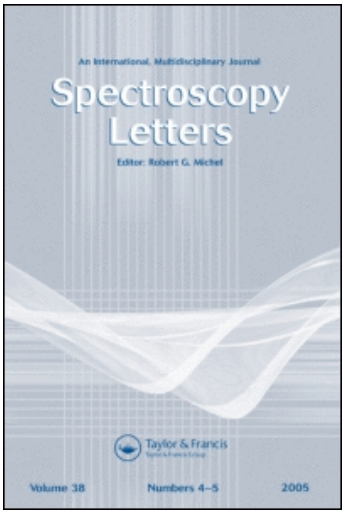

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NMR Studies of Drugs. Applications of Achiral and Chiral Lanthanide Shift Reagents to Acifran Methyl Ester. LSR Binding to a Multifunctional Substrate.

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NMR STUDIES OF DRUGS. APPLICATIONS OF ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS TO ACIFRAN METHYL ESTER. LSR BINDING TO A MULTIFUNCTIONAL SUBSTRATE.

Key Words: Europium, LSR, $Eu(FOD)_3$, $Eu(HFC)_3$, $Eu(FACAM)_3$, 4,5-Dihydro-5-methyl-4-oxo-5-phenyl-2-furancarboxylic acid methyl ester, Antihyperlipoproteinemic, Enantiomeric excess, Lanthanide-induced shifts, Analysis, Stereoisomer.

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ABSTRACT

The antihyperlipoproteinemic agent, acifran, has been studied as its racemic methyl ester, 1, by 60 MHz ^1H NMR in $CDCl_3$ solution at 28±1° 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), $Eu(FOD)_3$, 2, for spectral

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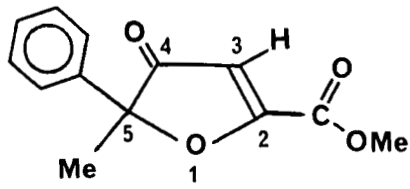
simplification, and with the chiral LSRs, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), $Eu(HFC)_3$, 3, and tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III), $Eu(FACAM)_3$, 4, for potential determinations of enantiomeric excess. Relative lanthanide-induced shift (LIS) magnitudes with the three LSRs were interpreted as consistent with major lanthanide binding at the 4-oxo carbonyl, but contrasting behavior in observed enantiomeric shift differences ($\Delta\Delta\delta$) with 3 versus 4 may suggest different bound complex geometries for 3 or 4 with 1.

INTRODUCTION

Acifran, known as 4,5-dihydro-5-methyl-4-oxo-5-phenyl-2-furancarboxylic acid, has been clinically evaluated as an antihyperlipoproteinemic (1,2); metabolic and pharmacokinetic studies in dogs and rats (3) and in humans (4) have been reported. The preparation of acifran and derivatives, as well as the resolution of acifran into its enantiomers was described (5,6). In addition to its potential importance as a drug, we were interested in acifran as part of our ongoing NMR studies. In particular, we were interested in examinations of acifran with lanthanide shift reagents (LSR). Despite its small size, acifran possesses numerous structural features



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that make LSR studies quite relevant. It is a multifunctional substrate. We planned to examine acifran as its methyl ester derivative, 1 (for reasons to be discussed below). As the methyl ester, 1 possesses different functional groups: a) exocyclic unhindered methyl ester; b) endocyclic hindered vinylogous ester. The dihydrofuran ring not only presents possibilities of monodentate binding of LSR at two sites (the carbonyl or the enol ether oxygen), but provides the potential for bidentate chelation of lanthanide in a potentially favorable five-membered ring via the appropriate conformer of the methyl ester carbonyl oxygen with the enol ether oxygen. In addition to investigating LSR binding sites with 1, we wanted to explore the possibility of using chiral LSRs for direct determination of enantiomeric excess (% e.e) of 1. Since acifran and 1 possess a single chiral center within a relatively rigid five-membered ring, adjacent to a possible LSR binding site (the 4-oxo group), these substrates were regarded by us as

structurally favorable for direct % e.e. determinations with chiral LSR. For example, the alpha methyl of a carbocyclic alpha methyl, alpha phenyl keto analog of 1 served as an excellent "reporter nucleus" for analytical purposes of e.e. determinations in a precursor to the drug, indacrinone, (7) with added chiral LSR.

