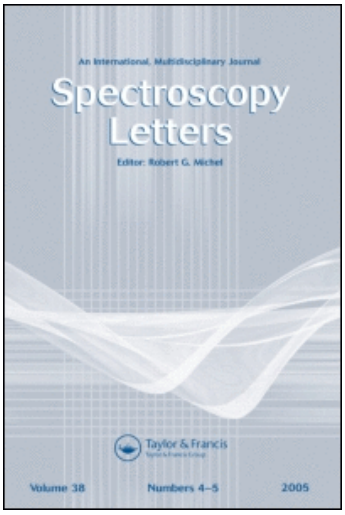
This article was downloaded by:
On: *30 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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

NMR Studies of Agricultural Compounds. Applications of Achiral and Chiral Lanthanide Shift Reagents to the Herbicide, Diclofop Methyl

Elisa Carbonell[a]; Robert Rothchild[ab]
[a] Department of Science, Toxicology Research and Training Center, The City University of New York, John Jay College of Criminal Justice, New York NY [b] The Doctoral Faculty, The Graduate School and University Center, City University of New York

To cite this Article Carbonell, Elisa and Rothchild, Robert(1995) 'NMR Studies of Agricultural Compounds. Applications of Achiral and Chiral Lanthanide Shift Reagents to the Herbicide, Diclofop Methyl', Spectroscopy Letters, 28: 3, 331 — 346
To link to this Article: DOI: 10.1080/00387019508009882
URL: http://dx.doi.org/10.1080/00387019508009882

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

SPECTROSCOPY LETTERS, 28(3), 331-346 (1995)

NMR STUDIES OF AGRICULTURAL COMPOUNDS. APPLICATIONS OF ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS TO THE HERBICIDE, DICLOFOP METHYL

Key words: 2-[4-(2,4-Dichlorophenoxy)-phenoxy]-propionic acid methyl ester, Europium, LSR, $Eu(FOD)_3$, $Eu(HFC)_3$, $Eu(FACAM)_3$, Analysis, Enantiomeric excess, Stereoisomer.

Downloaded At: 03:44 30 January 2011

Elisa Carbonell[a] and Robert Rothchild*[a,b]

a) The City University of New York, John Jay College of Criminal Justice, Department of Science, Toxicology Research and Training Center, 445 West 59th Street, New York NY 10019-1199; b) The Doctoral Faculty, The Graduate School and University Center, City University of New York.

ABSTRACT

The 60 MHz ^1H NMR spectra for the herbicide, diclofop methyl, 1, have been studied 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, and with the chiral LSRs, tris[3-

*To whom correspondence should be sent at John Jay College.

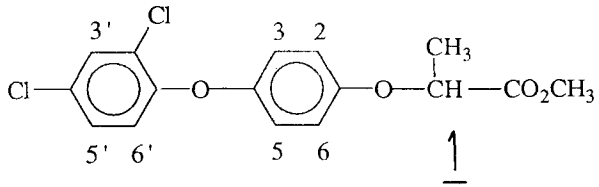
Copyright © 1995 by Marcel Dekker, Inc.

(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III)$_3$, Eu(HFC)$_3$, 3, and tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III), Eu(FACAM)$_3$, 4. Both 2 and 3 produced substantial lanthanide-induced shifts (LIS) consistent with predominant LSR binding at the ester carbonyl. Much smaller LIS magnitudes were observed with 4. Modest enantiomeric shift differences ($\Delta\Delta\delta$) were elicited with 3 for the OCH_3 and the CCH_3 resonances of 1. The former signal appears to offer greatest potential for the direct determination of enantiomeric excess of samples of 1, with 3:1 molar ratios ca. 0.3-0.4 resulting in valley heights as low as 33% of the average peak heights of the OCH_3 signals of the two enantiomers.

