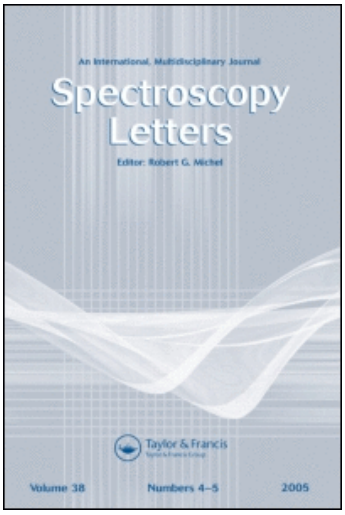

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NMR Studies of Agricultural Products. Applications of Achiral and Chiral Lanthanide Shift Reagents to the Fungicide, Triadimefon.

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NMR STUDIES OF AGRICULTURAL PRODUCTS. APPLICATIONS OF ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS TO THE FUNGICIDE, TRIADIMEFON.

Key Words: 1-(4-Chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone, Optical Purity, Enantiomeric Excess, Stereoisomer, Analysis, Europium, $Eu(FOD)_3$, $Eu(HFC)_3$, LSR, Spiking Experiment, Sense of Magnetic Nonequivalense.

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ABSTRACT

The 60 MHz ^1H NMR spectra of the systemic agricultural fungicide, triadimefon, 1, have been studied in $CDCl_3$ at 28±1° (as the racemic free base) 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 simplification, and with the chiral LSR, tris[3-(heptafluoropropylhydroxymethylene)-(+)-

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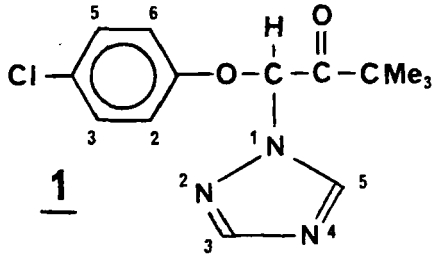
camphorato]europium(III), $Eu(HFC)_3$, 3, to induce enantiomeric shift differences ($\Delta\Delta\delta$) for several nuclei. Significant $\Delta\Delta\delta$ values were seen for the two protons of the heterocyclic ring, the OCH methine, and aryl H-2',6' of the chlorophenoxy ring. For each of these nuclei exhibiting $\Delta\Delta\delta$ with added 3, the $\Delta\Delta\delta$ magnitudes reached maximum values with 3:1 molar ratios ca. 0.18-0.29, and decreased with higher levels of 3. To confirm analytical utility of 3 for % e.e. determinations of 1, a nonracemic ("spiked") sample of racemic 1, with added R-(-) triadimefon, was examined with 3. At low 3:1 ratios, both triazole H-3 and H-5, as well as the OCH and aryl H-2',6' protons of (-)-1 showed a downfield sense of magnetic nonequivalence with (+)-3. With 3:1 ratios ca. 0.8, triazole proton H-3 reversed its sense of magnetic nonequivalence. The H-3 and H-5 signals were useful for % e.e determinations at this higher 3:1 ratio.

INTRODUCTION

NMR studies of drugs and agricultural products have been of special interest in our laboratories for a number of years. In particular, lanthanide shift reagents (LSR) have been studied as additives to these substrates, with achiral LSR used for NMR spectral simplification and chiral LSR for potential determinations of enantiomeric excess, % e.e. (1-4). Several examples of α-aminoketones have been examined, including the CNS stimulant cathinone (as the N-acetyl derivative) (5) and the antidepressant bupropion (6); related α-aminoamides studied with LSRs include the sedative-hypnotic thalidomide (7) and the cardiac antiarrhythmic tocainide (8). All four of these compounds possessed a chiral center at the alpha carbon next to the carbonyl. To extend these studies, we



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chose to examine the systemic agricultural fungicide, triadimefon, 1, 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone. Compound 1 has been reviewed (9,10). The partial resolution of the enantiomers of 1 by chiral HPLC using microcrystalline cellulose acetate as stationary phase has been reported (11) but only limited success was obtained; virtually no distinct valley was seen between the peaks of the enantiomers by UV absorbance detection. Analytical % e.e. determination required use of a polarimetric detector in series with the absorbance detector. We note that the dihydro analog of 1, known as triadimenol, has been chromatographically resolved into its enantiomers by GC (12) and by HPLC (13). Interestingly, the chiral GC stationary phase that sufficed to resolve all four stereoisomers of triadimenol, Chirasil-Val®, evidently failed to separate the enantiomers of 1 (12).