In several studies with LSR, the (methyl) ester derivative of a carboxylic acid was found superior, either for enhanced solubility of substrate in the low polarity solvents used with most LSR, for avoiding possible decomposition of the LSR, or for enhanced binding of LSR to ester versus free acid (8-10).

LSR techniques and principles have been reviewed (11-14). We selected the achiral 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 LSRs, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), 3, known as $Eu(HFC)_3$ or $Eu(HFBC)_3$, and tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III), 4, known as $Eu(FACAM)_3$ or $Eu(TFC)_3$, for potential use in % e.e. determination.

EXPERIMENTAL

A sample of racemic acifran (free acid, AY-25712-19) was kindly provided by Wyeth-Ayerst Research,

Princeton NJ 08543. Chloroform-d (99.8 atom % D) was obtained from Aldrich Chemical Corp. (Milwaukee WI 53201) or Norell, Inc. (Landisville NJ 08326). Shift reagents were obtained from Aldrich and stored over P_2O_5 in a desiccator. $CDCl_3$ was dried over 3Å molecular sieves and stored in a desiccator over P_2O_5. Other reagents were used as received.

For runs with LSR, an accurately weighed portion of drug methyl ester, 1, was added to $CDCl_3$ in an NMR sample tube and dissolved by shaking. Increments of solid LSR were added directly to the sample, dissolved by shaking, and the spectra immediately obtained. For runs with 4, immersion in a warm water bath was used to facilitate solution of LSR. The $CDCl_3$ contained about 0.5% tetramethylsilane (TMS) as internal standard at 0.00 ppm. The 60 MHz spectra were obtained with a Varian EM360A spectrometer at a probe temperature of $28\pm1°$. In runs with the chiral LSRs 3 or 4, when enantiomeric shift differences ($\Delta\Delta\delta$) were observed, average chemical shifts for the antipodes are presented.

Preparation of Acifran Methyl Ester, 1:
The ester was produced under Fischer esterification conditions as described in the patent (5). Thus, in a 100 ml round-bottom flask was placed 398 mg acifran (1.82 mmol), absolute methanol (50 ml), 3 drops of

conc. H_2SO_4 and a magnetic stirrer. The flask was fitted with a reflux condenser and heated to reflux with stirring. After about 68 hours of reflux, the clear colorless mixture was allowed to cool to room temperature and was stirred for four days. Solvent was removed by rotary evaporator (aspirator pressure, ca. 50° water bath temperature) and the residue diluted with anhydrous diethyl ether. The solution was washed quickly with excess saturated aqueous $NaHCO_3$, dried (anhydrous $MgSO_4$), filtered, and solvent removed on a rotary evaporator (as above) to constant weight, yielding 295 mg of a colorless viscous oil which spontaneously crystallized (white crystals), 1, mp(uncorr.) 59° [liter. mp 60-62° (5)], 69.8% yield. This material was used directly for all NMR studies.

RESULTS AND DISCUSSION

A solution of 0.418 molal 1 in $CDCl_3$ displayed the following ^1H NMR spectrum (ppm): 1.79(3H, s, CCH_3); 3.97(3H, s, CO_2CH_3); 6.23(1H, s, C=CH); ca. 7.38 (5H, mult., C_6H_5); 6.23(1H, s, C=CH); ca. 7.38 (5H, mult., C_6H_5). This is in excellent agreement (within 0.04 ppm) of the previously reported spectrum (5). Adding increments of the achiral $Eu(FOD)_3$, 2, produced substantial lanthanide-induced shifts (LIS) summarized in Figure 1. Spectral simplification was achieved in separation of the ortho proton signals from the meta