Downloaded At: 03:44 30 January 2011

INTRODUCTION

The free acid of Diclofop, and its corresponding methyl ester, known as Diclofop Methyl, 1, are of considerable interest for their herbicidal activity. The racemic methyl ester is known also as Hoe 023408 or methyl 2-[4-(2,4-dichlorophenoxy)phenoxy] propanoate. The class of aryloxyphenoxypropanoic acid derivatives and analogs has been reviewed (1); these compounds are notable for their selective herbicidal properties towards monocotyledonous species (rather than towards broad-leafed species), especially when applied post-emergence. Of special interest to us is the presence of a chiral center alpha to the carboxyl group. In general, the dextrorotatory R enantiomers in this series are the active herbicides for post-emergence applications, with about twice the racemate's activity; the S



1

enantiomers have almost no activity (1,2). When applied pre-emergence, racemization had been thought (1,2) to occur which largely eliminated the difference in activities. More recently, a microbially mediated conversion of the (S) enantiomer to the (R) enantiomer has been suggested (3a). Studies with 1 and the analog, Fenoxaprop Ethyl, showed that incubation of the separated enantiomers of the esters in soil led to rapid hydrolysis to the respective free acids. Analysis of the recovered esters by high performance liquid chromatography (HPLC) on a chiral stationary phase (CSP) of Chiralcel OK (cellulose tricinnamate absorbed on macroporous silica) indicated no racemization of these esters, but the hydrolyzed product acids had undergone inversion. In particular, the acids with S-configuration showed greater tendency for inversion than the R antipodes (3b).

Pure enantiomers in this series have been obtained by, for example, synthesis from chiral precursors or classical resolutions (2,3a). Recently, HPLC with a CSP was employed for the resolution of enantiomers of some free acid forms of the structurally related 2-aryloxypropanoic acids (using an α_1-acid glycoprotein CSP) and some related esters (using a "Pirkle-type" ionically bonded

Downloaded At: 03:44 30 January 2011

derivatized phenylglycine CSP) (4). From racemic diclofop methyl itself, basic hydrolysis to the racemic acid followed by resolution with (+)-cinchonine and re-esterification (CH_2N_2) resulted in the enantiomerically enriched antipodes of the methyl ester, 1; chiral syntheses starting from (-)-2-bromopropanoic acid or (-)-2-hydroxypropanoic acid ethyl ester yielded the (+)-(R) enantiomer of 1 (2). Nestler and Bieringer referred to the use of a chiral lanthanide shift reagent (LSR) for determination of enantiomeric excess of samples of 1, as well as polarimetric measurements (2). A related chiral LSR has been employed for the enantiomeric excess determination of the methyl ester of chlorazifop (3a).

Downloaded At: 03:44 30 January 2011

For some time, we have been interested in NMR examinations of pharmaceuticals or agricultural compounds using achiral and chiral LSRs for spectral simplification and studies of lanthanide binding sites, as well as for potential direct determinations of enantiomeric excess (% e.e.) with chiral LSRs. Theory and applications of LSR use have been reviewed (5-8). Because of the interest in 1, we undertook the 60 MHz ^1H NMR studies in $CDCl_3$ solution 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 with 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 $Eu(TFC)_3$.

EXPERIMENTAL

Racemic samples of diclofop methyl were kindly provided by the Hoechst-Roussel Agri-Vet Co., Somerville NJ 08876-1258, as HOE lot nos. 00ZB990002 and 00ZB990003, compound HOE-023408. Chloroform-d (99.8 atom % D) and shift reagents were obtained from Aldrich Chemical Corp., Milwaukee WI 53201. Materials were used as received except as noted. $CDCl_3$ was dried and stored over 3Å molecular sieves; LSR reagents were stored in a desiccator over P_2O_5. Samples of 1 were stored at -5° until used for solution preparation. For runs with shift reagent, accurately weighed portions of 1 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. A 60 MHz Varian EM360A spectrometer with EM3630 lock/spin decoupler accessory was employed, using a probe temperature of 28±1° with ca. 1% tetramethylsilane (TMS) added to sample solutions to serve as internal reference at 0.00 ppm. In runs with chiral LSR where enantiomeric shift differences were observed, average chemical shifts for corresponding nuclei in the antipodes are reported. Chemical shifts are believed accurate to ± 0.05 ppm and coupling constants to ± 0.2 Hz.

RESULTS AND DISCUSSION

The 60 MHz ^1H NMR spectrum for 1 as a 0.5047 molal solution in $CDCl_3$ showed signals as follows (δ in ppm relative to TMS at 0.00 ppm): 1.60, 3H, d (^3J ca. 6.6 Hz), CCH_3; 3.74, 3H, s, OCH_3; 4.73, 1H, q (^3J ca. 6.6 Hz), methine $\underline{CH}CH_3$; 6.88, 4H, s, OC_6H_4O; 6.78,

Downloaded At: 03:44 30 January 2011

1H, d (partly overlapped with peak at 6.88 ppm), aryl H-6′; 7.13, 1H, dd (^3J 8.7, ^4J 2.3 Hz), aryl H-5′; 7.43, 1H, d (^4J 2.2Hz), aryl H-3′. These shifts agree closely (within 0.04 ppm) with values reported earlier (2) for a "25%" solution in $CDCl_3$ (temperature not specified). Additions of 2 produced lanthanide-induced shifts (LIS) as shown in Figure 1.

