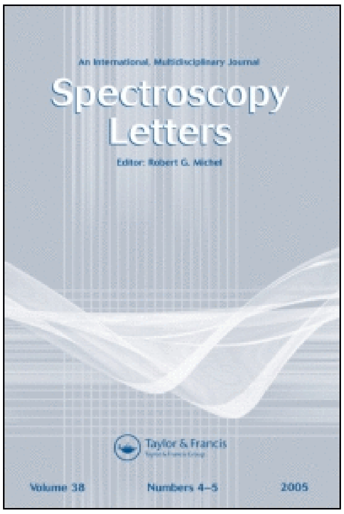

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NMR Studies of Hindered Rotations in Drugs. Use of Achiral and Chiral Lanthanide Shift Reagents with Mecloqualone, an Axially Chiral Drug of Abuse. Rigorous Definition of Spin Systems.

Ronnie Benshafrut[a]; Kevin Bynum[b]; Robert Rothchild[bc]
[a] Department of Organic Chemistry, The Hebrew University of Jerusalem, Givat Ram, Jerusalem, Israel
[b] Science Department, The City University of New York, John Jay College of Criminal Justice, New York, NY [c] The Doctoral Faculty, The Graduate School and University Center, New York

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NMR STUDIES OF HINDERED ROTATIONS IN DRUGS. USE OF ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS WITH MECLOQUALONE, AN AXIALLY CHIRAL DRUG OF ABUSE. RIGOROUS DEFINITION OF SPIN SYSTEMS.

Key Words: Dynamic NMR, One- and two-dimensional NMR, COSY, Restricted rotation, Stereochemistry, Enantiomers, Sedative/hypnotics, $Eu(FOD)_3$, $Eu(HFC)_3$.

Ronnie Benshafrut[a], Kevin Bynum[b], and Robert Rothchild[b,c]*

a) The Hebrew University of Jerusalem, Department of Organic Chemistry, Givat Ram, Jerusalem, Israel 91904;
b) The City University of New York, John Jay College of Criminal Justice, Science Department, 445 West 59th Street, New York NY 10019-1128; c) The Doctoral Faculty, The Graduate School and University Center, City University of New York

ABSTRACT

The axially chiral sedative/hypnotic drug of abuse, mecloqualone, 1, has been studied in $CDCl_3$ by ^1H NMR at 60 and 300 MHz with the added 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 LSR, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), 3. Rigorous distinctions between the two $(CH)_4$ spin systems of 1 with added 2 or 3 were achieved by two-dimensional homonuclear chemical shift correlation

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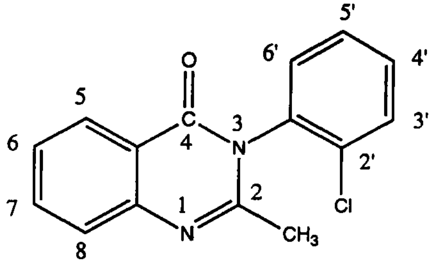
* To whom correspondence should be sent at John Jay College (for R.R.)

spectroscopy, COSY. Substantial upfield ("anomalous") shifts were observed for several nuclei of 1 with each LSR. Use of the chiral 3 elicited enantiomeric shift differences with baseline separations for several nuclei that should permit direct determinations of enantiomeric excess. COSY spectra allow determination of the relative sense of magnetic nonequivalence of selected nuclei of 1 with 3.

INTRODUCTION

Mecloqualone, 1, known as 3-(2-chlorophenyl)-2-methyl-4(3H)-quinazolinone, is a sedative/hypnotic listed in Schedule I of the Controlled Substances Act in the U.S. (1). It is a close analog of the better known methaqualone (MTQ), but where MTQ possesses a 2-methylphenyl, 1 has a 2-chlorophenyl. Hindered rotation about the N-aryl bond in MTQ has previously been demonstrated, leading to the existence of atropisomers and resolvable enantiomers. Thus, MTQ is axially chiral. We have earlier employed achiral and chiral lanthanide shift reagents (LSR) for studies of MTQ and demonstrated the potential of a chiral LSR for determination of enantiomeric excess due to the axial chirality (2). Related compounds have also been studied with LSRs, including a metabolite of MTQ (3) and the skeletal muscle relaxant, afloqualone (4). Axial chirality in the potential anti-psoriatic agent Sch40120, due to hindered N-aryl rotation, has been examined (5). Recently, LSR studies have been reported for chiral (famprofazone) (6) and achiral (antipyrine) (7) pharmaceuticals with potentially hindered N-phenyl rotations, and both ^{1}H and ^{13}C NMR have been discussed in relation to N-phenyl conformations in a series of antipyrine analogs (8). Hindered N-aryl rotations and potential axial chirality are therefore of much significance.

We wanted to examine mecloqualone, 1, with both achiral and chiral LSRs. The achiral tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III),



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2, known as Eu(FOD)$_3$, and the chiral tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III), 3, known as Eu(HFC)$_3$ or Eu(HFBC)$_3$, were selected, for potential spectral simplification and direct determination of enantiomeric excess, if rotation about the N-C_6H_4Cl bond in 1 were slow (on the NMR timescale). In compounds such as MTQ and its metabolite, as well as 1, the ^{1}H NMR assignments, with or without added LSR, are non-trivial. Each of these compounds may be considered to possess two separate $(CH)_4$ spin systems, i.e., a-b-c-d and a'-b'-c'-d' (= e-f-g-h), and have two possible LSR binding sites (at the carbonyl oxygen or the nitrogen at the 1-position of the quinazolinone framework). Earlier NMR studies for MTQ (2) and its metabolite (3) relied in part on chemical shift arguments for assignments. For MTQ, potential long range couplings to the methyl group of the $\underline{CH_3}C_6H_4$ moiety could be helpful. However, qualitative chemical shift arguments can be wrong. Also, the absence of the [o-tolyl] methyl in 1 further complicates assignments based on long range couplings. This present work, therefore, relies extensively on two-dimensional (2D) homonuclear ^{1}H-^{1}H chemical shift correlation experiments (COSY) to obtain unambiguous connectivity assignments without depending on qualitative chemical shift rationalizations. This is particularly crucial in spectra of 1 with added LSR, since lanthanide-induced shifts (LIS) may potentially occur to lower field as well as to higher fields. One would expect differing LIS magnitudes for the different nuclei depending on the relative contributions of the different LSR binding sites (9). In fact, these analyses can be quite complex, particularly since both "normal" downfield LIS values as well as "anomalous" upfield shifts may be observed with europium LSRs in these systems (2-4,6).