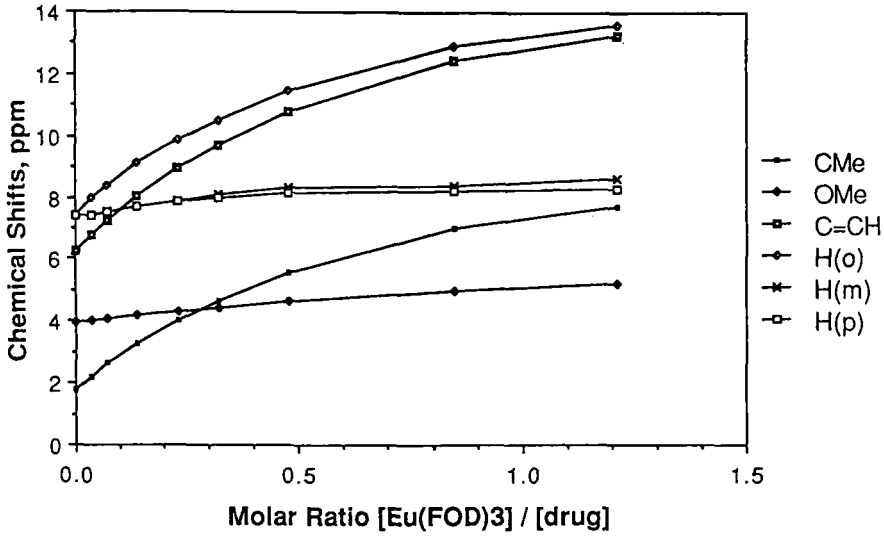

Figure 1. Variation of chemical shifts (δ, ppm) for nuclei of 1 with $[Eu(FOD)_3]/[1]$ molar ratio.

and *para*. Further discussion of relative LIS magnitudes relevant to proposed LSR binding is presented below.

With $Eu(HFC)_3$, 3, added to 0.420 molal 1, substantial LIS magnitudes were achieved (see Figure 2) as well as enantiomeric shift differences, $\Delta\Delta\delta$, for both the C-5 methyl and the vinyl H-3 protons (see Figure 3). The C-5 methyl resonance is potentially more attractive as an analytical "marker signal" (reporter nucleus) because of superior signal-to-noise ratios and larger $\Delta\Delta\delta$ magnitudes, but resolution between each enantiomer's CCH_3 signal by the valley

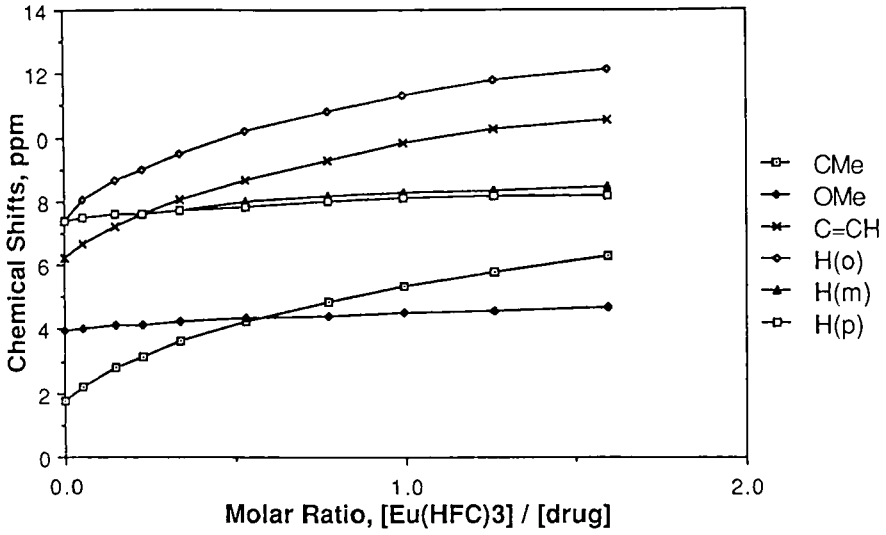

Figure 2. Variation of chemical shifts (δ, ppm) for nuclei of 1 with $[Eu(HFC)_3]/[1]$ molar ratio.