Increments of the chiral 3, $Eu(HFC)_3$, to 0.5204 molal 1 produced the LIS values summarized in Figure 2. Of particular note was the observation of clear enantiomeric shift differences, $\Delta\Delta\delta$, for the OCH_3 and CCH_3 signals, as shown in Figures 3 and 4. Slightly larger $\Delta\Delta\delta$ magnitudes were seen for the methoxy resonance, with optimum potential analytical utility for direct % e.e. determinations of samples of 1 using 3:1 molar ratios ca. 0.3-0.4. The valley height was as low as 33% of the average peak heights for the OCH_3 signals from each enantiomer of 1. The CCH_3 resonance offered less analytical utility because of greater overlap of each enantiomer's doublet signal. Any $\Delta\Delta\delta$ for the methine $\underline{CH}CH_3$ signal could not be observed due to greater multiplicity and lower intensity (1H versus 3H) with resultant poor signal-to-noise ratio (S/N). The earlier use of a chiral LSR for % e.e. determination of 1 (2) employed a 100 MHz spectrometer and the LSR 4 at a 30 weight % level ("30 Gew.-%"). The reported $\Delta\Delta\delta$ magnitudes for racemic 1 were only 0.01 ppm (1 Hz) for each methyl group, and 0.02 ppm (2 Hz) for the methine CH. Under our conditions using 3, our sample contained 74.6 mg 1 in 420.1 mg $CDCl_3$, i.e., 17.8% 1, with 79.1 mg of added 3 to produce a 3:1 molar ratio of 0.303, resulting in $\Delta\Delta\delta$ of 3.4 Hz (0.057 ppm at 60 MHz). In

Downloaded At: 03:44 30 January 2011

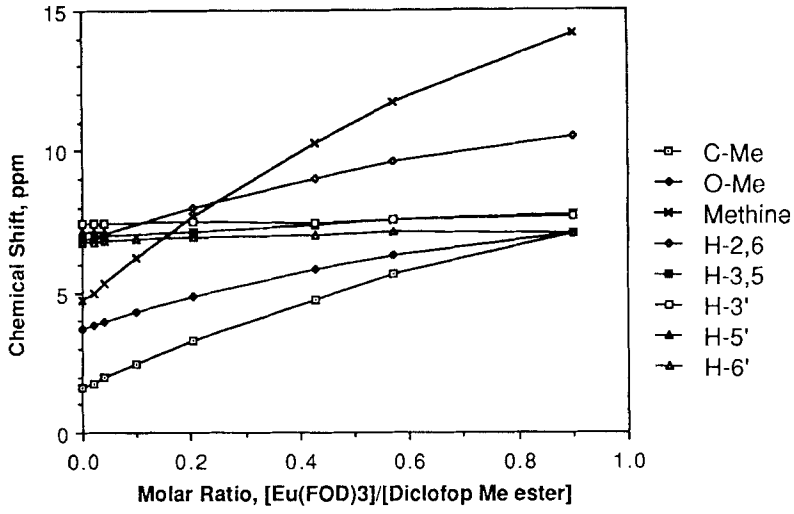


Figure 1. Variation of chemical shift (δ, ppm) of nuclei of 1 with molar ratio of [$Eu(FOD)_3$]:[1].

