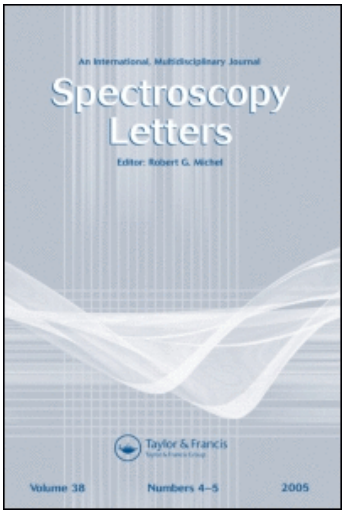

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

NMR Studies of Drugs. Applications of Achiral and Chiral Lanthanide Shift Reagents to the Anticonvulsant, Methetoin, 5-Ethyl-1-Methyl-5-Phenyl-2, 4-Imidazolidinedione

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To cite this Article Shields, Diana , Tran, Han , Venkatasubban, Kunisi S. , Rothchild, Robert and Wyss, Helen(1994) 'NMR Studies of Drugs. Applications of Achiral and Chiral Lanthanide Shift Reagents to the Anticonvulsant, Methetoin, 5-Ethyl-1-Methyl-5-Phenyl-2, 4-Imidazolidinedione', Spectroscopy Letters, 27: 1, 23 — 39
To link to this Article: DOI: 10.1080/00387019408002505
URL: http://dx.doi.org/10.1080/00387019408002505

SPECTROSCOPY LETTERS, 27(1), 23-39 (1994)

NMR STUDIES OF DRUGS. APPLICATIONS OF ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS TO THE ANTICONVULSANT, METHETOIN, 5-ETHYL-1-METHYL-5-PHENYL-2,4-IMIDAZOLIDINEDIONE.

Key Words: ^{1}H NMR, LSR, Europium, Eu(FOD)$_3$, Eu(HFC)$_3$, NMR shift reagents, Lanthanide, Stereoisomers, Enantiomeric excess, Analysis, 5-Ethyl-1-methyl-5-phenylhydantoin, Hydantoins.

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ABSTRACT

The 200 MHz ^{1}H NMR spectra of the anticonvulsant, methetoin, 1, have been studied in $CDCl_3$ solution at ambient temperatures in the presence of the achiral lanthanide shift reagent tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, and the chiral reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-

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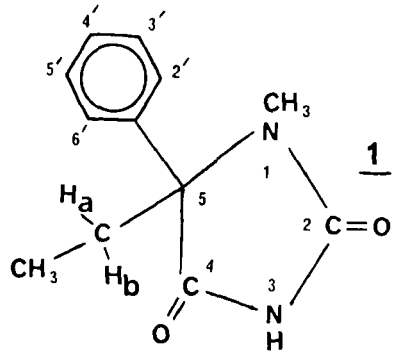
camphorato]europium(III), 3. With added 3, appreciable enantiomeric shift differences, $\Delta\Delta\delta$, can be induced for the aryl protons and both methyl groups of 1. In particular, using 3:1 molar ratios from ca. 1.2-2, with 0.046 molar 1, signals from the $\underline{CH_3}CH_2$ and the phenyl ortho protons for the enantiomers of 1 are well resolved, exhibiting excellent potential for direct determinations of enantiomeric excess of 1. Relative magnitudes of lanthanide-induced shifts for the different nuclei of 1 with added 2 or 3 are compared and discussed.

INTRODUCTION

NMR studies of drugs with lanthanide shift reagents (LSR) have been an ongoing interest in our laboratories, both for spectral simplification and for potential direct determinations of enantiomeric excess (% ee). In recent years, enantiomeric composition has been of growing concern, because of advances in enantioselective synthesis and chiral chromatographic methods. For pharmaceuticals, there has been increasing awareness of the potential for enantiomers to differ markedly in their potency, toxicity or pharmacology.