EXPERIMENTAL

Racemic 1 was kindly provided as the free base from the Research Triangle Institute (Research Triangle Park, NC) through the Research Technology Branch of the National Institute on Drug Abuse (Rockville, MD). $CDCl_3$ (99.8 at % D) and shift reagents were obtained from Aldrich Chemical Corp. (Milwaukee, WI 53201). $CDCl_3$ was dried and stored over 3Å Molecular Sieves. Drug and LSRs were stored in a desiccator over P_2O_5 or anhydrous $CaSO_4$ and were used as supplied. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS) as internal standard at 0.00 ppm. Runs with added LSR were obtained by accurately weighing solid LSR directly into the NMR sample tube, and shaking to dissolve, or by addition of weighed portions of a stock solution of LSR in $CDCl_3$. NMR spectra were acquired using a 60 MHz CW spectrometer (Varian EM360A) with a probe temperature of 28°, or on 300 MHz FT-NMRs. The latter work employed either a Bruker ACF300 with QNP probe and ASPECT A3000 data system (ambient temperature) or a General Electric QE-300 with 27° probe temperature. For nuclei which exhibited enantiomeric shift differences ($\Delta\Delta\delta$) in the presence of the chiral LSR, 3, reported chemical shifts are the average values for the two enantiomers.

RESULTS AND DISCUSSION

The 300 MHz ^1H reference spectrum for 1 is shown in Figure 1. Five separate 1H intensity aryl H multiplets are seen, centered at (ppm): 8.29, dd(J=7.9,1.0); 7.79, approx dt (J=8.3, 1.4); 7.70, d (J =7.8); 7.63, mult.; and 7.35, mult. The latter two multiplets present a mirror image

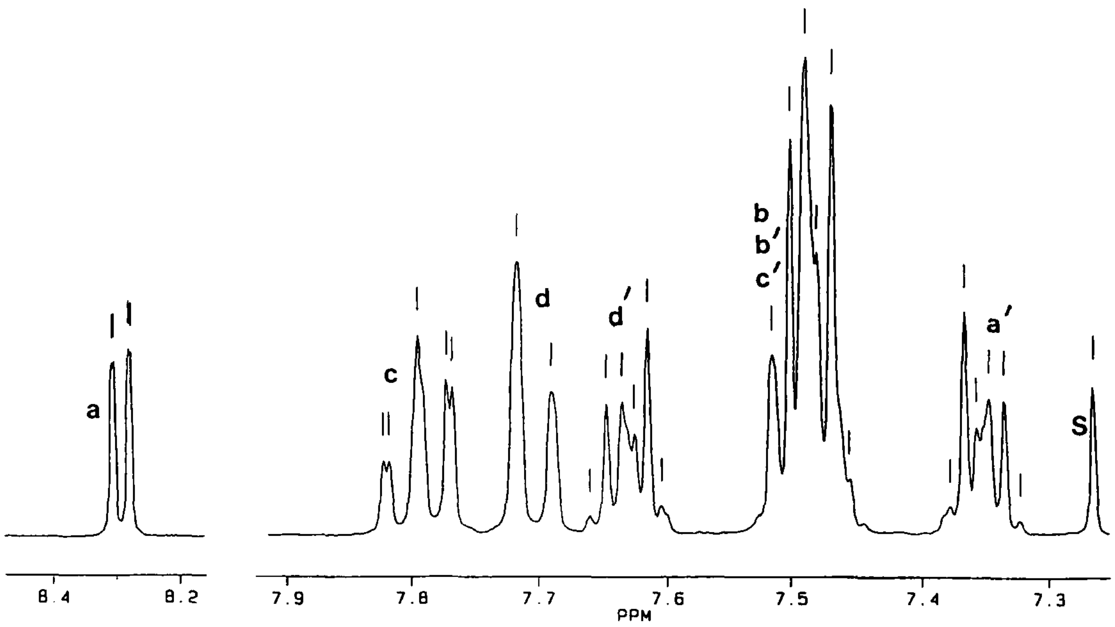


Figure 1. The 300 MHz ^{1}H NMR spectrum of 1 in $CDCl_3$, 0.0233 molal, ambient temperature, aryl region. (The $CHCl_3$ impurity is noted S.)