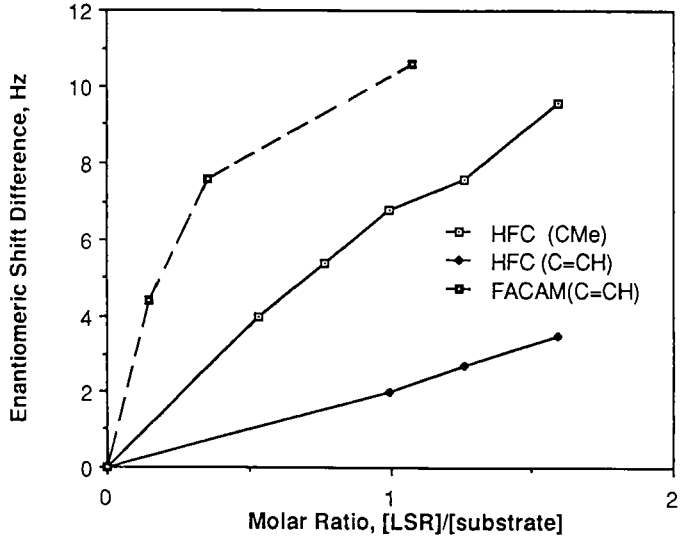

Figure 3. Variation of enantiomeric shift differences ($\Delta\Delta\delta$, in Hz) for nuclei of 1 versus $[Eu(HFC)_3]/[1]$ molar ratio (lower two solid lines) or $[Eu(FACAM)_3]/[1]$ molar ratio (uppermost broken line). Concentrations of 1 were 0.420 molal with 3 and 0.429 molal with 4.

height criterion was never better than about 40-50% (Figure 4). Surprisingly, despite the attachment of this methyl at the chiral center and near the (presumed) main LSR binding site, $\Delta\Delta\delta$ is of only limited analytical use. Because of very high solubility of 3, high 3:1 molar ratios (up to 1.59) could be examined; no viable conditions for % e.e. determination were observed. Significance of relative LIS magnitudes is discussed below.

When increments of $Eu(FACAM)_3$, 4, were added to ca. 0.41 molal 1, results were appreciably different than with 3. The LSR 4 appeared to be substantially less soluble than 3 in the solution of 1. A maximum 4:1 ratio near 1.08 was employed, but this should be regarded as a nominal value. After gentle heating to achieve solution (warm water bath) and filtration to remove a small amount of particulates [using a Pasteur filter tip pipet (15)] some further deposition of solids, presumably 4, occurred on standing at NMR probe temperature. Thus, the true 4:1 ratio at highest LSR level was presumably somewhat less than the nominal 1.08 value. In contrast, LSR 3 was remarkably soluble in the solution of 1, with a 3:1 ratio of 1.59 readily achievable.

Perhaps most significant are the differences between 3 and 4 with respect to induced $\Delta\Delta\delta$. With 4,