We believe that chiral LSRs serve as important complementary tools to chromatographic techniques for ee determination. Certain molecular characteristics appear to enhance the likelihood that chiral LSRs will offer potential for direct ee determination. A relatively rigid five- or six-membered ring with a functional group suitable for binding lanthanide is often favorable. Ideally, the LSR binding site should be close to the chiral center, and a



suitable analytical "marker" group (i.e., "reporter" nucleus) for the NMR should also be proximal to the chiral center and LSR binding site. The analytical NMR signal should have minimal multiplicity and high intensity for optimal signal-to-noise ratio. We have recently examined numerous substrates of pharmaceutical interest possessing an "amide"-type carbonyl (within the ring) to bind LSR, including cyclic imides (1-3), hydantoins (4) and an oxazolidinone (5) as well as analogs cited as references within these articles. The hydantoin structure has historically been of great importance because of the extensive application of hydantoins as anticonvulsants. We therefore wanted to extend our LSR studies with methetoin, 1, known as 5-ethyl-1-methyl-5-phenyl-2,4-imidazolidinedione or 5-ethyl-1-methyl-5-phenylhydantoin, using the achiral LSR, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, $Eu(FOD)_3$, and the chiral LSR, tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]europium(III), 3, known as

$Eu(HFC)_3$ or $Eu(HFBC)_3$. The basic principles and techniques for use of achiral and chiral LSRs have been discussed (6-10).

EXPERIMENTAL

Racemic 1 was obtained through Sandoz Pharmaceuticals Corporation, East Hanover NJ 07936. $CDCl_3$ (99.8 at. % D) and shift reagents were obtained from Aldrich Chemical Corp. (Milwaukee WI 53201). The $CDCl_3$ was dried and stored over 3Å molecular sieves. Drug and LSRs were stored in a desiccator over P_2O_5 and were used as supplied. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS) at 0.00 ppm. In runs with LSR, increments of solid shift reagent were accurately weighed directly into a 5 mm thin-walled oven-dried NMR tube containing an aliquot of a standard solution of drug. The LSR was dissolved by shaking and the spectra immediately obtained. NMR studies were performed with a Bruker AC200-F Fourier transform NMR spectrometer with Aspect 3000 data system operating at a ^1H observe frequency of 200.13 MHz. Spectra were obtained in the FT mode at ambient temperatures using a switchable $^1H/^{13}C$ probe. Chemical shifts were obtained from spectral peak tables and are believed accurate to $\pm$0.02 ppm. Coupling constants and enantiomeric shift differences were calculated by subtraction of values from peak frequency lists and are believed accurate to $\pm$0.2 Hz. Typical FT-NMR parameters were as follows: 4032 Hz spectral width (about -4 to + 16 ppm) over 64 K complex 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; 128 FIDs were accumulated. No line broadening or resolution enhancement was applied. 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.

RESULTS AND DISCUSSION

Some hydantoins (2,4-imidazolidinediones) have been studied using LSRs with NMR (4,11-13), including mephenytoin (11,13). Mephenytoin is the N-methyl isomer of 1, possessing the methyl group at the N(3) position in contrast with the N(1) position of methetoin. Our present LSR studies of 1 began with increments of the achiral LSR, $Eu(FOD)_3$, 2, added to a 0.0477 molar solution of 1 in $CDCl_3$. The unshifted reference spectrum of 1 showed resonances as follows (δ, ppm from TMS): 0.969, 3H, t (^3J = 7.322 Hz), $\underline{CH_3}CH_2$; 2.022, 1H, approx. sextet (^3J = 7.267 Hz, ^2J = 14.53 Hz), H_a; 2.606, 1H, approx. sextet (^3J = 7.225 Hz, ^2J = 14.450 Hz), H_b; 2.797, 3H, s, NCH_3; 7.29-7.47, 5H mult. (centered near 7.37), aryl H; 8.917, 1H, br s, NH.