appearance. The 7.79 ppm and 7.70 ppm distinctly lean towards each other. A complex 3H intensity multiplet is centered at 7.49 ppm. The 3H methyl singlet appears at 2.24 ppm. Thus, even at 7 Tesla, three of the aryl protons of 1 are closely overlapped. Our primary interest was an unambiguous separation of the two $(CH)_4$ spin systems. One of these systems corresponds to the aryl H-5,6,7 and 8 positions of the quinazolinone ring, i.e., a-b-c-d, and the other to H-3′,4′,5′ and 6′ of the chlorophenyl moiety, i.e., a′-b′-c′-d′ (= e-f-g-h). The two spin systems were established from COSY spectra. The "high resolution" COSY90 spectrum (Figure 2) shows crosspeaks from the lowest field doublet at 8.29 ppm ("a") to the approximate triplet at 7.79 ppm and the multiplet at 7.49 ppm. The leaning doublet at 7.70 ppm is correlated to both the 7.79 and 7.49 ppm absorptions. The high resolution COSY allows crosspeaks to be discerned as 3x3 (triplet to triplet) or 2x3 (doublet to triplet) matrices. For near-first order systems, protons at the ends of the $(CH)_4$ spin system should be gross doublets, e.g., a-b-c-d, and the non-terminal protons should be gross triplets, e.g., a-b-c-d. Similarity in the crosspeak intensities do not permit distinguishing b versus c, that is, we do not know whether the proton vicinal to the 8.29 ppm doublet ("a") resonates at 7.79 or ca. 7.49 ppm. The answer is suggested by the fact of the severe leaning between the 7.79 and 7.70 ppm signals, implying that they are strongly coupled to each other through a large ^3J vicinal coupling, and would constitute c (triplet at 7.79 ppm) and d (doublet at 7.70 ppm). Confirmation is obtained from a full-spectrum COSY with low digital resolution (GE "Quick COSY hypercomplex TPPI") in which the most intense off-diagonal crosspeaks are seen mainly for ^3J vicinal couplings with much weaker responses for the long-range ^4J "W" couplings (spectrum not shown). This alternative experiment incontrovertibly establishes the a-b-c-d spin system with b as part of the 3H multiplet and c as the 7.79 ppm triplet. The second

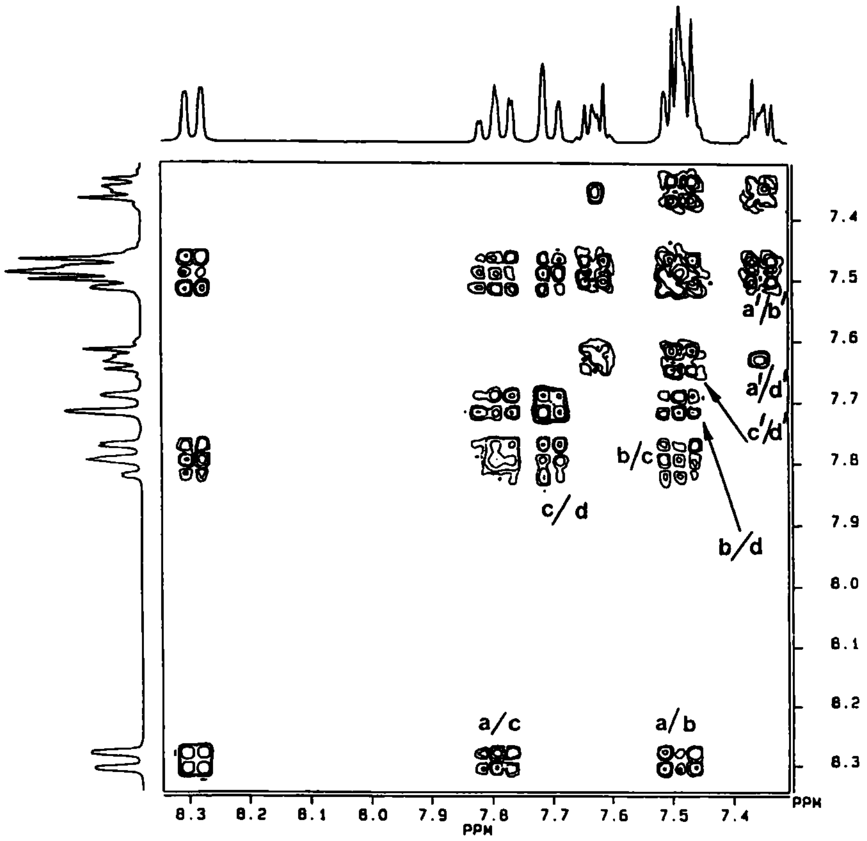


Figure 2. "High Resolution" 300 MHz COSY90 spectrum of 0.0233 molal 1 in $CDCl_3$ (aryl region). Spectral width in f_2 was 312.3 Hz. Spectrum is in the magnitude mode, with 2 dummy scans and 8 acquisitions for each of 128 increments in t_1, zero-filled once in the f_1 dimension and twice in f_2 for a final data matrix of 512 x 256. Data were processed with unshifted sine-bell apodization in both dimensions, and symmetrized. Standard Bruker software was used.

$(CH)_4$ spin system consists of mirror-image multiplets near 7.63 and 7.35 ppm plus two remaining hydrogens absorbing within the 3H multiplet ca. 7.49 ppm. In contrast to the clear gross doublets or triplet patterns seen for a,c and d, the complex multiplets at 7.63 and 7.35 ppm must reflect higher order effects, and may be "virtual coupling." For example, if the 7.63 and 7.35 ppm signals arise from the terminal protons of the second spin system, i.e., a′-b′-c′-d′ (alternatively, e-f-g-h), they would be strongly coupled (via vicinal ^3J coupling) to the non-terminal protons, b′ and c′ (f and g). These non-terminal protons have nearly identical chemical shifts and are about equally separated from the terminal proton signals, a′ and d′. Virtual coupling could account for the large number of lines in these signals (10). In the low-digital resolution "Quick COSY," strong crosspeaks of vicinal coupling are seen from the ca. 7.49 ppm (3H) multiplet to each of the complex multiplets at 7.63 and 7.35 ppm, with a very much weaker crosspeak between the 7.63 and 7.35 ppm signals. Thus, these 1H multiplets must be due to terminal protons a′ and d′ (= e and h) in the second $(CH)_4$ spin system, with the weak crosspeak denoting the very long range ^5J coupling between them. This completes the rigorous separation of the two spin systems.

