiral separations were achieved for succinimides (including 1) although resolutions were achieved for such drug classes as barbiturates, glutarimides and hydantoins (21). This emphasizes the need for ongoing studies in the complementary areas of chromatographic and spectroscopic methods for enantiomeric excess determination.

The achiral LSR, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, known as $Eu(FOD)_3$, was used for preliminary spectral simplification for consideration of LSR binding sites on 1. The chiral LSR, tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]europium(III), 3, known as $Eu(HFC)_3$ or $Eu(HFBC)_3$, was used to elicit

enantiomeric shift differences, $\Delta\Delta\delta$, to determine potential utility for e.e. determinations. Non-racemic samples of 1, prepared by "spiking" racemic material with a portion of one enantiomer, were used to determine the sense of magnetic nonequivalence.

EXPERIMENTAL

Samples of 1 were provided by Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co., Ann Arbor MI, as PD008966-0000, lot T (racemic material), PD053238-0000, lot P (dextro-(+) material), and PD053237-0000, lot P (levo-(-) material); stereochemical descriptors are based on rotations in glacial acetic acid. Chloroform-d, (99.8 atom % D), obtained from Aldrich Chemical Corp., Milwaukee WI 53201 or from Norell, Inc., Landisville NJ 08326, 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 received except as noted.

For runs with shift reagents, an accurately weighed portion of drug was added to $CDCl_3$ [containing about 0.5% tetramethylsilane (TMS) as internal standard] in an NMR sample tube and dissolved by shaking; increments of solid shift reagent were added directly to the sample, dissolved

by shaking, and the spectra immediately obtained. Drug concentrations were typically from 0.4-0.6 molal. Spectrometer probe temperature was 28±1°. Chemical shifts are believed accurate to ±0.05 ppm, and apparent coupling constants to ± 0.2 Hz.

In some runs, particularly with higher levels of LSR, substantial amounts of insoluble particulates were observed, which necessitated filtration through cotton with a Pasteur filter tip pipet. Substrate concentrations and molar ratios of LSR:1 at these high LSR levels must be considered approximate. Where LSR peaks obscured the TMS reference signal, $CHCl_3$ (present as an impurity in the solvent) generally provided a secondary reference signal. With 3, when enantiomeric shift differences were observed, average chemical shifts for the antipodes of 1 are presented here.

Spectra were obtained at 60 MHz on a Varian EM360A ^1H NMR spectrometer.

RESULTS AND DISCUSSION

Racemic 1, 0.589 molal in $CDCl_3$, had the following spectrum (chemical shifts, ppm): 0.98 (3H, t, J = 7.2 Hz, CH_3), 2.10 (2H, q, J = 7.2 Hz, $\underline{CH_2}CH_3$), 3.18 and 2.95 (2H, AB q, $^2J_{gem}$ = 18.4 Hz, H_a and H_b), 7.40 (5H, narrow m, phenyl), 9.38 (1H, br s, NH).

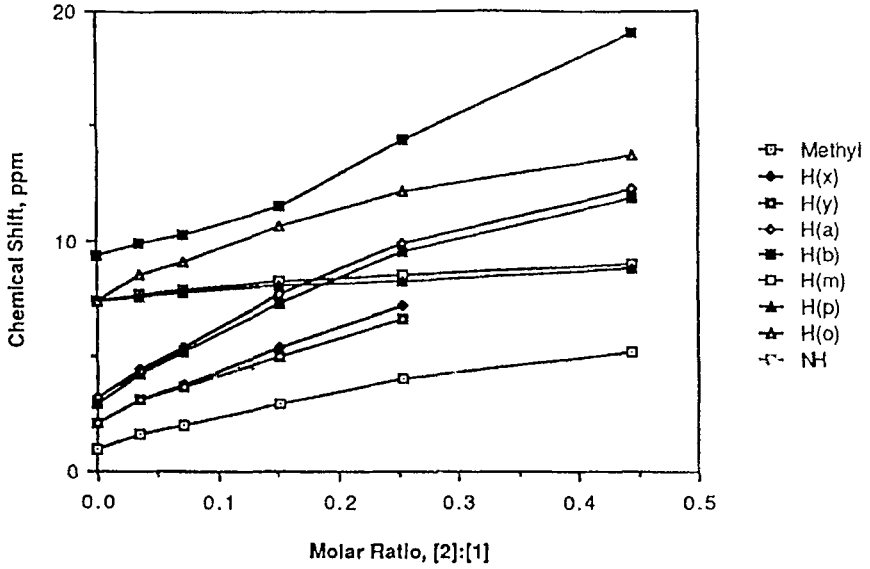


Fig. 1. Variation of chemical shift, δ (in ppm), with molar ratio of 2:1.