It is striking that the two diastereotopic protons of the sidechain methylene, $CH_3\underline{CH_2}$, exhibit such a considerable chemical shift difference. The two nonequivalent nuclei are assigned labels of H_a (for the higher field signal) and H_b (for the lower field signal), respectively. Each resonance appears as a clean sextet, consistent with a first-order approximation (based on observed apparent coupling constants) in which the geminal coupling, $^2J(a,b)$, is twice the vicinal

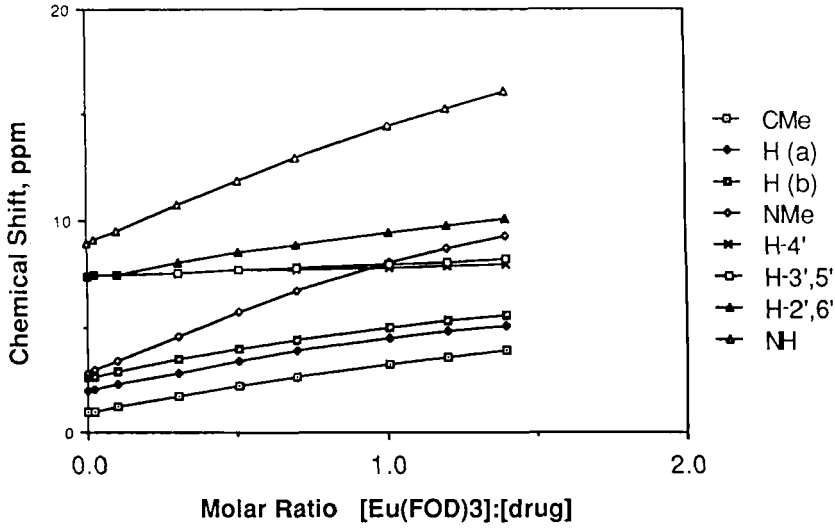


Figure 1. Variation of chemical shifts (δ, ppm) with molar ratios of [$Eu(FOD)_3$]/[methetoin] for 0.0477 M 1 in $CDCl_3$.

coupling ^3J, e.g., $J(H_a\text{-}CH_3)$ or $J(H_b\text{-}CH_3)$. The apparent sextets result from partial overlap of two quartets. The estimated splittings are reasonable in terms of expected magnitude values (14). The listed ^3J values agree within 0.1 Hz, which is reasonable in terms of experimental accuracy. The addition of 2 produces significant lanthanide-induced shifts (LIS), summarized in Figure 1.

A parallel series of runs was performed with additions of the chiral $Eu(HFC)_3$, 3, with 0.0458 molar 1. This unshifted solution of 1 displayed an NH resonance at 8.729 ppm, nearly 0.2 ppm at higher field than for the more concentrated solution noted above; other resonances for the

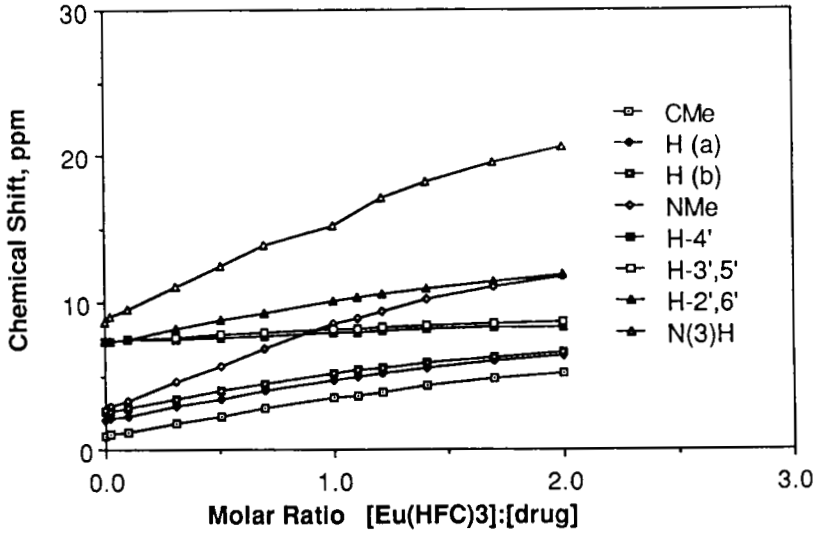


Figure 2. Variation of chemical shifts (δ, ppm) with molar ratios of [Eu(HFC)$_3$]/[methetoin] for 0.0458 M 1 in $CDCl_3$.