During the initial studies of 1 at 60 MHz, we examined nine different [2]/[1] molar ratios up to 1.09 (with 0.355 molal 1) and ten different [3]/[1] molar ratios up to 1.02 (with 0.378 molal 1). LSR 2 provided good spectral simplification, resulting in only a single pair of aryl protons showing overlapped signals for [2]/[1] ratios from 0.68-1.09. Within this window, three clear doublets were seen to low field and three clear triplets to higher field, with a 2H intensity multiplet (consisting of an overlapped doublet and triplet) at intermediate shift, as shown in Figure 3. The simple doublets and triplets implied breaking of the virtual coupling seen for unshifted 1.

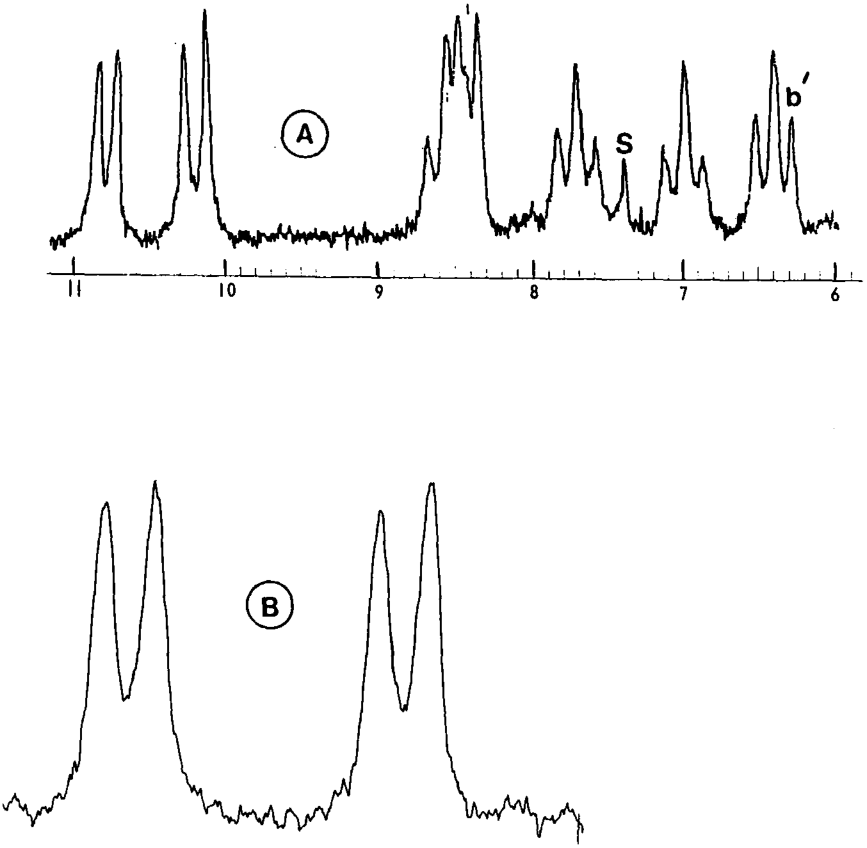
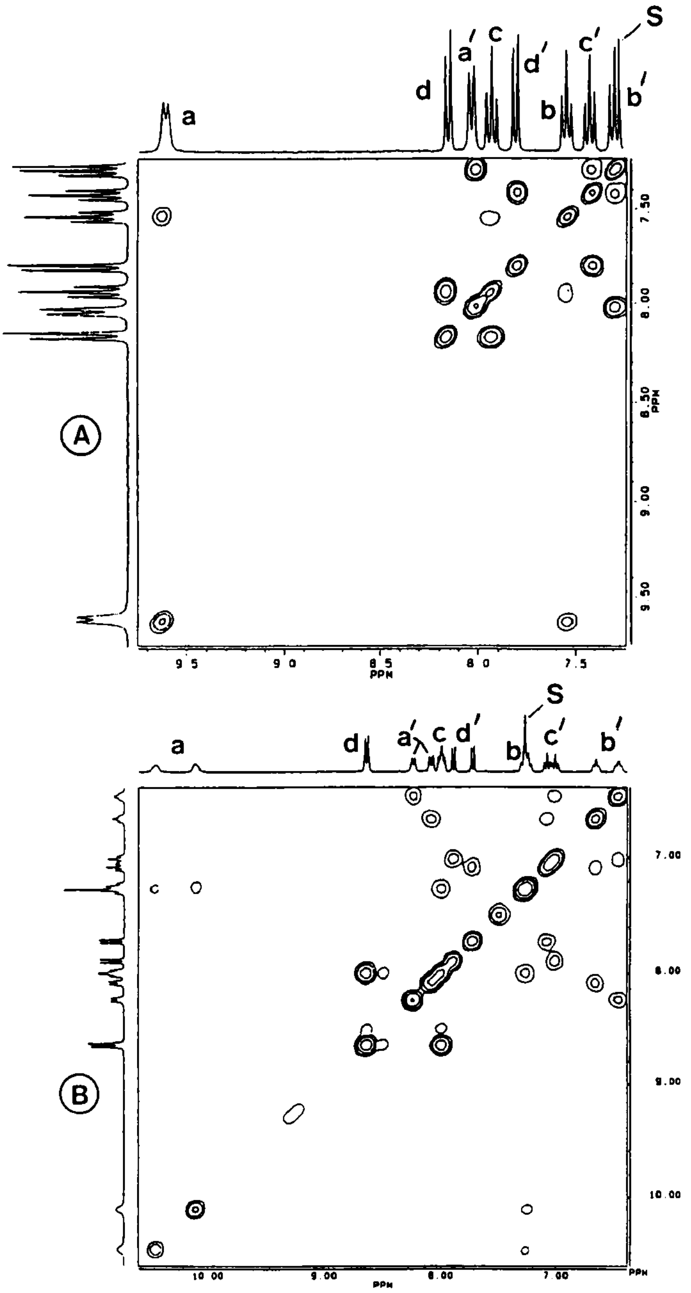


Figure 3. The 60 MHz ^1H NMR spectra of 1, at 28° in $CDCl_3$: (a) 2/1 molar ratio = 0.951; only the aryl region signals are shown; (b) 3/1 molar ratio = 0.642; expansion of lowest field doublet signals of nucleus a for the two enantiomers, centered at 12.75 ppm with $\Delta\Delta\delta$ = 43.4 Hz.