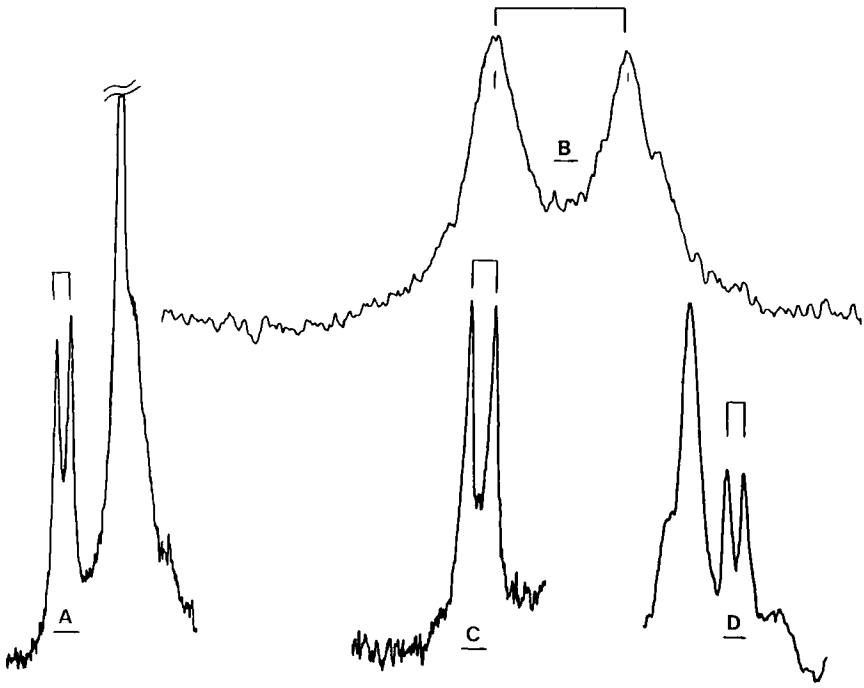

Figure 4. Spectral expansions of 1 with added chiral LSR. For each trace, the observed nucleus, chemical shift, $\Delta\Delta\delta$, and [LSR]:[1] ratio are shown; a) CCH_3, 4.87 ppm, 5.4 Hz, [3]:[1] ratio 0.771; b) CCH_3, 5.33 ppm, 6.8 Hz, [3]:[1] ratio 0.995; c) CCH_3, 6.30 ppm, 9.6 Hz, [3]:[1] ratio 1.59; d) C=CH, 7.23 ppm, 7.6 Hz, [4]:[1] ratio 0.353. Brackets show the signals of the enantiomers for each trace. Note that different spectral widths have been used for the different traces.

only the vinyl hydrogen H-3 exhibited $\Delta\Delta\delta$, with no separation between the signals of the antipodes of 1 for the C-5 methyl, the methyl ester or the aryl ortho proton signals, even at the highest 4:1 ratios. The $\Delta\Delta\delta$ magnitudes observed for H-3 with 4 were larger than

those seen for H-3 or the C-5 methyl in the presence of 3 at comparable molar ratios of [LSR]:1. (See Fig. 3). We attribute these results to differences in bound complex geometries of 1 with 3 versus 1 with 4. Despite the structural similarities of 3 and 4 there appear to be significant differences with these reagents in binding to 1; this is further discussed with respect to relative LIS magnitudes (see below). Significant differences in ability to elicit $\Delta\Delta\delta$ for different chiral LSRs had been noted earlier (16,17). Variations in chemical shift produced by 4 are summarized in Figure 5.

Analytical utility for direct determination of % e.e. for samples of 1 did not appear achievable at 60 MHz with either 3 or 4. With 4, the signal of the vinyl H-3 displayed moderate $\Delta\Delta\delta$ values but suffered from interference with the resonance of the aryl meta and para protons, as well as marginal signal-to-noise ratio. Valley heights for the H-3 absorption were not better than ca. 40%. See Figure 4.

Table 1 summarizes the LIS magnitudes for the proton NMR signals of 1 with added 2, 3 or 4. These data correspond to slope values from the plots of chemical shift versus [LSR]:[1] molar ratios from Figs. 1,2 and 5. The raw, unnormalized slope values as well as normalized values are presented; the normalized