In these present studies, the achiral LSR tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), $Eu(FOD)_3$, 2, was used with 1 for NMR spectral simplification. To induce enantiomeric shift differences, $\Delta\Delta\delta$, the chiral reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), 3, known as $Eu(HFC)_3$ or $Eu(HFBC)_3$, was used.

EXPERIMENTAL

Samples of the racemic free base triadimefon and the (-) enantiomer were kindly provided by Bayer AG, 51368 Leverkusen, Germany. Chloroform-d was obtained from Aldrich Chemical Corp., Milwaukee WI 53201, or from Norell, Inc., Landisville NJ 08326. Shift reagents were obtained from Aldrich. Materials were used as received except as noted. NMR solvents were dried and stored over 3Å molecular sieves; LSR reagents were stored in a desiccator over P_2O_5 or anhydrous $CaSO_4$. R-(-)-Triadimefon, with stated $[\alpha]_D$ -24.2° ($CHCl_3$) and enantiomeric excess >99%, sample no. KTU-135, was employed for spiking experiments.

For runs with shift reagent, accurately weighed portions of drug were added to weighed solvent 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 60 MHz work, a Varian EM360A spectrometer with EM3630 lock/spin decoupler accessory was employed, using a probe temperature of 28±1° with ca. 1% tetramethylsilane (TMS) as internal reference at 0.00 ppm in the solvent. In runs with chiral LSR where $\Delta\Delta\delta$ was observed, average chemical shifts for the antipodes are presented.

RESULTS AND DISCUSSION

The 60 MHz ^1H NMR spectrum for 1 as a 0.3155 molal solution in $CDCl_3$ showed signals as follows (δ in ppm relative to TMS at 0.00 ppm): 1.28, 9H, s, t-butyl; 6.93, 1H, s, OCH; 6.97, 2H, d (J = 9.1 Hz), aryl H-2',6'; 7.28, 2H, d (J = 9.1 Hz), aryl H-3',5'; 8.02 and 8.50, each 1H, s, triazole ring protons. Additions of increments of the achiral $Eu(FOD)_3$ to a 0.316 molal solution of 1 produced significant lanthanide-induced shifts (LIS) for all the signals of 1; 2:1 molar ratios

up to 0.850 were employed. These results are summarized in Figure 1. Relatively small LIS magnitudes were seen for the t-butyl group and large LIS magnitudes were seen for the signals of the protons of the heterocyclic ring (see Table 1). Intermediate shift magnitudes were seen for the methine OCH signal. All signals displayed reasonable sharpness throughout the range of 2:1 ratios employed. We interpret this as consistent with 1 acting predominantly as a monodentate ligand for 2, with major binding of LSR at N-4 of the triazole ring. Significant LSR binding at the carbonyl oxygen would seem unlikely due to small LIS magnitudes seen for the t-butyl and OCH signals. Preferential binding of lanthanide at N-2 of the triazole would be expected to lead to larger LIS magnitudes for the OCH methine and the triazole H-3 signal, in particular. Instead, the similarity of LIS magnitudes for the two triazole protons, H-3 and H-5, favors major europium binding at N-4, separated from both of these protons by only two bonds. Certainly steric factors would disfavor binding at the carbonyl and N-2 compared to N-4. Also, the formal possibility of bidentate chelation of europium in a six-membered ring via N-2 and the carbonyl oxygen does not appear significant. Such localization of the metal would be expected to favor induced shifts for just one of the triazole protons, H-3, and for the OCH and t-butyl. In addition, bidentate chelation can cause significant signal broadening, not observed here (4).