The ring methylene protons, H-4 ($H_{a,b}$), appeared as an AB quartet due to the diastereotopic nature of the two protons of the methylene. This is in fairly good agreement with an earlier report (22). Addition of the achiral LSR, $Eu(FOD)_3$, 2, produced the results shown in Figure 1. Lanthanide-induced broadening was appreciable at higher molar ratios. There is remarkably little difference in the lanthanide-induced shifts (LIS) for these H-4 protons, in contrast with the very large shift differences seen for the diastereotopic CH_2 of the sidechain. The

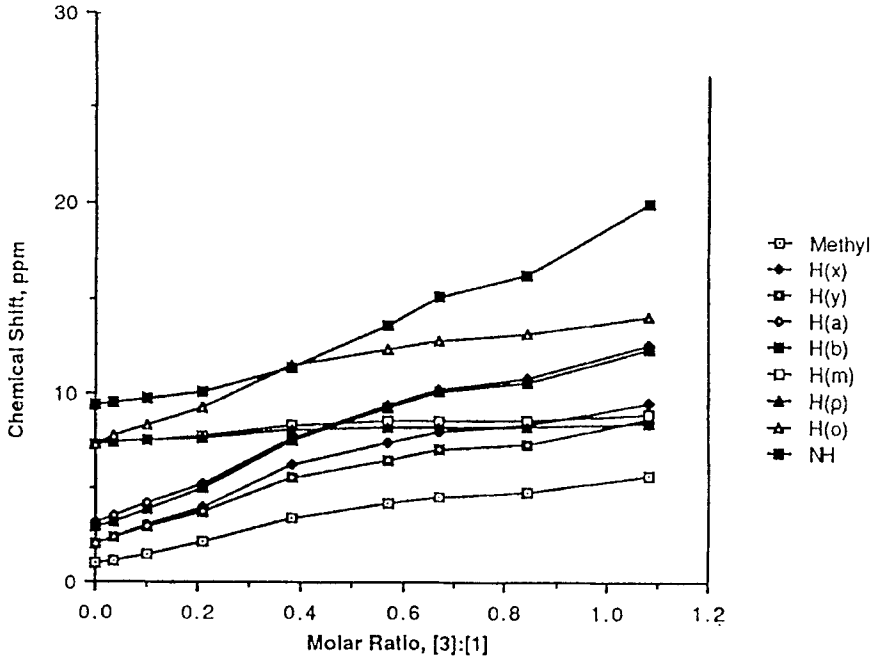


Fig. 2. Variation of chemical shift, δ (in ppm), with molar ratio of 3:1.

latter protons, H_x and H_y, become largely separated from each other with a 2:1 molar ratio ca. 0.25. With the exception of the NH signal, the plots of chemical shift vs. 2:1 molar ratio for each nucleus are relatively well-behaved, with a slight leveling-off noted at the highest 2:1 ratio employed, 0.445. The results for NH seem anomalous, since the slope at lower 2:1 ratios (up to ca. 0.15) is low, but increases at the higher LSR levels. This unusual result was also seen with LSR 3 (see below).

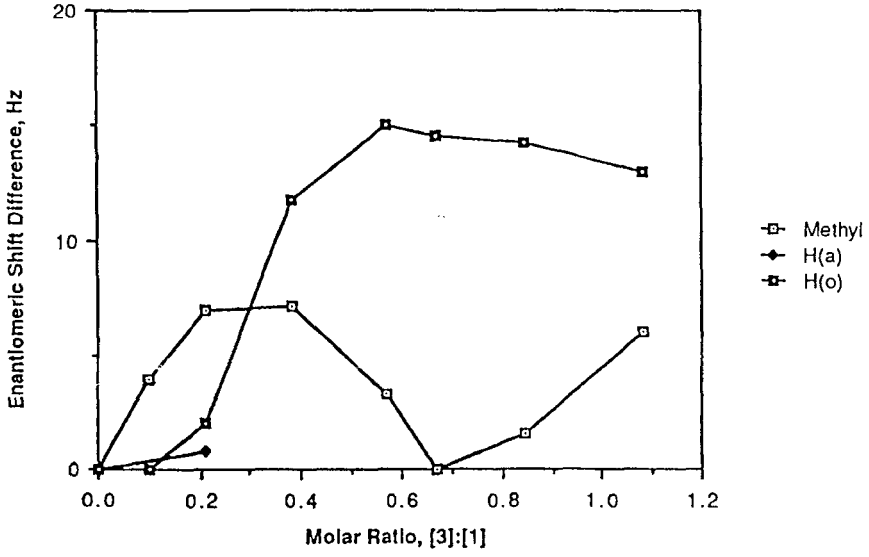


Fig. 3. Variation of enantiomeric shift differences (in Hz) with molar ratio of 3:1.

