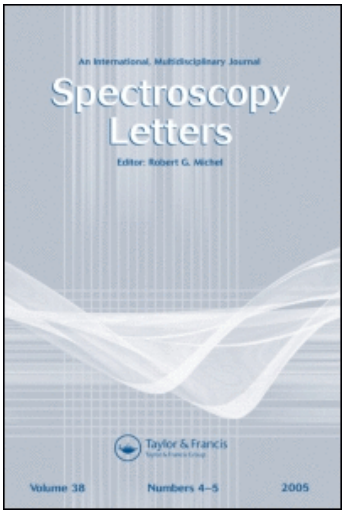


Spectroscopy Letters

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

¹H NMR Spectral Simplification with Achiral and Chiral Lanthanide Shift Reagents. Tocainide. Method for Direct Optical Purity Determination and Observation of an "Anomalous" Shift

Hassan Y. Aboul-enein[a]; Joel Ross[bc]; Robert Rothchild[b]

[a] Drug Development Laboratory Radionuclide and Cyclotron Operations Department King, Faisal Specialist Hospital and Research, Riyadh, Kingdom of Saudi Arabia [b] Department of Science, The City University of New York John Jay College of Criminal Justice Toxicology Research and Training Center, New York, N.Y. [c] St. Michael's College, Winooski, VT

To cite this Article Aboul-enein, Hassan Y. , Ross, Joel and Rothchild, Robert(1989) '¹H NMR Spectral Simplification with Achiral and Chiral Lanthanide Shift Reagents. Tocainide. Method for Direct Optical Purity Determination and Observation of an "Anomalous" Shift', Spectroscopy Letters, 22: 5, 641 — 658

To link to this Article: DOI: 10.1080/00387018908053912

URL: http://dx.doi.org/10.1080/00387018908053912

SPECTROSCOPY LETTERS, 22(5), 641-658 (1989)

^{1}H NMR SPECTRAL SIMPLIFICATION WITH ACHIRAL AND CHIRAL LANTHANIDE SHIFT REAGENTS. TOCAINIDE. METHOD FOR DIRECT OPTICAL PURITY DETERMINATION AND OBSERVATION OF AN "ANOMALOUS" SHIFT

Key Words: Tocainide, Lanthanide, NMR

Shift Reagents, Optical Purity,

Enantiomers, Chiral

Hassan Y. Aboul-Enein

Drug Development Laboratory
Radionuclide and Cyclotron Operations Department
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354, Riyadh 11211, Kingdom of Saudi Arabia

Joel Ross[+] and Robert Rothchild*

The City University of New York
John Jay College of Criminal Justice
Toxicology Research and Training Center
Department of Science
445 West 59th Street, New York, N.Y. 10019-1199

* To whom correspondence should be addressed

+ On leave from St. Michael's College, Winooski, VT

ABSTRACT

The 60 MHz ^1H NMR spectra of racemic tocainide, 1, have been studied in $CDCl_3$ solution at 28° with the achiral shift reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, and the chiral reagent, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-europium(III), 3. Substantial lanthanide induced shifts, $\Delta\delta$, were observed with both 2 and 3. A significant "anomalous" upfield shift for the CH signal of 1 was seen with added 2. The chiral reagent 3 led to appreciable enantiomeric shift differences for the CH_3CH and amide NH signals. The potential for direct optical purity determinations of 1 using 3 was demonstrated for a non-racemic ("spiked") sample of 1, based on the CH_3 resonance. The sense of magnetic non-equivalence for these resonances was also determined.