With the chiral LSR, 3, added to 0.3155 molal 1, relative LIS magnitudes were qualitatively similar to results with 2 (see Table 1). However, significant enantiomeric shift differences, $\Delta\Delta\delta$, were observed for both protons of the triazole ring, for the

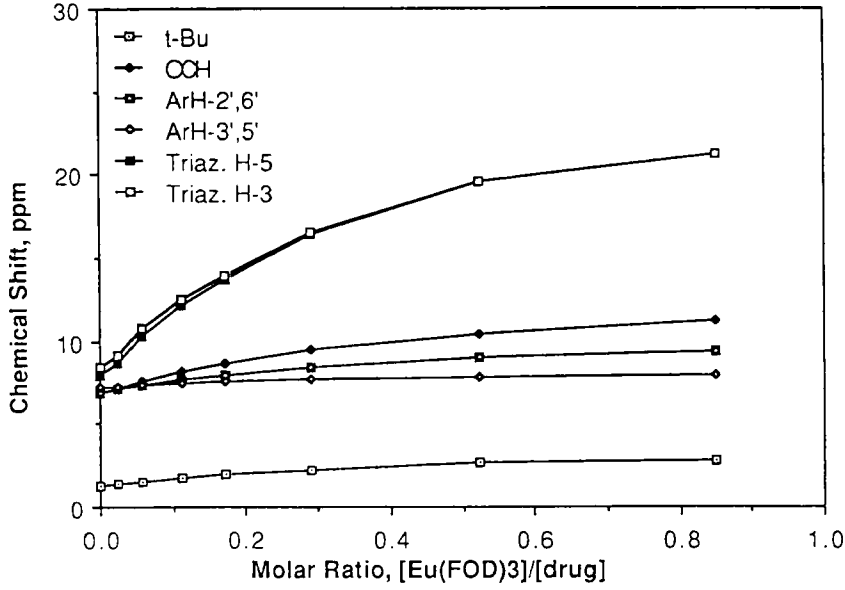

Figure 1. Variation of chemical shifts (δ, ppm) for nuclei of 1 with $[Eu(FOD)_3]/[1]$ molar ratio.

OCH methine and for H-2',6' of the chlorophenoxy ring. These results are summarized in Figures 2 and 3. Of special interest is the fact that $\Delta\Delta\delta$ magnitudes go through maxima and then decrease as the 3:1 ratios are raised. For one of the triazole protons, the $\Delta\Delta\delta$ magnitude appears to go through a maximum, decreases to ca. zero, and then increases again. This is consistent with a changeover in the sense of magnetic nonequivalence occurring at higher LSR levels, possibly suggesting changing geometry in the bound complex of 1 with LSR as a new complex of different stoichiometry forms, e.g., 2:1 LSR:1 versus 1:1 complex (14,15). One of the triazole proton signals exhibits maximum $\Delta\Delta\delta$ magnitudes at least two-and-one-half times greater than