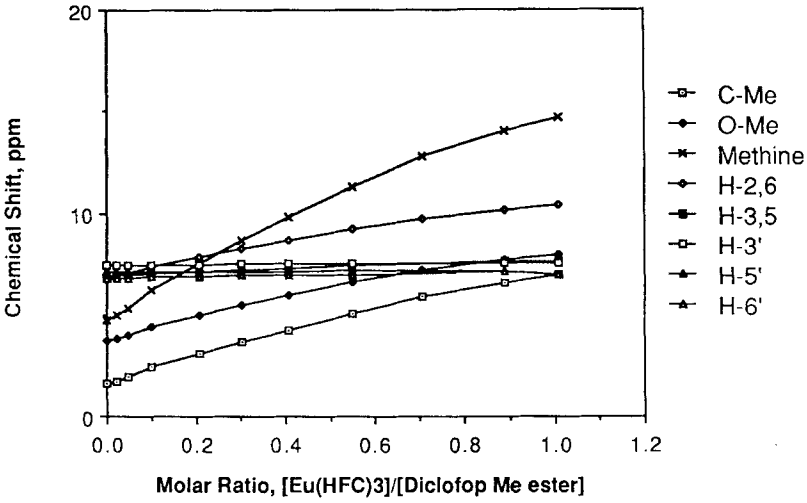


Figure 2. Variation of chemical shift (δ, ppm) of nuclei of 1 with molar ratio of [$Eu(HFC)_3$]:[1].

Downloaded At: 03:44 30 January 2011

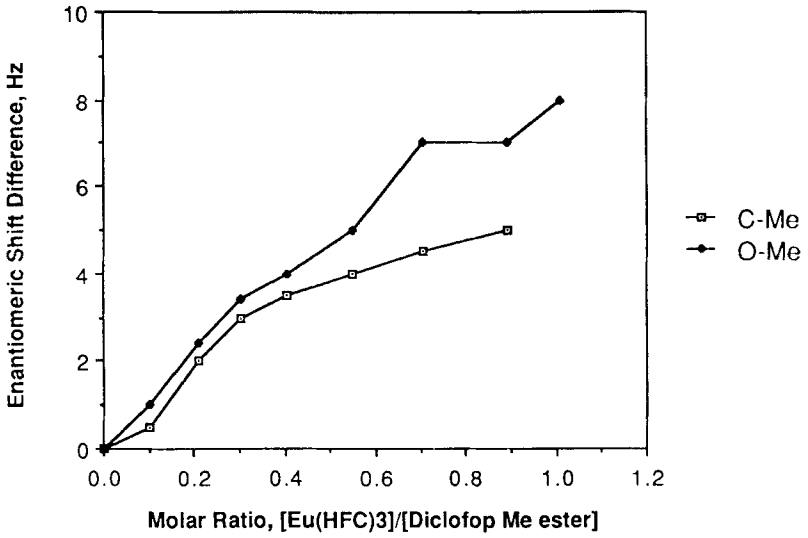


Figure 3. Variation of enantiomeric shift differences (in Hz) with molar ratio of [Eu(HFC)$_3$]:[1].

Downloaded At: 03:44 30 January 2011

a separate report for chiral LSR use for % e.e. determination of the aryloxyphenoxypropanoate analog, chlorazifop methyl ester, the praseodymium reagent, Pr(HFC)$_3$, had been employed (3a).

We also carried out additions of 4 to 0.5247 molal 1. Solubility problems were encountered with our sample of 4 such that 4:1 ratios could be examined with a maximum value of only 0.316 (for the 0.5247 molal 1). To examine higher 4:1 molar ratios, additional $CDCl_3$ solvent was added to our sample solution, yielding a molality of 1 of 0.267. With this diluted solution, higher 4:1 ratios from ca.