two solutions agreed within $\pm$0.02 ppm. The NH concentration dependence must reflect increased hydrogen bonding in the more concentrated sample with a concomitant downfield shift. The corresponding LIS values are summarized in Figure 2. In particular, enantiomeric shift differences, $\Delta\Delta\delta$, are elicited for several nuclei of 1, summarized in Figure 3. The $\Delta\Delta\delta$ values seen for the sidechain methyl, $\underline{CH_3}CH_2$, demonstrated outstanding potential for direct determination of enantiomeric excess of 1, with valley heights between the signals from each enantiomer of less than 1.0% seen at the highest 3:1 molar ratio employed. Significant $\Delta\Delta\delta$ values can be seen for the ortho aryl protons, H-2',6', and for the NCH_3

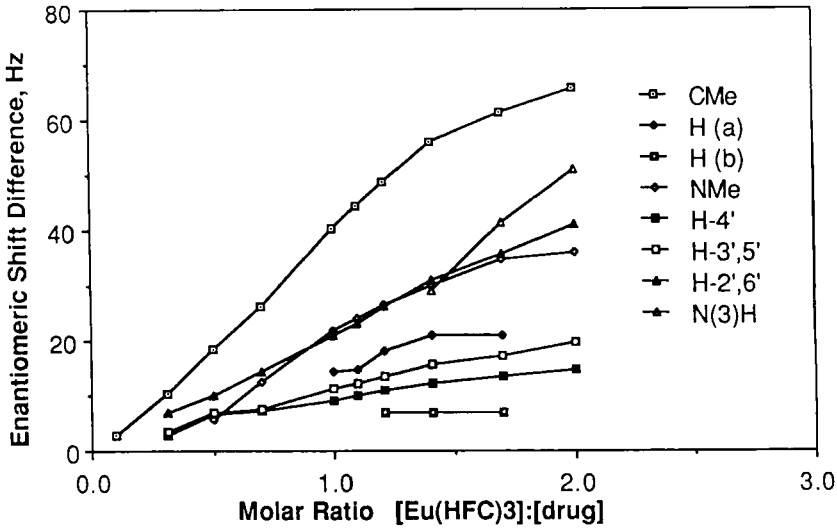


Figure 3. Variation of enantiomeric shift differences ($\Delta\Delta\delta$, in Hz at 200 MHz) with molar ratio of [3]/[1] for 0.0458 M 1.

signal; see Figure 4. The % valley heights for these signals were: $\underline{CH_3}CH_2$ 4.5, 4.3, 1.3, 0.9; H-2′,6′ 22.5, 14.3, 8.1, - ; NCH_3 37.5, 30.0, 17.5, -; for 3:1 molar ratios of 1.207, 1.408, 1.698 and 2.002, respectively. (Signal overlaps prevented valley height measurements at the highest 3:1 ratio for the ortho and NCH_3 absorptions). It is noteworthy that the $\Delta\Delta\delta$ magnitudes for the sidechain methyl are substantially greater than the values estimated for H_a and H_b despite the greater distance from the methyl to the chiral center at C-5 and, presumably, from the methyl to the expected LSR binding sites at the C-2 and C-4 carbonyls. The $\Delta\Delta\delta$ values estimated for H_a and H_b were based on the increased complexity (number