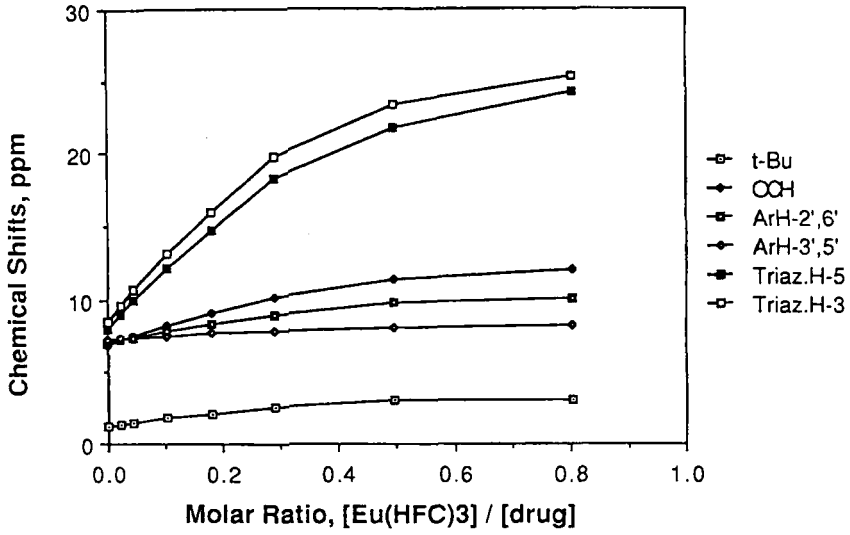

Figure 2. Variation of chemical shifts (δ, ppm) for nuclei of 1 with [Eu(HFC)$_3$]/[1] molar ratio.

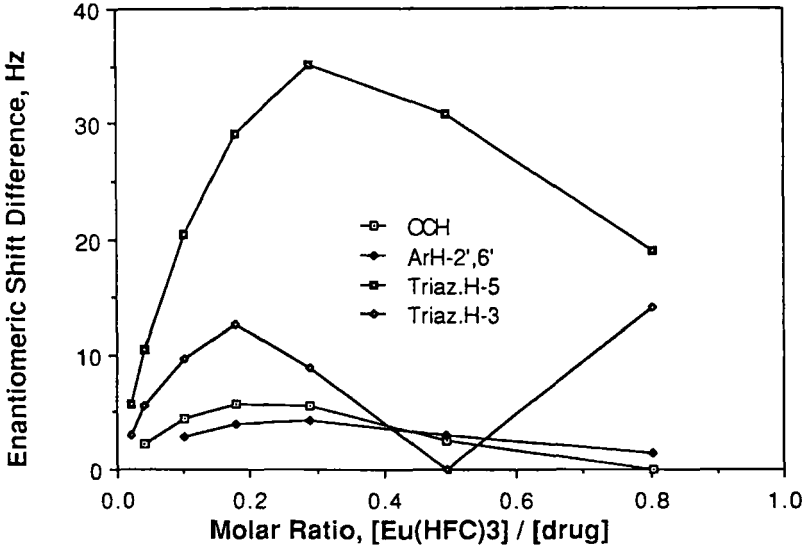

Figure 3. Variation of enantiomeric shift differences ($\Delta\Delta\delta$, in Hz) for nuclei of 1 versus [Eu(HFC)$_3$]/[1] molar ratio.

that of any of the other protons, although the LIS magnitudes of both triazole protons are very similar. Because of this, we tentatively assign to triazole proton H-5 the signal with highest $\Delta\Delta\delta$, initially at higher field for unshifted 1. The H-5 proton is closer to the chiral center at the methine OCH and might therefore exhibit the larger $\Delta\Delta\delta$ versus H-3.

The assignment of aryl H-2′,6′ as the higher field signals from the chlorophenoxy ring (relative to H-3′,5′) in unshifted 1 is based on expected values for substituent effects on the aromatic ring (for chlorine versus alkoxy) (16) as well as the larger magnitudes of LIS and $\Delta\Delta\delta$ expected for H-2′,6′ due to proximity to the basic LSR binding sites and to the chiral center.

In Table 1 we have shown the unnormalized ("raw") slope values for the nuclei of 1 with 2 or 3, in addition to normalized slope values relative to slopes of 1.0 assigned for the lines calculated from the OCH signals. Since the very high unnormalized slope values for the triazole H-3 and H-5 strongly suggest major LSR binding at N-4, these two protons could be close enough [two bonds away from N-4] to bound LSR to have appreciable Fermi contact shift contributions, and so were not selected as reference nuclei for the slopes. If there were significant contributions from a bound complex with lanthanide bound at the carbonyl, Fermi contact contributions at the alpha proton, OCH, might also be possible (17,18). Such contact shift contributions could affect the relative slopes shown in Table 1. In fact, the normalized slope values relative to the OCH protons are in very good agreement for data based on either LSR 2 or 3, except for aryl H-3′,5′ (ca. 12% difference) and the triazole H-5 (for which some contact contribution may be operative to produce a

Table 1. Slopes of lanthanide-induced shifts vs. molar ratios of [LSR]/[triadimefon] for nuclei of 1 with added 2 or 3.