With the chiral 3, many overlapping aryl signal multiplets resulted at all 3/1 ratios due to additional peaks resulting from induced $\Delta\Delta\delta$. This added spectral complexity made it evident that clear assignments and measurement of $\Delta\Delta\delta$ magnitudes would require higher field spectra and 2D capabilities. Clear $\Delta\Delta\delta$ was seen in the 60 MHz spectra of 1 with 3, however, for the lowest field doublet, even with 3/1 molar ratios as low as 0.076, with near-baseline separation of these signals for 3/1 ratios of 0.35 or more; see Figure 3. Thus, even at 60 MHz, direct % e.e. determinations should be possible. However, because of assignment difficulties for these low field spectra, we will not present this data in further detail.

We were eager to pursue the LSR studies of 1 using a 300 MHz FT-NMR spectrometer to possibly take advantage of improved sensitivity and dispersion, and most importantly, to employ 2D COSY correlation spectra for proper assignments and elucidation of observed $\Delta\Delta\delta$. This series of experiments employed COSY45 or COSY90 spectra with coarse digital resolution. For example, selecting only the aryl proton region with a 2/1 molar ratio of 0.34, i.e., from ca. 7.2-9.8 ppm, using 64 increments in f_1, with two dummy scans and four acquisitions at each increment, as little as 11-12 min total acquisition time was needed. With digital resolution of ca. 6 Hz/point in f_2, fine structure in the COSY crosspeaks was not observed, and vicinal couplings were essentially the only correlations seen. At this 2/1 ratio, four separated triplets and four separated doublets were seen, allowing the full connectivity a-b-c-d and a′-b′-c′-d′ (= e-f-g-h) to be readily mapped out (see Figure 4). With $Eu(FOD)_3$, two aryl protons, b′ and c′ (=f and g) are progressively shifted to higher field; these would be "anomalous shifts" since tris-β-diketonates of Eu(III) are normally considered downfield reagents. It is clear that with 1, as with analogs studied earlier, the lanthanide-induced shifts are critically dependent upon the angular part of the simplified McConnell-Robertson equation, not simply the r^{-3} distance part (11). [Note: In our labeling, we have designated the lowest field aryl doublet signal for unshifted and shifted 1 as a, and the highest field aryl triplet with added LSR as b′ (=f), i.e., b′ moves fastest to higher field.]

Increments of the chiral 3 were added to 1, and COSY spectra at 300 MHz were examined. The spectra of 1 shifted by 3 have added complexity because of enantiomeric shift differences. The COSY spectra now serve an added purpose. Not only can one define simple connectivity within the $(CH)_4$ spin systems, but one may hope to establish connectivity within each enantiomer, that is, determine the sense of magnetic nonequivalence for those nuclei with observed $\Delta\Delta\delta$. This is illustrated in Figure 4. With a 3/1 molar ratio of 0.66, signals for each enantiomer of 1 are essentially baseline resolved for four of the aryl protons: a, a′ (=e), b′(=f), and d′ (=h), with smaller $\Delta\Delta\delta$ magnitudes seen for b, c and c′ (=g). The COSY45 shows that the lowfield signal for a correlates to the lower field signal for b. The $\Delta\Delta\delta$ for c is not large enough (at this digital resolution) to distinguish its sense of magnetic nonequivalence. In the second $(CH)_4$ spin system, the lower field b′ triplet is clearly correlated to the lower field c′ triplet, but note that this is correlated to the higher field doublet d′. Lastly, the lower field b′ triplet correlates to the higher field a′ doublet. Thus, a′ and d′ have opposite senses of magnetic nonequivalence relative to b′ and c′. The same enantiomer for which the a′ and d′ resonances are at lower field produces the b′ and c′ signals at higher field. This might be simply explained if the origins of the observed $\Delta\Delta\delta$ were associated with differential binding constants for the chiral LSR 3 with the two enantiomers of 1. The more tightly bound enantiomer of 1 might be expected to exhibit larger LIS magnitudes (12,13). Indeed, the nuclei b′ and c′ exhibit "anomalous" upfield shifts (with both 2 and 3), so that the


a
d
a′
c
d′
b
c′
S
b′
A
9.5
9.0
8.5
8.0
7.5
PPM
7.50
8.00
8.50
PPM
9.00
9.50
a
d
a′
c
d′
b
S
c′
b′
B
10.00
9.00
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PPM

b′ and c′ resonances showing greatest LIS magnitude (irrespective of direction of shift) are in the same enantiomer for which a′ and d′ signals have moved furthest downfield. Greater line broadening, leading to less signal height, is seen for the higher field b′ and c′ absorptions and for the lower field a′ signal, supporting this analysis. (The differential line broadening is not so obvious with d′.) Note that the use of COSY spectra to establish relative senses of magnetic nonequivalence is an extremely powerful method, since it can be applied to racemic samples, without the need for enantiomerically enriched material required for "spiking" experiments. For a recent example of the latter, see ref. (14).