Results of adding the chiral reagent, 3, $Eu(HFC)_3$, to 0.556 molal 1 are summarized in Figures 2 and 3. The LIS magnitudes with 3 were about half those with 2 for comparable molar ratios of [LSR]:1, but the results are otherwise qualitatively similar. In particular, the slope of the plot of NH chemical shift vs. 3:1 ratio increases at higher LSR levels. Substantial nonequivalence is achieved for the diastereotopic protons $H_{x,y}$ and severe line broadening is seen for H-4 with 3:1 ratios above ca. 0.4. Only estimated shifts for $H_{a,b}$ are plotted in Fig. 2 for the higher LSR levels.

Because of considerable amounts of insoluble particulates observed at the high 3:1 levels, samples had to be filtered. In addition, signals of 3 overlapped and obscured the TMS peak at the higher 3:1 molar ratios, so the molar ratios and chemical shifts indicated in the Figures must be considered approximate, particularly for ratios of 0.57 or more.

Significant enantiomeric shift differences, $\Delta\Delta\delta$, were clearly seen for the methyl signal at lower 3:1 ratios, from 0.1 to 0.4. The $\Delta\Delta\delta$ magnitude appears to decrease and then may increase again, which would be consistent with a change in the sense of magnetic nonequivalence, but (because of line broadening) this must be regarded as tentative. The methyl signal appears clearly as an apparent quartet due to overlapping triplet signals from each enantiomer for 3:1 ratios of 0.2 to 0.4, with $\Delta\Delta\delta$ roughly equal to the vicinal coupling. At high 3:1 ratios, the methyl signal is excessively broadened and of no analytical utility, but distinct separation is seen for the approximate doublet of each enantiomer's ortho proton signal. A valley height of about 50% was observed with a 3:1 ratio of 0.57 for the separation between the approximate doublet signals of the antipodes. A very small $\Delta\Delta\delta$ is apparent for the H-4 proton at lower field, H_a, with 3:1 ratios of ca. 0.2.