Downloaded At: 03:44 30 January 2011

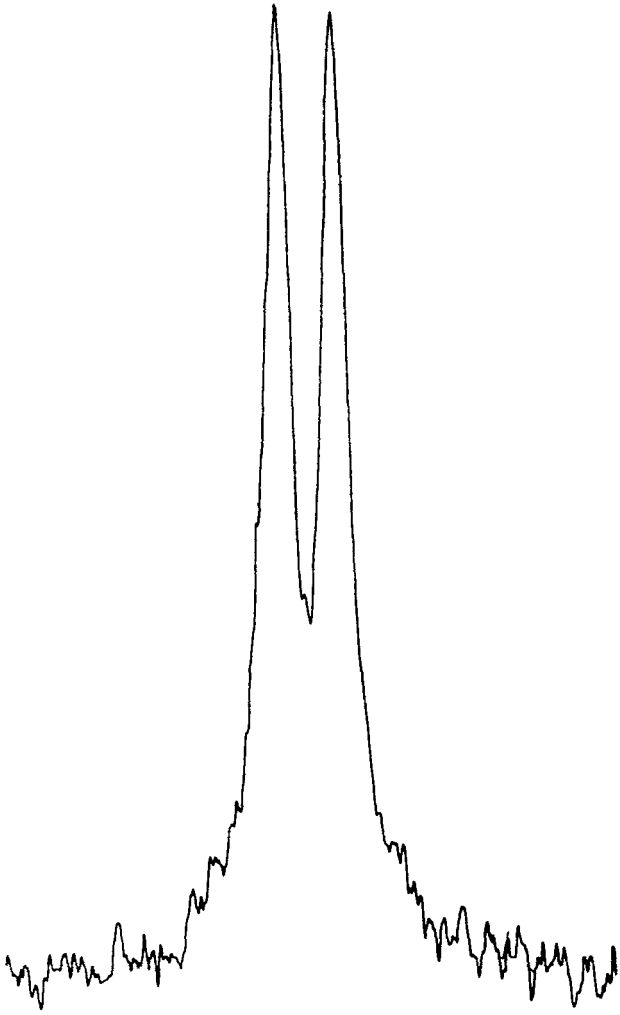


Figure 4. Spectral expansion of racemic 1, 0.520 molal, with 3:1 molar ratio of 0.407, showing the OCH_3 resonance centered at 5.98 ppm and $\Delta\Delta\delta$ = 4.0 Hz; valley height is 36%.

0.406-0.710 were examined. The LIS values of 1 with 4 are summarized in Figure 5. The "breaks" in the plotted lines near a 4:1 molar ratio ca. 0.4 are merely artifacts of the dilution, which (as expected) slightly decreased LIS magnitudes. No $\Delta\Delta\delta$ was seen using our sample of 4.

We can not fully account for the differences in our results compared with those reported earlier with 4 (2). Nestler and Bieringer report nearly identical chemical shifts for the CCH_3, OCH_3 and methine $\underline{CH}CH_3$ resonances using racemic 1 with 30 weight % 4 as with 15 weight % 4 on samples of 1 that were substantially enriched in either enantiomer. Their average chemical shifts were ca. 2.0 ppm (CCH_3), 4.1 ppm $(OCH)_3$, and 5.45 ppm ($\underline{CH}CH_3$) for racemic 1 with 30 weight % 4, compared with 2.01 ppm (CCH_3), 4.18 ppm (OCH_3), and 5.44 ppm ($\underline{CH}CH_3$) with 15 weight % 4 on a sample of 1 measured as having about 50% e.e. (+)-1 by NMR, e.g., about 75:25 enantiomer ratio by NMR integration of the methine signals with $\Delta\Delta\delta$=0.03 ppm (3 Hz at 100 MHz). Our results suggested that 3 may have even greater analytical potential for direct % e.e. determinations of samples of 1 using NMR spectrometers operating at higher field strengths/frequencies than at 60 MHz.

In Table 1 we have shown the unnormalized ("raw") slope values for the protons of 1 with added 2, 3 or 4, from the data of Figs. 1,2 and 5. These slope values reflect least squares line fitting for the early (low molar ratio region) part of the plots of chemical shift versus [LSR]:[1] molar ratio. The early portion of these curves is usually expected to exhibit greater slope values, since some "levelling

Downloaded At: 03:44 30 January 2011

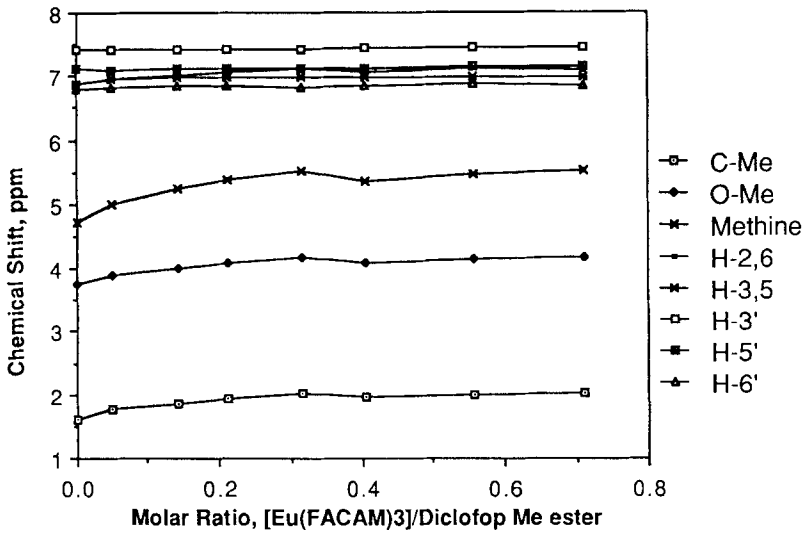


Figure 5. Variation of chemical shift (δ, ppm) of nuclei of 1 with molar ratio of [Eu(FACAM)$_3$]:[1].