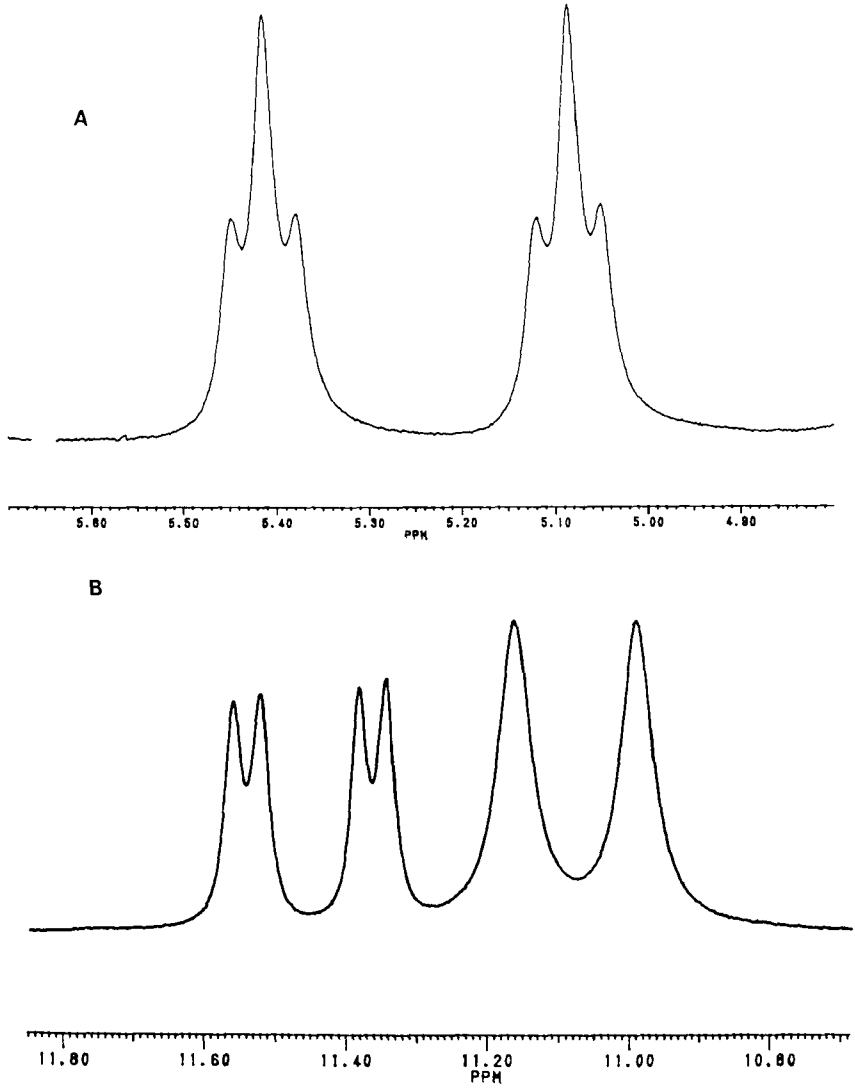


Figure 4. ^{1}H NMR spectral expansions at 200 MHz for 1 with added 3: (a) $\underline{CH_3}CH_2$ triplets centered at 5.25 ppm, 65.7 Hz $\Delta\Delta\delta$, 0.9% valley height, with [3]/[1] ratio 2.00; (b) aryl ortho doublets centered at 11.46 ppm, 35.7 Hz $\Delta\Delta\delta$, 8.1% valley height and NCH_3 singlets centered at 11.08 ppm, 34.6 Hz $\Delta\Delta\delta$, 17.5 % valley height, with [3]/[1] ratio 1.70.

of lines) in the multiplets for H_a and H_b; distinct well-separated signals from each optical antipode of 1 were not achieved. The $\Delta\Delta\delta$ values for H_a and H_b plotted in Fig. 3 must therefore be regarded as rough estimates, reflecting uncertainties in evaluating the multiplet widths. The large $\Delta\Delta\delta$ values for the $\underline{CH_3}CH_2$ and ortho protons may reflect the favored conformations in the diastereomeric bound complexes of the enantiomers of 1 with chiral 3, based on the simplified form of the McConnell-Robertson equation for pseudocontact (dipolar) shifts (15). The observed degree of resolution between the methyl ($\underline{CH_3}CH_2$) signals of the enantiomers of 1 with 3 at a 3:1 ratio of ca. 2.0 should permit detection of 1% of a minor enantiomer, or better. Despite the rather high LSR:1 ratios employed, a very low degree of line-broadening permits excellent potential for direct % ee measurements. Note that despite large $\Delta\Delta\delta$ magnitudes for the N(3)H signal, poor resolutions of these signals from each enantiomer are observed, i.e., high valley heights, due to the appreciable broadness of the signals of this nucleus. Analytical utility was not achieved for the NH.