	$Eu(FOD)_3$ data		$Eu(HFC)_3$ data	
Nucleus	Unnorm.	Normalized	Unnorm.	Normalized
t-Bu	4.126	0.394	4.375	0.386
OCH	10.474	1.0	11.322	1.0
ArH(2′,6′)	6.089	0.581	6.858	0.606
ArH(3′,5′)	1.812	0.173	2.188	0.193
H-3(Triaz.)	34.537	3.297	37.111	3.278
H-5(Triaz.)	33.217	3.171	41.272	3.645

Notes: Slopes are based on least-squares line fitting from Figs. 1 and 2. Normalized values are given relative to a value of 1.0 for the slope of the line for the signals assigned to the OCH resonance. See Results and Discussion for numbers of experimental points used in determining line equations and the correlation coefficients, R.

difference of ca. 15%). When the relative slopes were recalculated based on the aryl H-2',6' signals (values now shown), agreement was even better, with a maximum relative difference of only about 10% observed for the triazole H-5. Since the aryl protons of the chlorophenoxy moiety are far from potential lanthanide binding sites (at carbonyl or nitrogen), these aryl protons should exhibit negligible contact shift contributions. Our results may thus support some slight carbonyl binding of LSR and a modest contact shift term for the OCH. It is likely that the geometries of the main bound complexes of 1 with 2 or 3 are quite similar. The complicated behavior of $\Delta\Delta\delta$ magnitudes with variations in [3]:[1] molar ratio (as shown in Fig. 3) may, in part, reflect different rotamer conformations in bound complexes of differing stoichiometries (14,15) as noted above.

For the slope calculations of 1 with $Eu(FOD)_3$, correlation coefficients R=1.00 were obtained for the t-butyl, OCH and aryl H-2',6' protons, using five experimental points up to a 2:1 ratio of 0.171; for the aryl H-3',5', and the triazole H-3 and H-5 protons, R was 0.99. Using $Eu(HFC)_3$, R values of 1.00 were obtained for all nuclei, using six experimental points up to a 3:1 ratio of 0.290 (except for the triazole H-3 and H-5 protons, for which five experimental points were employed, up to a 3:1 ratio of 0.181).

Good analytical potential for direct enantiomeric excess determinations of samples of 1 using added 3 requires adequate signal-to-noise ratio, S/N, for the analytical signal, as well as adequate resolution between the signals of the two enantiomers for the absorption of a particular "reporter" nucleus. With 3, the unusual variations in $\Delta\Delta\delta$ magnitudes for the different nuclei of 1 result in recommended "windows"

of 3:1 molar ratios for optimal % e.e. determination. Resolution for the OCH resonance appeared best with a 3:1 ratio of 0.181 where it exhibited its greatest $\Delta\Delta\delta$ and a valley height of ca. 13%. With 3:1 ratios of ca. 0.29-0.49, near baseline resolution is achieved for the triazole proton initially at higher field for unshifted 1 and at higher field with added 3, with the higher molar ratio providing slightly superior results. Spectral expansions are shown in Figure 4.

For the "spiking" experiment, 39.9 mg of racemic 1 and 16.5 mg of the R-(-) enantiomer (with stated enantiomeric excess > 99%), for a total of 0.192 mmol of substrate, were dissolved in 0.6118 g $CDCl_3$ to give a solution 0.3138 molal in total triadimefon. Increments of chiral LSR 3 were added to produce [3]:[total triadimefon] molar ratios of 0.148, 0.305, 0.485 and 0.813, corresponding to low, intermediate and high LSR levels. Replicate scans of the spectral regions corresponding to the triazole H-3 and H-5 protons were acquired and peak height measurements were employed for analytical estimates of % e.e. Peak heights rather than integral step heights were employed because of limited S/N ratios and some overlap between the signals of corresponding nuclei in the two enantiomers of 1. Runs of racemic 1 with 3 indicated little or no differential lanthanide-induced line broadening for the antipodes, so that peak height measurements should, under these conditions, be more accurate than integrations. At the lower LSR levels for the nonracemic ("spiked") sample of 1 with added 3 (i.e., [3]:[total 1] of 0.148 or 0.305 molar ratio), replicate spectral scans for analytical purposes were not attempted, but qualitative peak height determinations unambiguously permitted establishing the sense of magnetic nonequivalence for the various