Downloaded At: 03:44 30 January 2011

off" of the curves is usually encountered at higher LSR levels, particularly for LSR:substrate ratios approaching 0.5 or more. In part, this may reflect greater contributions from bound complexes with differing stoichiometries with higher LSR levels. Preferential LSR binding is expected at the ester carbonyl rather than at either aryl ether oxygen due to both steric hindrance and reduced basicity of the aryl ethers (resulting from delocalization of oxygen lone pair electron density into the aromatic rings) (5,8). With 2, the slopes for nuclei a-c, e and h were based on four experimental points with 2:1 ratios up to 0.1. For nuclei d and f, five points with 2:1 ratios to 0.2 were used, and for nucleus g,

Downloaded At: 03:44 30 January 2011

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

	Eu(FOD)$_3$ data		Eu(HFC)$_3$ data		Eu(FACAM)$_3$ data	
Nucleus	Unnorm.	Normalized	Unnorm.	Normalized	Unnorm.	Normalized
a) CCH_3	8.751	1.	8.236	1.0	1.537	1.
b) OCH_3	5.644	0.645	6.639	0.806	1.555	1.012
c) Methine	15.249	1.743	14.875	1.806	2.931	1.907
d) H-2,6	5.598	0.640	5.317	0.646	0.860	0.560
e) H-3,5	2.987	0.341	1.677	0.204	0.672	0.437
f) H-3′	0.277	0.032	0.389	0.047	0.036	0.023
g) H-5′	-0.247	-0.028	0.025	0.003	0.038	0.025
h) H-6′	1.510	0.173	0.542	0.066	0.387	0.252

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 slope of the line for the signals assigned to the CCH_3 resonance. See Results and Discussion for numbers of experimental points used in determining line equations and the correlation coefficients, R.

three points with 2:1 ratios to 0.04 were used. The correlation coefficients were R=1.00 except for f and h (R=0.99) and g (R=0.30). For LSR 3, four experimental points were used for all nuclei, with 3:1 molar ratios up to 0.1. R values were 1.00 (a-c), 0.99 (d,e), 0.89 (f), 0.09(g), and 0.83 (h). For LSR 4, four points were used with 4:1 ratios up to 0.21 for nuclei a-d, and three points with 4:1 ratios up to 0.14 for nuclei e-h. The R values were 0.97 (a,b), 0.98 (c), 0.99 (d), 0.93 (e), 0.76 (f), 0.18 (g), and 0.90 (h). The unnormalized values were in rather good agreement for LSRs 2 and 3, with much smaller slope magnitudes for 4, suggesting a much less active reagent with respect to LIS magnitudes. Normalized slope values were calculated relative to slopes of 1.0 assigned for the lines calculated from the CCH_3 signals. These signals were used for normalization for two reasons: a) their large LIS magnitudes mean that the experimental error contribution is relatively low, and b) the separation of the CCH_3 protons from the presumed LSR binding site on the carbonyl is sufficient to assure negligible Fermi contact shift contributions to the LIS (9,10). The normalized slopes for 2 and 3 are in excellent agreement, with the exception of the OCH_3 slope. Although the nuclei with smaller LIS magnitudes are more subject to experimental error (reflected in lower correlation coefficient values, R), it is possible to confidently distinguish the H-2,6 and H-3,5 resonances of the dioxyphenylene ring based on larger normalized slopes for the former, expected as a result of greater proximity of H-2,6 to lanthanide bound at the ester (11). These nuclei are

Downloaded At: 03:44 30 January 2011

accidently isochronous (chemical shift equivalent) for unshifted 1 but begin to exhibit an approximate AB quartet pattern (actually AA'BB') as LSR renders the nuclei anisochronous. With the distal dichlorophenyl ring, the aryl protons H-3',5',6' may be assigned for unshifted 1 based on observed multiplicities and relative chemical shifts. H-6' is at higher field, ortho to oxygen, and H-3' is at lower field, ortho to two chlorine substituents (12). The H-6' resonance exhibits higher normalized slopes than H-3' or H-5' for all three LSRs, again consistent with geometric aspects of the simplified McConnell-Robertson equation (11). The small anomalous (upfield) shifts seen for H-5' with 2 most likely reflect experimental error because of small LIS magnitudes.