We note here that the observed $\Delta\Delta\delta$ values reported above for the aryl ortho (H-2′,6′) and meta (H-3′,5′) protons of 1 with 3 could conceivably be the result of slow rotation of the phenyl group. If the rotation about the sp^2-sp^3 bond between the phenyl and C-5 of the hydantoin ring were slow on the NMR timescale, the pairs of ortho and meta protons would be diastereotopic and potentially anisochronous because of

their different environments with respect to the chiral center at C-5. It is only a rapid phenyl rotation on the NMR timescale that interchanges the nuclei within each pair. The appearance of a single doublet for H-2',6' and a single triplet for H-3',5' when the achiral 2 is used (up to a 2:1 molar ratio of ca. 1.4) strongly supports our designation of the doubled signals (in runs with the chiral 3) as being authentic enantiomeric shift differences rather than anisochronous diastereotopic nuclei due to a slow phenyl rotation.

Table 1 compares both unnormalized and normalized values of the slopes from the linear portions of the plots of chemical shift versus [LSR]/[1] molar ratio, from the data of Figs. 1 and 2, based on a linear least squares line fitting. Despite the conformational flexibility of the sidechain ethyl group, we have selected the sidechain methyl as the reference group, for several reasons. This methyl is separated from the expected LSR binding sites (on the carbonyl oxygens) by a sufficient number of bonds to assure that Fermi contact shift contributions are negligible; this may not be true for the NCH_3 or NH signals (16,17). In addition, the $\underline{CH_3}CH_2$ chemical shift values are accurately measurable, which is less true for the complex H_a and H_b multiplets.

While LSR binding at both carbonyls of 1 is expected, with rapidly interconverting bound complexes of various species, the two oxygens are expected to differ both sterically and electronically. The C-2 carbonyl is hindered by a coplanar NCH_3 while the C-4 carbonyl is hindered by the

Table 1. Slopes of lanthanide-induced shifts versus molar ratios of [LSR]/[drug] for nuclei of 1. (See Notes and Results and Discussion.)

	$Eu(FOD)_3$ data		$Eu(HFC)_3$ data	
Nucleus	Unnormalized	Normalized	Unnormalized	Normalized
CCH_3	2.528[a]	1.0	2.635	1.0
H_a	2.631	1.04	2.777[c]	1.05
H_b	2.613	1.03	2.798	1.06
NCH_3	5.663	2.24	5.938	2.25
H-4′ (para)	0.533[b]	0.21	0.577[c]	0.22
H-3′,5′(meta)	0.548[d]	0.22	0.825[c]	0.31
H-2′,6′ (ortho)	2.283[a]	0.90	2.816[c]	1.07
NH	5.233[d]	2.07	7.330	2.78

Notes: Slopes are based on least-squares line fitting for each nucleus with either 2 or 3. Normalized values are relative to a value of 1.0 for the signal assigned to the CCH_3. For all nuclei, a correlation coefficient R = 1.00 was obtained. Data are taken from Figs. 1 and 2. See Results and Discussion. Six experimental points were selected for each line except as noted. (a) Five experimental points. (b) Four experimental points. (c) Seven experimental points. (d) Nine experimental points.

disubstitution of phenyl and ethyl at C-5. Electronically, the carbonyls also differ since one is "amide-type" (C-4) and one is "urea-type" (C-2). Simple inspection of the tabulated slope values does not permit a clearcut determination of a predominant LSR binding site.

The normalized values for runs with 2 and 3 in Table 1 are striking in the very close agreement seen for all nuclei except for N(3)H, and the aryl ortho and meta protons. We interpret this as follows. The similarity of values to within ±0.02 for CCH_3, H_a, H_b, NCH_3, and H-4′ (para) implies a high degree of isostructurality in the bound complexes of 1 with 2 versus 1 with 3. Differing values of normalized slopes for the meta and ortho protons for the two LSRs may suggest a different rotational angle of the phenyl ring with respect to the bond between the aryl ipso C-1′ and hydantoin C-5 carbons. This would change the geometric factors for the aryl meta and ortho protons but not for the aryl para proton, since phenyl ring rotation does not affect distance or angular relations for the para proton. Differing normalized values for the NH proton may be accounted for by Fermi contact shift contributions (16,17). Identical normalized values for the CCH_3, H_a and H_b nuclei imply comparable conformations of the ethyl sidechain with the two LSRs, despite expected conformational mobility of this alkyl group. Note that correlation coefficients, R, were equal to 1.00 for all cases, indicating good experimental linearity.