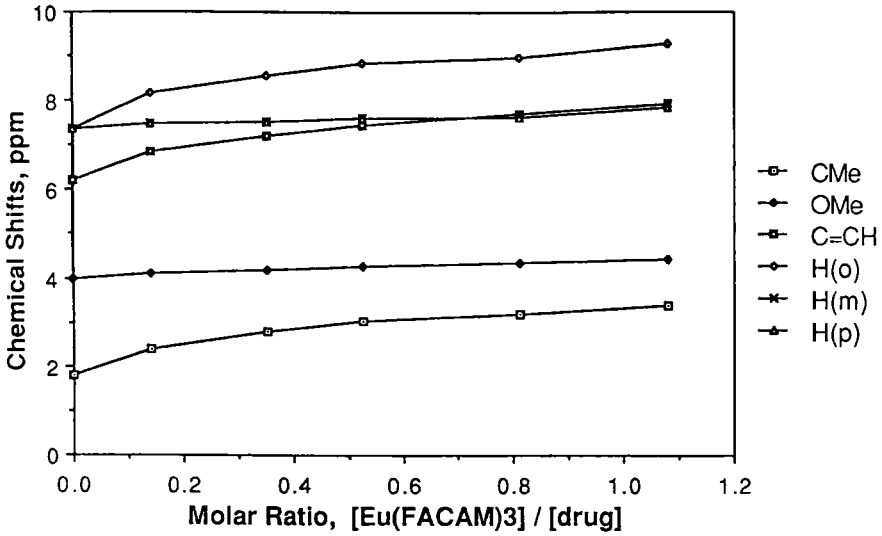

Figure 5. Variation of chemical shifts (δ, ppm) for nuclei of 1 with [Eu(FACAM)$_3$]/[1] molar ratio.

values are given relative to the slope for the CCH_3 signal defined as 1.0. This C-5 methyl resonance was selected for normalization for several reasons: a) it is sufficiently far from possible LSR binding sites to assure that Fermi contact shift contributions to the LIS will be negligible (18,19); b) the LIS magnitudes for this methyl are large enough to reduce the significance of experimental error in chemical shift measurements; and c) the methyl group is directly attached to the relatively rigid five-membered ring so that the position of this methyl with respect to the other nuclei of the cyclic framework of 1 is nearly fixed.

Table 1. Slopes of lanthanide-induced shifts vs. molar ratios of [LSR]/[acifran methyl ester] for nuclei of 1 with added 2, 3 or 4.

	$Eu(FOD)_3$ data		$Eu(HFC)_3$ data		$Eu(FACAM)_3$ data	
	Unnorm.	Normalized	Unnorm.	Normalized	Unnorm.	Normalized
Nucleus						
CMe	10.440	1.0	6.692	1.0	4.275	1.0
OMe	1.551	0.149	1.000	0.149	0.911	0.213
C=CH (H-3)	12.710	1.217	6.609	0.988	4.345	1.016
H(ortho)	11.896	1.139	8.157	1.219	5.396	1.262
H(meta)	2.147	0.206	1.393	0.208	0.841	0.197
H(para)	2.147	0.206	1.393	0.208	0.841	0.197

Notes: Slopes are based on least-squares line fitting from Figs. 1,2 and 5. Normalized values are given relative to a value of 1.0 for the CCH_3 resonance with each LSR. See Results and Discussion for the numbers of experimental points used, and resulting correlation coefficients, for the line equation of each nucleus. Note that the aryl H_{meta} and H_{para} resonances were not fully separated at the low LSR levels used for slope calculations, so that these nuclei are listed here with identical slope values. See text.

For acifran methyl ester with $Eu(FOD)_3$, correlation values of R = 1.00 were obtained for all nuclei except H_{ortho} (R = 0.99). Line equations used either four experimental points with a maximum 2:1 ratio of 0.141 (for CCH_3, C=CH and H_{ortho}) or five experimental points with a maximum 2:1 ratio of 0.232 for the other nuclei. With $Eu(HFC)_3$, only three experimental points were used, keeping the maximum 3:1 ratio to 0.149; R values of 1.00 were obtained for all nuclei except H_{ortho} (R = 0.98). For the LSR, $Eu(FACAM)_3$, only the first two experimental points were used in order to get the initial, steepest slopes, with an upper 4:1 ratio of only 0.143. Usually, simple monofunctional substrates which bind LSR strongly via a simple 1:1 bound complex stoichiometry are expected to exhibit (11,14) fairly linear plots of chemical shift versus [LSR]/[substrate] molar ratio up to molar ratios of about 0.5. Any "leveling" or "flattening" of the plot typically is most obvious at higher LSR levels. However, with acifran methyl ester, curvature was apparent in the plots from 2, 3 or 4 even at relatively low LSR levels. We have generally chosen to tabulate and compare the early (steeper) slopes observable at [LSR]/[1] ratios ca. 0.15 or less, even though this means that fewer experimental points are used to determine the line slopes. We confirmed that use of additional experimental points with higher [LSR]/[1]