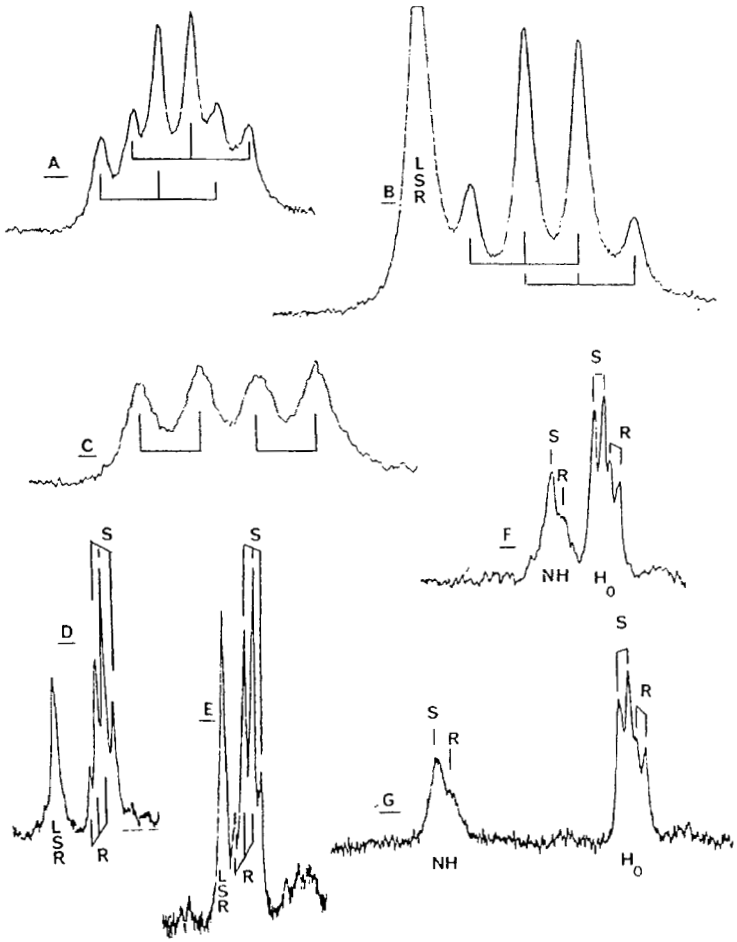


Fig. 4. Spectral traces showing enantiomeric shift differences for selected protons in racemic 1, 0.556 m, with added 3, under specified conditions: observed nucleus, nominal [3]:[1] ratio, average chemical shift in ppm [enantiomeric shift difference in Hz]: (a) CH_3, 0.101, 1.55 [4]; (b) CH_3, 0.209, 2.18 [7]; (c) H_{ortho}, 0.570, 12.3 [15]. The sweep width for (a)-(c) was 1 ppm. Results for non-racemic 1, 0.408 m, (S):(R) ratio of 2.07, e.e. = 34.8 % (S)-(-)-1, are shown in traces (d)-(g) at a 10 ppm sweep width, with the indicated observed nuclei and 3:1 molar ratios: (d) CH_3, 0.131; (e) CH_3, 0.182; (f) NH and H_o, 0.557; (g) NH and H_o, 0.73. Assignments for each enantiomer's multiplets are shown.

While these results would not appear to offer an especially high degree of analytical utility for e.e. determinations (with a 60 MHz NMR spectrometer), we proceeded to examine a sample of non-racemic 1 with added 3 to try to determine the sense of magnetic nonequivalence for the CH_3 and ortho proton signals, as shown in Figure 4. A portion of the (S)-(-)-1 enantiomer of 1 was added to racemic 1 to give a mixture with (S):(R) ratio of 2.07, corresponding to an e.e. of 34.8%. The high field side of the methyl "quartet" was clearly enhanced (relative to the spectra of racemic 1) for 3:1 ratios of 0.13-0.18 for the sample which was 0.408 molal in total 1. Thus, a peak height ratio of 2.00 was seen for the highest field branch versus the lowest field branch of the apparent quartet. Each of these branches corresponds to a separate enantiomer; we have not attempted to correct this raw ratio for leaning in each enantiomer's triplet signal (which is appreciable at this 3:1 ratio). Using higher 3:1 ratios near 0.56, an unambiguous difference is seen in the size of each enantiomer's doublet signal for H_{ortho}. The sense of magnetic nonequivalence is clearly downfield for (S)-(-)-1, opposite to that for the methyl. Ratios of the average peak heights for the low field doublet

and the high field doublet of the ortho proton signal (3:1 ratio of 0.56) averaged 1.485 (N = 6, coefficient of variation = 3.8%) in only fair agreement with the actual enantiomer ratio in the non-racemic sample of 1. No attempt was made to correct for interfering spinning sideband contributions from the NH signal to the ortho resonance. The results are quite clear with respect to the sense of magnetic nonequivalence for H_o.

Surprisingly, the non-racemic 1 exhibits a distinct asymmetry for the NH signal, with 3:1 molar ratios of ca. 0.56-0.74, suggesting some $\Delta\Delta\delta$ and a downfield sense of magnetic nonequivalence for the NH of (S)-(-)-1. A $\Delta\Delta\delta$ was not clearly seen for the NH signal when racemic 1 was examined, presumably a consequence of the LSR-induced broadening.

The unusual variation of chemical shift for the NH as LSR is added to 1 may be consistent with increasing contributions from a bound complex with a 2:1 stoichiometry of LSR:1. If LSR is bound to both carbonyls of 1, at C-2 and C-5, the effect of the lanthanides flanking the imide proton may be to significantly increase LIS magnitudes of the proximal NH.

Table 1 summarizes the relative LIS magnitudes for the different nuclei of 1, expressed as the

Table 1. Slopes[a] of lanthanide-induced shifts (LIS) versus molar ratios of [LSR]/[drug] for nuclei of 1 with added 2 or 3.

	Eu(FOD)$_3$ data[b]		Eu(HFC)$_3$ data[f]	
Nucleus	Unnormalized	Normalized	Unnormalized	Normalized
Methyl	11.755	1.000	5.823	1.000
H_x	19.731	1.679	9.418	1.617
H_y	17.059	1.451	8.089	1.389
H_a	26.020	2.214	10.301	1.769
H_b	25.389	2.160	9.938	1.707
H_{meta}	4.367[c]	0.372	1.962	0.337
H_{para}	3.474[c]	0.296	1.477[c]	0.254
H_{ortho}	18.227[c]	1.551	9.072	1.558
NH low MR	13.904[d]	1.183	3.299	0.567
NH high MR	25.506[e]	2.170	11.993[c,g]	2.060