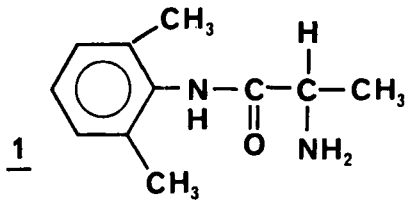
INTRODUCTION

Tocainide, 1, 2-amino-N-(2,6-dimethylphenyl)propanamide, is a cardiac antiarrhythmic of considerable clinical interest. Recently, it has been the subject of numerous review articles (1-5). Of considerable interest to us have been the reports of stereoselectivity with respect to the two enantiomers of 1 in different aspects of their pharmacology (6-12). Increasing concern for, and appreciation of, the stereochemical implications of pharmaceuticals has been accompanied by a growing interest in

enantioselective synthesis, in methods for resolving enantiomers from racemic mixtures, and in techniques for determining optical purity. In the case of tocainide, a number of different chromatographic methods have been employed to determine optical purity, including the use of chiral derivatizing agents and GC (12,13), achiral derivatizing agents with a GC chiral stationary phase (CSP) (14-16), HPLC on a CSP (17,18), and HPLC with a chiral derivatizing agent (19).

There do not appear to have been any reports of the use of the non-chromatographic technique based on NMR with chiral lanthanide shift reagents (LSR). The use of achiral LSR for spectral simplification and chiral LSR for direct optical purity determinations has been reviewed (20-27).

We undertook studies of the 60 MHz ^{1}H NMR spectra of both racemic and non-racemic samples of 1 using achiral and chiral LSR. Use of achiral LSR was expected to result in spectral simplifications. With chiral LSR, we hoped to explore a method for direct optical purity determinations of 1.



1

EXPERIMENTAL

A sample of racemic tocainide hydrochloride, 1-HCl, was provided by Astra Pharmaceutical Products, Inc., 50 Otis St., Westborough MA 01581-3398, U.S.A., as lot no. 14P. A sample of the S-(+) enantiomer of tocainide hydrochloride, as lot no. H181/68, was obtained from the same source. Chloroform-d, (99.8 tom % D) obtained from Aldrich Chemical Corp., Milwaukee WI 53201, U.S.A., or from Norell, Inc., Landisville NJ 08326, U.S.A., was dried over 3A molecular sieves. Shift reagents were obtained from Aldrich and were stored in a desiccator over P_2O_5. Materials were used as supplied except as noted.

In general, an accurately weighed portion of 1, as the free base (see below), typically 14-41 mg, was added to 650-700 mg $CDCl_3$ [containing about 0.5% tetramethylsilane (TMS) as internal standard] in an oven-dried NMR sample tube and dissolved by shaking; increments of shift reagent were added, dissolved by shaking (and gentle warming in a water bath, if required), and the spectra immediately recorded.

All spectra were obtained with a Varian EM360A 60 MHz ^1H NMR spectrometer at a probe temperature of 28°. Chemical shifts are reported in parts per million (δ) relative to TMS and are believed accurate to $\pm$0.05 ppm. In spectra where TMS was obscured by shift reagent peaks, $CHCl_3$ (present as an impurity in the solvent) was used as internal standard. For samples with chiral 3 added, when enantiomeric shift differences, $\Delta\Delta\delta$, were

observed, average chemical shift values for the two optical antipodes are reported here.

Preparation of Free Base of Racemic 1: Racemic 1-HCl (454.0 mg, 1.987 mmol) was dissolved in 10ml H_2O and treated with ca. 10 ml aq. 5% NaOH and 2.0 gm NaCl. The mixture was extracted with CH_2Cl_2 (15 ml) followed by four additional 5 ml portions of CH_2Cl_2. The combined organic extracts were dried over K_2CO_3 (anh) and solvent was removed on a rotary evaporator (at aspirator pressure and a bath temperature of 50°) to constant weight, to give 367.7 mg of the free base of 1, 91.0% recovery of an off-white oil that crystallized on standing, mp (uncorr.) 54-60°. [lit. 55-56° (13)].

Preparation of Free Base of S-(+)-1: The hydrochloride salt of S-(+)-1, mp (uncorr.) 274-277°, was treated with 5% aq. NaOH, NaCl, and extracted with CH_2Cl_2 as above. After drying over anh. Na_2CO_3 and solvent removal to constant weight (rotary evaporator, aspirator pressure, bath 45-48°), S(+)-1 was obtained, 93.3% recovery. The sample crystallized on standing, mp (uncorr.) 76-77°. Samples of racemic and S-(+)-1 free base were used for NMR runs without further purification. All free base tocainide samples were routinely stored under N_2.