ratios ca. 0.25-0.35 gave substantially lower slopes, quantitatively confirming the "leveling off" in the curves that was apparent by visual inspection. (With our runs with 4, we had primarily been seeking improved analytical utility for % e.e. analyses, using high levels of 4, so that extensive runs with very low 4:1 ratios were not acquired.) The fact that early nonlinearities, i.e., "leveling off", are seen with acifran methyl ester using all three LSRs may suggest the result of rather low binding constants of this substrate with the shift reagents, or may reflect the presence of more than one kind of bound complex from 1 with the LSRs (11,13,14). The relatively low numerical values of unnormalized ("raw") slopes presented in Table 1 are consistent with weak binding, and could result from intrinsically poor binding to the hindered vinylogous ester structure present in the ring of 1. Using the early parts of these curves for comparisons of the LSRs should permit more valid conclusions to be drawn. At the low levels of LSR employed here for the slope calculations, the meta and para protons of the phenyl ring were not well resolved; these nuclei are thus shown with identical slopes. High LSR levels, as expected, resulted in some separation between these signals, with larger LIS magnitudes for the meta protons.

Comparing the normalized slope values of Table 1 indicates generally excellent agreement for LSRs 2 and 3 for all nuclei except the olefinic proton, H-3. This nucleus, alpha to the endocyclic carbonyl, may be close enough to lanthanide bound at this carbonyl to result in significant Fermi contact shift contributions (18,19). With 4, a somewhat larger normalized slope value is seen for the ester OCH_3 resonance compared to values for 2 or 3. This is consistent with modestly different bound complex geometry with 4, possibly a greater fraction of binding at the ester carbonyl. This would also be in accord with the absence of observable $\Delta\Delta\delta$ for the CCH_3 with 4, and slightly larger $\Delta\Delta\delta$ magnitudes for the vinyl H-3, than with 3. If chiral LSR spends more time at the $-CO_2CH_3$ group, further from the chiral center and the CCH_3, these differences could be accounted for. However, it seems clear that predominant LSR binding with 2, 3 or 4 is at the endocyclic vinylogous ester carbonyl rather than at the methoxycarbonyl, based on relative slope magnitudes.

CONCLUSIONS

The antihyperlipoproteinemic drug, acifran, has been examined as its methyl ester, 1, for ^1H NMR studies at 60 MHz in $CDCl_3$ with added achiral LSR, $Eu(FOD)_3$, 2, or with chiral reagents, $Eu(HFC)_3$, 3, and

$Eu(FACAM)_3$, 4. Relative LIS magnitudes suggest that predominant LSR binding occurs at the hindered vinylogous ester carbonyl with each LSR. Rather low values of these induced shifts, together with obvious curvature ("flattening out") in plots of chemical shift versus [LSR]/[1] molar ratio even at low LSR levels, suggests that LSR binding of 1 is not strong. Average bound complex geometry with 2 or 3 appears similar, but 4 may involve somewhat more contribution from LSR bound at the methoxycarbonyl. This latter suggestion is also consistent with larger $\Delta\Delta\delta$ magnitudes for the CCH_3 signal with 3 versus the C=CH signal with 4. Neither 3 nor 4 achieves sufficient resolution of signals of the antipodes of 1 to permit analytical utility for % e.e. determination.

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