In runs with added 2, we noted a small but consistent decrease in the observed ^3J for the sidechain methyl triplet,

from J = 7.32 Hz (unshifted 1) to J = 7.11 Hz (2:1 ratio of 1.40). This change is close to the expected experimental error but was a regular monotonic change. The variation of the measured coupling versus 2:1 molar ratio followed the equation for the line: y = 7.303 - 0.122 x, with the relatively high correlation coefficient R = 0.96. [Least squares line fittings were not performed for couplings with other nuclei or for runs with 3, where variations of J(observed) were less regular.] It is possible that such a change is artifactual based on slight relative changes in contributions from second order spectral effects in the $CH_3CH_aH_b$ spin system accompanying LIS variations. Alternatively, the coupling constant changes may be real, reflecting slight changes in electronegativities, hybridizations or bond angles associated with formation of the bound complex of 1 with LSR. Small and less regular decreases were also seen for the apparent ^3J values estimated for H_a and H_b; for H_a, the values went from 7.27 Hz to 7.18 Hz, and for H_b, from 7.22 Hz to 7.00 Hz (with 2:1 ratios from 0.0 to 1.4). In contrast, slight increases were measured for the observed ^3J values of the aryl protons. Analogous changes with 3 were less regular.

CONCLUSIONS

The 200 MHz ^1H NMR spectra of the anticonvulsant, methetoin, 1, have been studied at ambient temperatures in $CDCl_3$ with added $Eu(FOD)_3$ or $Eu(HFC)_3$. The chiral 3 elicited substantial $\Delta\Delta\delta$ values, especially clear for the side chain methyl and NCH_3 signals, and the three sets of aryl protons.

With 0.0458 M 1 and 3:1 molar ratios of 1.70 and 2.00, the CH_3CH_2 triplet signals from the enantiomers were separated by valley heights of only 1.3 and 0.9%, respectively, indicating excellent potential for direct determination of % ee for samples of 1. With a 3:1 molar ratio of 1.70, the H-2′,6′ ortho proton doublets and the NCH_3 singlets from each enantiomer displayed valley heights of 8.1 and 17.5%, respectively. Direct % ee determinations for samples of 1 should be optimal using the aryl ortho resonances at 3:1 ratios ca. 1.7-2; the method would appear to be fairly robust and applicable to samples of 98% ee or more. The relative magnitudes of lanthanide-induced shifts for the nuclei of 1 with added 2 or 3 have been compared to qualitatively evaluate isostructurality of the bound complexes of 1 with the two LSRs. Some variations of observed coupling constants with LSR addition are discussed.

ACKNOWLEDGMENTS

We are grateful to Kathleen Roskaz, Sandoz Research Institute, Sandoz Pharmaceuticals Corp., East Hanover NJ, for assistance in obtaining a sample of racemic 1. Partial support has been provided by the U.S. Education Department Minority Science Improvement Program (grant no. G008641165), the National Science Foundation (grants no. USE-8851684 and USE-9152822), the Hewlett-Packard Corporation (grant no. 0017-80769), U.S. Department of Energy ERLE (grants no. AL-89-169 and AL-90-092), Hoffmann-La Roche Inc., Berlex Laboratories, Inc., the Forty-Five Foundation, and the Professional Staff Congress - City University of New York

(PSC-CUNY 24) research award program (grant no. 664182), to R.R. Additional support was provided by the Petroleum Research Fund of the American Chemical Society and the Research Corporation (to K.S.V.) and by the University of North Florida for purchase of the Bruker 200 MHz NMR spectrometer.

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Date Received: August 20, 1993
Date Accepted: September 29, 1993