Because the COSY-based assignments in the LSR-shifted spectra of 1 provide such rigor in distinguishing the two $(CH)_4$ spin systems, we are somewhat reluctant to introduce more speculative notes regarding more precise signal assignments and predominant LSR binding site preferences. However, it may be significant that in one of the $(CH)_4$ spin systems, a-d, only the a nucleus exhibits large $\Delta\Delta\delta$ with added 3, i.e., 123 Hz for a 3/1 molar ratio of 0.66, with b, c and d showing small $\Delta\Delta\delta$ (less than 15 Hz). In contrast, spin system a′-d′ (e-h) includes three nuclei exhibiting rather large $\Delta\Delta\delta$ of ca. 50-60 Hz, and only one (c′=g) shows a $\Delta\Delta\delta$ as low as 18 Hz with the same 3/1 ratio. If $\Delta\Delta\delta$ is enhanced for nuclei being close to a chiral center or chiral axis, and being close to bound LSR, this is suggestive that the a′-d′ system lies on the

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Figure 4. Aryl region COSY spectra of 1 (300 MHz ^1H). (a) ca. 0.0206 molal in $CDCl_3$, COSY45 with 2/1 molar ratio = 0.34; spectral width in f_2 was 761.0 Hz, with 64 increments in t_1, zero-filled once in f_1 and f_2 for a final data matrix of 256 x 128; (b) ca. 0.0218 molal in $CDCl_3$, COSY45 with 3/1 molar ratio = 0.66; spectral width in f_2 was 1282.1 Hz and other parameters as in (a). Both spectra were in the magnitude mode, with 2 dummy scans and 4 acquisitions for each t_1 increment. Data were processed with unshifted sine-bell apodization in both dimensions, and symmetrized. (Note: S =$CHCl_3$)

chlorophenyl ring, proximal to the chiral axis of 1. The quinazolinone positions H-5,6,7,8 are more remote from the chiral axis. Other factors might include LIS magnitudes and lanthanide-induced line broadening, but interpretations would be complicated if there are significant contributions from bound complexes with LSR at different binding sites. Figures 5 and 6 summarize the variation in chemical shifts for the proton resonances of 1 with added $Eu(FOD)_3$, or $Eu(HFC)_3$, respectively, and Figure 7 shows the $\Delta\Delta\delta$ dependence for 1 with added 3. It is clear that there is excellent potential for direct determination of enantiomeric excess (% e.e.) of samples of 1 with the $Eu(HFC)_3$ reagent, with full baseline resolution between the signals of the enantiomers of 1 for several nuclei. Unfortunately, the intense methyl signal is never fully baseline resolved and is not analytically useful. Thus, with 3 at 300 MHz, the valley heights for the methyl absorptions (relative to the average peak heights for the CH_3 signal of each enantiomer of 1) decreased from ca. 11% with 3/1 ratios of 0.15 or 0.30 to no better than ca. 6% with a molar ratio of 0.66. This degree of resolution was much more favorable than was seen in the 60 MHz work (at higher concentrations of 1 and 3). For these 60 MHz runs, valley heights for the CH_3 resonance decreased to ca. 45-55% with 3/1 molar ratios of 0.64-0.88, and were more than ca. 60% with 3/1 ratio of 1.02. The methyl signal was partly overlapped with an absorption of 3 at LSR levels that minimized the valley heights; this was not a problem at the lower concentrations employed in the 300 MHz runs. However, the robustness of the method for % e.e. measurements appears amply demonstrated using 3 at either 60 or 300 MHz, with the lowest field a absorption completely baseline separated. Thus, even the lower field NMR provides adequate dispersion, while the higher field NMR is highly useful despite the expectation that LSR-induced chemical exchange broadening would worsen as the square of the spectrometer field strength! (15)

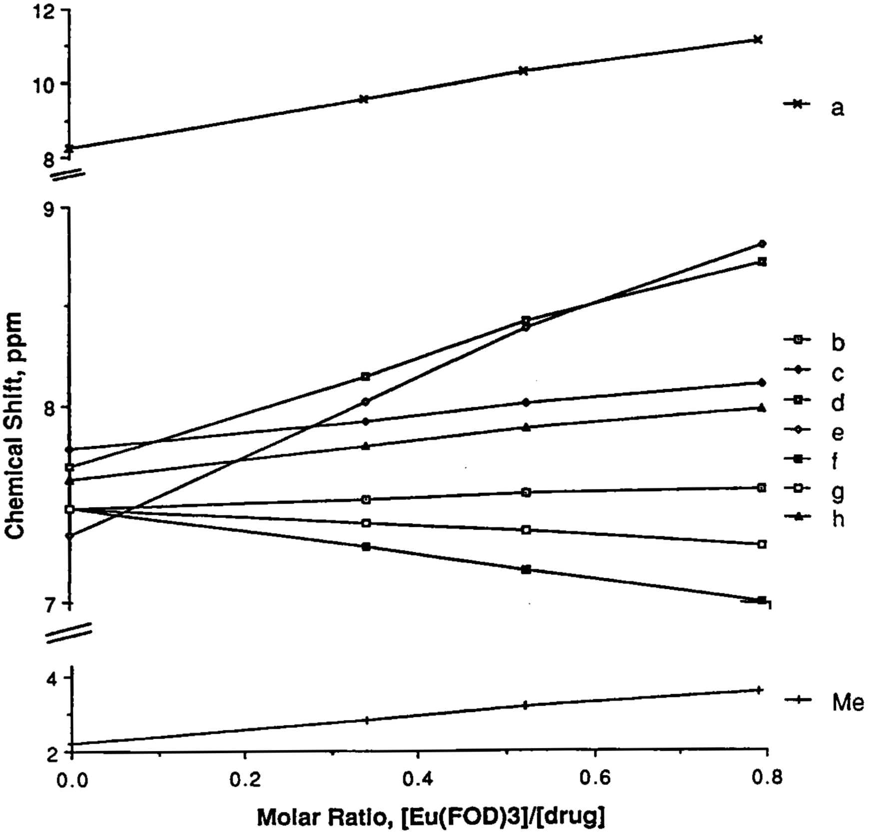

Figure 5. Variation of chemical shifts with molar ratio of $[Eu(FOD)_3]/[\underline{1}]$ from 300 MHz data.