Downloaded At: 03:44 30 January 2011

CONCLUSIONS

The 60 MHz ^1H NMR spectra for diclofop methyl have been examined in $CDCl_3$ with the added LSRs, $Eu(FOD)_3$, 2; $Eu(HFC)_3$, 3; and $Eu(FACAM)_3$, 4. Large LIS magnitudes were observed with 2 and 3 and smaller values with 4, but normalized slope values (calculated from plots of chemical shifts versus LSR:1 molar ratios) for all three LSRs are similar. The slopes are consistent with major LSR binding at the ester carbonyl. With the chiral LSR, 3, substantial $\Delta\Delta\delta$ values are seen for the OCH_3 and CCH_3 resonances, with the former nucleus offering optimum conditions for potential direct determinations of % e.e. for samples of 1 with 3:1 molar ratios ca. 0.3-0.4.

ACKNOWLEDGMENTS

We are grateful to AgrEvo USA Company, Wilmington, DE 19808, for samples of racemic diclofop methyl. Partial support has been provided by the U.S. Education Department Minority Science Improvement Program (grant nos. G008641165 and 1-132553815-A1), 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 research award program (PSC-CUNY 24 grant no. 664182 and PSC-CUNY 25 grant no. 665283) to R.R. Further support was provided by the CUNY PIPELINE Diamond Foundation (to E.C.).

Downloaded At: 03:44 30 January 2011

LITERATURE CITED

1. Nestler H.J. Phenoxy-phenoxypropionic acid derivatives and related compounds. In: Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel, vol. 8. R. Wegler, ed. Berlin, Heidelberg, New York: Springer-Verlag, 1982, pp. 1-25.

2. Nestler H.J., Bieringer H. Synthesis and herbicidal activity of the D- and L-methyl 2-[4-(2,4-dichlorophenoxy)-phenoxy]-propionate enantiomers. Z. Naturforsch. 1980, 35B(3): 366-371.

3. a) Cartwright D. The synthesis, stability and biological activity of the enantiomers of pyridyloxyphenoxyproprionates. Brighton Crop Protection Conference - Weeds - 1989; 7A-2: 707-716, and references cited therein; b) Wink O., Luley U. Enantioselective transformation of the herbicides Diclofop-methyl and Fenoxaprop-ethyl in soil. Pestic. Sci. 1988; 22(1): 31-40.

4. Blessington B., Crabb N. Proposed primary reference methods for the determination of some commercially important chiral aryloxypropionate herbicides in both free acid and ester forms. J. Chromatogr. 1989; 483: 349-358.

5. Cockerill A.F., Davies G.L.O., Harden R.C., Rackham D.M. Lanthanide shift reagents for nuclear magnetic resonance spectroscopy. Chem. Rev. 1973; 73(6): 553-588.

6. Aboul-Enein H.Y. NMR methods for optical purity determination of pharmaceuticals. Anal. Lett. 1988; 21(12): 2155-2163.

7. Morrill T.C. ed. Lanthanide Shift Reagents in Stereochemical Analysis. New York: VCH, 1986.

8. Wenzel T.J. NMR Shift Reagents. Boca Raton FL: CRC Press, 1987.

9. Peters J.A., Nieuwenhuizen M.S., Raber D.J. Analysis of multinuclear lanthanide-induced shifts. 1. Investigations of some approximations in the procedure for separation of diamagnetic, contact, and pseudocontact shifts. J. Magn. Reson. 1985; 65: 417-428.

10. Raber D.J., Peters J.A., Nieuwenhuizen M.S. Analysis of multinuclear lanthanide-induced shifts. Part 2. The geometry of ketone binding to lanthanides. J. Chem. Soc. Perkin Trans. II 1986; 853-859.

11. McConnell H.M., Robertson R.E. Isotropic nuclear resonance shifts. J. Chem. Phys. 1958; 29(6): 1361-1365.

12. Abraham R.J., Fisher J., Loftus P. Introduction to NMR Spectroscopy. Chichester, New York, etc.: John Wiley, 1988, p. 28.

Date Received: October 18, 1994
Date Accepted: November 28, 1994

Downloaded At: 03:44 30 January 2011