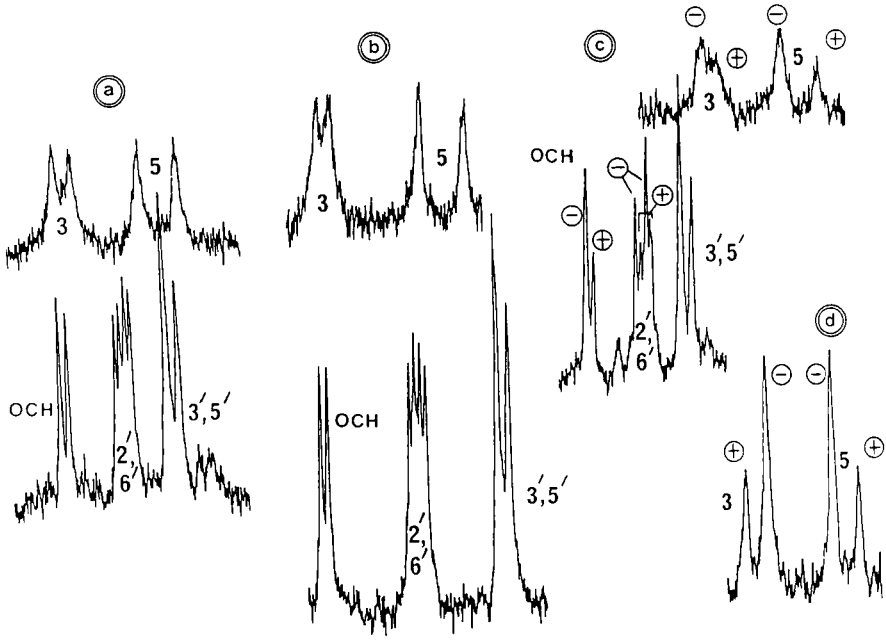

Figure 4. Spectral expansions or partial spectra of racemic (a,b) and nonracemic (c,d) 1 with added (+)-$Eu(HFC)_3$: a) racemic 1, 0.3155 molal, [3]:[1] ratio = 0.181, chemical shifts in ppm [$\Delta\Delta\delta$ in Hz]: H-3: 16.01[12.6]; H-5: 14.77[29.1]; OCH: 9.10[5.7]; H-2',6': 8.33[4.0]; H-3',5': 7.70[ca. 0.0]; b) racemic 1, 0.3155 molal, [3]:[1] ratio = 0.290, chemical shifts in ppm [$\Delta\Delta\delta$ in Hz]: H-3: 19.83[8.8], H-5: 18.27[35.0]; OCH: 10.23[5.6]; H-2',6': 9.00[4.2]; H-3',5': 7.90 [ca.0.0]; c) nonracemic "spiked" 1, (-):(+) ratio ca. 1.81, total 1 concentration 0.314 molal, [3]:[1] ratio = 0.148, approximate chemical shifts in ppm: H-3: 15.3; H-5: 14.2; OCH: 8.9; H-2',6': 8.2; H-3',5': 7.6; d) nonracemic "spiked" 1, (-):(+) ratio ca. 1.81, total 1 concentration 0.314 molal, [3]:[1] ratio = 0.813, representative trace showing H-3 (ca. 25.8 ppm) and H-5 (ca. 24.7 ppm). Assignments of enantiomers of 1 are shown by (+) and (-). See Results and Discussion. (Note that spectral scales are not uniform in the above spectra).