Table 1 summarizes data from Figs. 5 and 6 with linear least squares line fitting applied to the plots of chemical shifts of the protons of 1 versus molar ratios of [LSR]/[1] for each LSR. Somewhat more curvature appears in the $Eu(HFC)_3$ series, presumably due to "leveling off" of the curves at the higher molar ratios; this is reflected by generally higher correlation coefficients, R, observed with 2 than with 3. With 2, all R values were 1.00 except for b

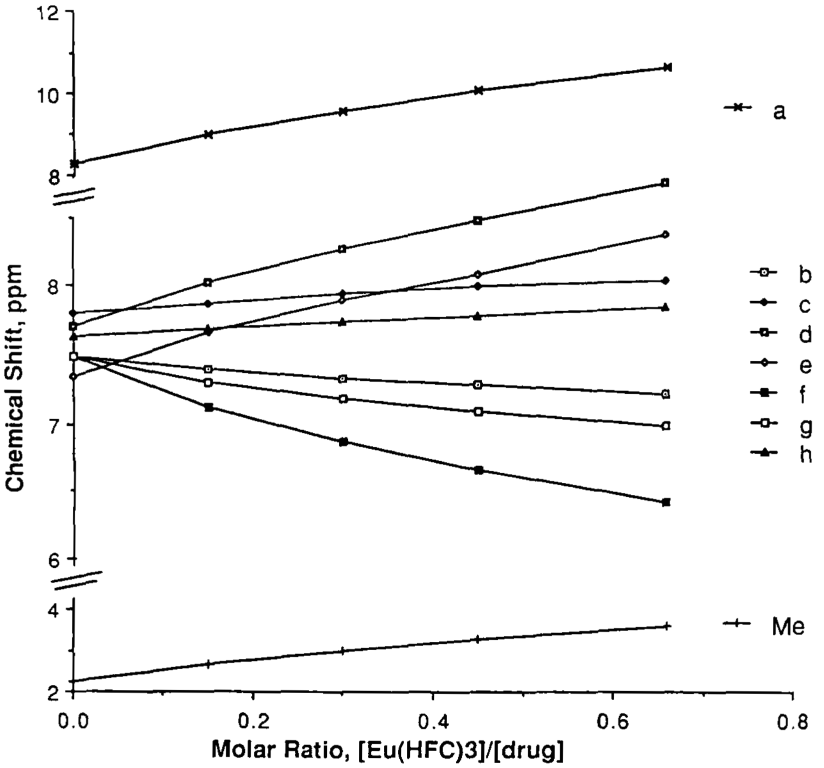

Figure 6. Variation of chemical shifts with molar ratio of [Eu(HFC)$_3$]/[1] from 300 MHz data.

which had R=0.99. With 3, R values of 1.00 were obtained only for d and d′ (=h), with R=0.98 for c and c′(=g), and with R=0.99 for other nuclei. Some qualitative differences between 2 and 3 may be seen. Perhaps most obvious is that with 2, only two nuclei (b′ and c′) exhibit upfield "anomalous" shifts, whereas with 3, nuclei b, b′ and c′ are all shifted upfield; nuclei b′ and c′ have appreciably greater magnitudes for these upfield shifts using 3 than with 2. [For examples and discussions of some "anomalous shifts" and relevant geometry effects, see refs. 16 and

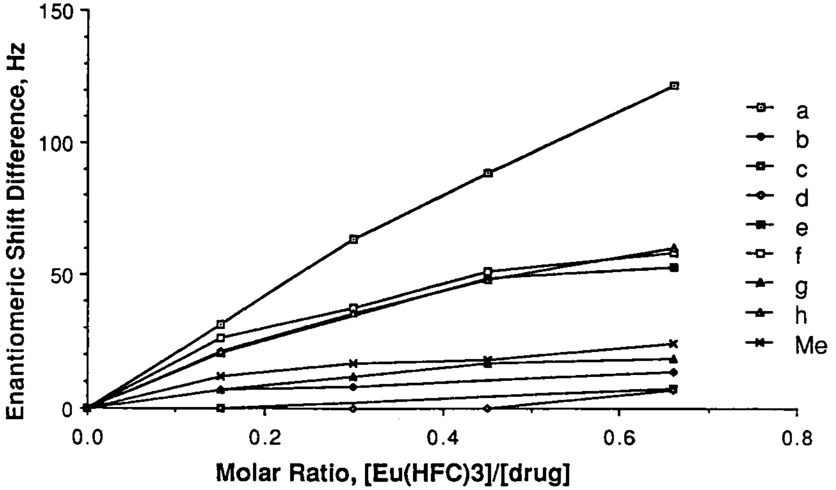

Figure 7. Variation of enantiomeric shift difference, $\Delta\Delta\delta$ (in Hz), with molar ratio of $[Eu(HFC)_3]/[\underline{1}]$.