Notes: a) Slopes are based on least-squares line fitting for data from Figs. 1 and 2, with correlation coefficients R=1.00 unless noted. Normalized values are given based on a value of 1.0 for the methyl, CH_3CH, for each LSR. b) Slope values based on five experimental points with [2]:[1] ratios 0-0.254 (except for NH). c) Correlation coefficient R=0.99. d) Slope value based on four experimental points with [2]:[1] ratios 0-0.151. e) Slope value based on three experimental points with [2]:[1] ratios 0.151-0.445. f) Slope values based on four experimental points with [3]:[1] ratios 0-0.209 except for "NH high MR." g) Slope value based on five experimental points with [3]:[1] ratios 0.381-1.08.

slopes from plots versus [LSR]:[1] ratios, in the presence of added 2 or 3. Unnormalized "raw" slopes are presented as well as normalized values, using the CH_3 proton signal as the reference. Shifts for the CH_3 are assumed to be largely pseudocontact (dipolar). The tabulated slopes are obtained from a simple least squares fitting for lower LSR:1 ratios, i.e., using the linear portions of the plots, before "leveling-off" is apparent. The two NH values

reflect the early, lower slope (low molar ratio) portions, as well as the higher slope (high molar ratio) portions. Significant differences in the normalized slopes for the two different reagents, 2 adn 3, would normally be considered as evidence that the corresponding bound complexes with 1 are not isostructural if Fermi contact shifts and diamagnetic complexation shifts can be ignored. Opposite senses of magnetic nonequivalence for different nuclei in a substrate molecule with added chiral LSR could indicate that the $\Delta\Delta\delta$ values result from different geometries of the bound complex of the substrate enantiomers with LSR, and not simply different binding constants for each enantiomer with the LSR (23,24). However, in the present case of 1 with 3, we were unable to assign the sense of magnetic nonequivalence (with non-racemic 1) for both the CH_3 and H_{ortho} at the same 3:1 ratios, due to small $\Delta\Delta\delta$ magnitudes, interfering overlapped peaks, or line-broadening. The fact that the CH_3 signal of (S)-(-)-1 was clearly at higher field (for low 3:1 ratios) while the H_o signal was at lower field (for higher 3:1 ratios) may actually reflect a change in the sense of magnetic nonequivalence for the CH_3, suggested by Fig. 3, or contributions from different

bound complex stoichiometries at higher LSR levels. The greatest differences in the normalized slopes are seen for the NH at low LSR levels (roughly a factor of two). Moderate differences for the meta and para aryl protons may, in part, reflect greater contributions from experimental error due to smaller LIS magnitudes for these nuclei. The normalized slopes for $H_{a,b}$ are about 20% larger with 2 than with 3. The values for $H_{x,y}$ and H_{ortho} agree quite closely, and even the meta and para proton values agree within ca. 15%. We interpret these results as consistent with a major degree of isostructurality in the bound complexes of 1 with either 2 or 3. The large deviations for NH at low LSR levels of 2 versus 3 (but not at high levels) may reflect the particular sensitivity of the NH nucleus to the angular part of the simplified McConnell-Robertson equation (25). We note that in earlier work with a 4-oxazolidinone using 2, 3, $Pr(FOD)_3$ and $Pr(HFC)_3$, the HFC reagents for both Eu and Pr resulted in normalized slope values for the NH nucleus of about half the values of the corresponding FOD reagents (14), as is seen in this present work for low LSR levels. It may also be possible that for the NH nucleus, there is some contact (or complexation) shift contribution in these

systems, as was observed for protons alpha to carbonyl in ketones (26,27); these effects may also contribute to observed values for $H_{a,b}$ in 1 (28,29).

CONCLUSIONS

The ^1H NMR spectra of the anticonvulsant, 3-ethyl-3-phenylpyrrolidine-2,5-dione, 1, have been studied in $CDCl_3$ solution with the added LSR reagents $Eu(FOD)_3$, 2, or $Eu(HFC)_3$, 3. Relative LIS magnitudes for both reagents were in the sequence: H-4 ($H_{x,y}$) > H_{ortho}, CH_2CH_3 > CH_3 > H_{meta} > H_{para}. Values for the NH proton appeared to behave anomalously, with increasing slopes in the plot of LIS vs. [LSR] : [1] molar ratio at high LSR levels. Appreciable $\Delta\Delta\delta$ values were clearly seen with added 3 for the CH_3 and ortho proton signals which permitted determination of the relative sense of magnetic nonequivalence for these nuclei based on runs with non-racemic 1.

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