nuclei. Thus, with the [LSR]:[substrate] molar ratio of 0.148, for the R-(-) enantiomer of 1, the OCH, aryl H-2',6', and triazole H-3 and H-5 protons all exhibited a downfield sense of magnetic nonequivalence. (See Figure 4.) At the highest molar ratio of 0.813, the triazole H-3 has reversed its sense of magnetic nonequivalence, with the (-) enantiomer of 1 now appearing upfield. The triazole H-5 nucleus retains the downfield sense of magnetic nonequivalence for (-)-1. With [3]:[1] ratios of 0.485 or 0.813, the antipodal signals of the OCH nucleus were not well resolved. While only partially resolved, the triazole H-3 signal may be "crossing over" in its sense of magnetic nonequivalence between the 0.305 and 0.485 molar ratios of [3]:[1].

Analytical % e.e. determinations appeared most promising at the highest level of 3 using the above spiked sample, based on the triazole H-5 signal or the H-3 signal. Lower levels of LSR may actually result in greater $\Delta\Delta\delta$ magnitudes for H-5 but in our hands the H-5 signal exhibited less lanthanide-induced line broadening and superior S/N ratio at the higher LSR molar ratio. The severity of lanthanide-induced line broadening most commonly is seen to increase with higher LSR levels, along with lanthanide-induced shift (LIS) magnitudes (1,4). However, there are some cases in which the line broadening goes through a maximum at modest LSR levels and then decreases (19).

The "spiked" sample described above contained a ratio of (-)-triadimefon to (+)-triadimefon of approximately 1.827 assuming 100% e.e. for the spike of the (-) enantiomer; a ratio of 1.805 is calculated assuming a 99:1 ratio of enantiomers in the "spike" portion. Peak height ratios for the H-5 signals (with LSR:triadimefon ratio of 0.813) averaged 1.79 for a set

of six replicate scans, with a range from 1.61-2.09 (standard deviation, s = 0.183; coefficient of variation, C.V. = 10.2%; variance, s^2 = 0.0334 (20). The corresponding peak height ratios for the H-3 signals ranged from 1.70 - 2.03, with an average of 1.86 for a set of five scans (standard deviation 0.137; C.V. = 7.4%; variance = 0.0188). In a separate series of six replicate scans of the H-5 and H-3 signals for this spiked sample, the following results were obtained: H-5 mean peak height ratio 2.01 (s = 0.206; C.V. = 10.2%; s^2 = 0.0423); and H-3 mean peak height ratio 1.81 (s = 0.174; C.V. = 9.6%; s^2 = 0.0303) (20). This suggests substantial potential for analytical utility in % e.e. determinations, with the H-3 or H-5 signals being the preferred reporter nucleus, at [3] : [1] ratios ca. 0.8. Peak height ratios of the OCH signal with 3:1 ratio ca. 0.15 appeared less accurate despite superior S/N presumably because of overlap of the signals of the enantiomers.

CONCLUSIONS

The ^{1}H NMR spectra of racemic and nonracemic samples of triadimefon, 1, have been studied at 60 MHz in $CDCl_3$ at 28±1° with added $Eu(FOD)_3$, 2, or (+)-$Eu(HFC)_3$, 3. Lanthanide-induced shift magnitudes are interpreted as consistent with predominant LSR binding at N-4 of the triazole ring; a small amount of lanthanide complexation at the carbonyl may also contribute. Enantiomeric shift differences, $\Delta\Delta\delta$, were observed with added 3 for both triazole protons and for the OCH and aryl H-2',6' signals. "Spiking" experiments with R-(-)-1 showed a downfield sense of magnetic nonequivalence for all four of these protons with (-)-1 (ca. 0.3 molal) and low levels of (+)-3 (ca. 0.15 ratio of 3:1). With higher 3:1 ratios (ca. 0.8), the triazole H-3 signal reversed its sense of magnetic

nonequivalence. Analytical potential for direct determination of % e.e. of samples of 1 was demonstrated using peak height ratios of the triazole proton signals with a 3:1 ratio near 0.8. Less than 5% of a minor enantiomer should be detectable using the triazole proton signals with a 3:1 ratio near 0.8. Detection limits would appear limited by S/N ratio.

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