17.] These results might be consistent with differences in bound complex geometries for 1 with 2 versus 1 with 3. Table 1 also shows normalized slope values, given relative to a value of 1.0 for the slope of the line assigned to the c resonance for each LSR. Though this choice is somewhat arbitrary, our selection is based on the following. We wanted a nucleus that displayed: (a) large enough shifts so that experimental measurement errors would be small, and (b) a signal that was free from overlaps in unshifted 1, to permit an accurate chemical shift at an [LSR]/[1] molar ratio of zero. Nuclei exhibiting anomalous shifts were excluded (as a "reference nucleus" for the Normalized Slopes) since their shifts might be excessively sensitive to bound complex geometry. Lastly, we avoided nuclei at the ends of the $(CH)_4$ spin systems, a,d,a′ (=e), d′ (=h), to reduce the likelihood of Fermi contact shift (through-bond) contributions to the observed LIS for nuclei that might be very close to bound LSR (18, 19). For example, H-

Table 1. Equations from least squares line fittings of chemical shifts versus [LSR]/[1] molar ratios. (See Notes below.)

	Eu(FOD)$_3$, 2		Eu(HFC)$_3$, 3	
Nucleus		Normalized Slopes		Normalized Slopes
a	y = 8.332 + 3.731x	9.012	y = 8.419 + 3.356x	9.616
b	7.489 + 0.136x	0.329	7.467 - 0.426x	-1.221
c	7.795 + 0.414x	1.0	7.808 + 0.349x	1.0
d	7.713 + 1.299x	3.138	7.751 + 1.538	4.407
a′(=e)	7.375 + 1.866x	4.507	7.400 + 1.479x	4.238
b′(=f)	7.490 - 0.613x	-1.481	7.403 - 1.599x	-4.582
c′(=g)	7.492 - 0.242x	-0.585	7.443 - 0.767x	-2.198
d′(=h)	7.642 + 0.467x	1.128	7.636 + 0.297x	0.851
Me	2.252 + 1.685x	4.070	2.309 + 2.032x	5.822

Notes: Line equations are based on least-squares line-fittings for plots of chemical shifts vs. molar ratios, from 300 MHz data of Figs. 5 and 6. Normalized Slope values are given relative to a value of 1.0 for the slope of the line assigned to c for each LSR. Correlation coefficients, R, are discussed in the text. See Results and Discussion.

5 and H-8 of the quinazolinone ring of 1 would be separated by only four or three bonds, respectively, from the binding sites for LSR bound to the carbonyl or to nitrogen N-1. Comparison of these Normalized Slope values with 2 versus 3 suggests moderate agreement except for nuclei exhibiting anomalous shifts. Relevant bound complex geometries may be quite sensitive to steric effects with 1 for 2 compared to 3.

The three nuclei in unshifted 1 exhibiting overlapping resonances, b, b′ (=f) and c′ (=g), were all assigned the approximate chemical shift of 7.49 ppm. With 2, the intercepts from the line equations for these nuclei were all 7.49 ppm, i.e., extrapolated to a [2]/[1] molar ratio of zero. This suggests that the 7.49 ppm estimated shift is close to the true correct value, since reagent 2 resulted in good linearity. With 3, where more curvature was apparent in the plots (of Fig. 6) the intercept values indicated good agreement for b, but deviated somewhat for b′ (7.40 ppm) and c′ (7.44 ppm). While it might be possible to obtain a more accurate set of values for the correct chemical shifts of b,b′, and c′ by successive iterations using these intercept values, we have not attempted that, since our primary goal was rigorous distinction of the $(CH)_4$ spin systems by use of COSY for LSR-shifted spectra.

CONCLUSIONS

We have examined the ^1H NMR spectra of the axially chiral abuse drug, mecloqualone, 1, with added achiral LSR, $Eu(FOD)_3$, 2, and with chiral $Eu(HFC)_3$, 3, in $CDCl_3$ at both 60 and 300 MHz. At 60 MHz, excellent spectral simplification is achieved with 2, with only a single pair of overlapping aryl proton resonances observed for 2:1 ratios from 0.68-1.09. With the chiral 3 at 60 MHz, baseline-separated doublet signals are seen for the lowest field absorptions of the enantiomers of 1, and $\Delta\Delta\delta$ is observed for other resonances of 1, showing that the rotation of the aryl rings of 1 is slow even on the timescale of the 60 MHz experiment. Thus, 1, like MTQ and analogs, is an axially chiral system; direct % e.e. determinations should be feasible with 3 even with a 1.4 T spectrometer. With a 7 T spectrometer (300 MHz ^{1}H observe frequency) [working with lower concentrations of 1], the achiral 2 readily provides full baseline separation of all eight aryl signals (essentially first order) and the chiral 3 provides substantial $\Delta\Delta\delta$ for most of the nuclei of 1, both aryl and methyl. Several of the aryl protons of 1 exhibit baseline separation for the signals of the enantiomeric atropisomers with added 3; % e.e. determinations should be readily achieved. (Quantitation for % e.e. should be based on peak areas rather than peak heights to avoid potential errors resulting from any slight differential lanthanide-induced line broadening of the signals of the two enantiomers.) It is notable that lanthanide-induced line broadening is rather low with either 2 or 3, even at 300 MHz.

Most importantly, we have rigorously defined the two aryl $(CH)_4$ spin systems of 1 with added LSR at 300 MHz using 2D COSY spectra at each LSR increment, completely eliminating the uncertainties of qualitative chemical shift arguments. Use of COSY not only is invaluable for spin system assignments but also, with 3, for determining the relative senses of magnetic nonequivalence for the absorptions of those nuclei exhibiting $\Delta\Delta\delta$; this technique avoids the need for spiking experiments.

Finally, using the rigorous COSY assignments, least squares line fitting was performed to generate line equations for the variations of chemical shift versus molar ratio of [LSR]/[1] for each proton of 1. Anomalous upfield shifts were found for two aryl protons with 2 and for three aryl protons with 3.

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