RESULTS AND DISCUSSION

The 60 MHz ^1H NMR spectrum of racemic 1 as a 0.308 molal solution in $CDCl_3$ at 28° showed signals as follows (δ) ppm: 8.8 (1H, br s, amide NH), 7.05 (3H, s, aryl $H_{3,4,5}$), 3.63 (1H, q,

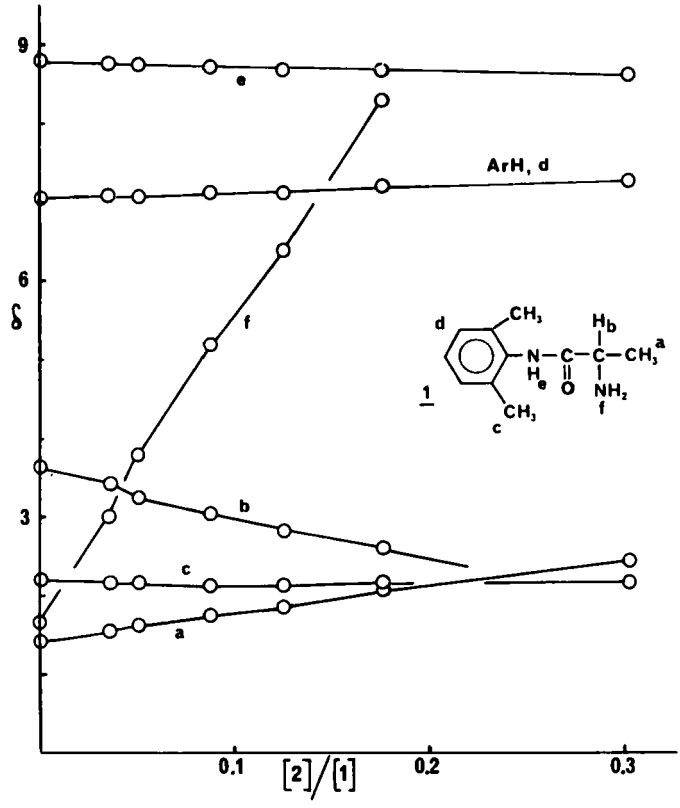


FIG 1. Variation of chemical shift, δ (in ppm), with molar ratio of 2:1.

CH), 2.21 (6H, s, aryl CH_3), 1.65 (2H, br s, NH_2), 1.42 (3H, d, $\underline{CH_3}CH$). It was expected that addition of LSR would lead predominantly to binding at the basic NH_2 group (22). Variation of chemical shifts observed upon incremental addition of the achiral reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), 2, is shown in Figure 1. The

lanthanide induced shift, $\Delta\delta$, is defined as the chemical shift of a nucleus in the presence of LSR minus the chemical shift of the same nucleus with no added LSR. Organic tris-β-diketonates of Eu(III) are generally considered to be "downfield" shift reagents. That is, the dipolar (pseudocontact) part of the lanthanide induced shifts for these reagents usually causes the resonances of shifted signals to move downfield. Most reports of anomalous pseudocontact shifts are now understood to reflect the angular dependence in the McConnell-Robertson equation (28) although contact shift contributions may play a role for some nuclei, particularly if close to the LSR binding site. As expected, $\Delta\delta$ values for the NH_2 signal reflected large downfield shifts consistent with major binding here by 2. The $\underline{CH_3}CH$ signal displayed the second largest magnitudes of downfield shift.

Surprisingly, considerable upfield shifts were found for the methine CH signal over the range of 1:2 molar ratios examined here. (Solubility limits resulted in a maximum attainable 1:2 ratio of 0.303.) The $\Delta\delta$ value for the amide NH signal showed a very small upfield shift as 2 was added, while $\Delta\delta$ for the aryl CH_3 was essentially zero. For the aryl $H_{3,4,5}$ $\Delta\delta$ definitely showed a modest downfield shift despite these aryl protons being further from the LSR's expected NH_2 binding site and separated from this site by the same or a greater number of bonds than the aryl CH_3. The absence of observed $\Delta\delta$ for the aryl CH_3 is thus

consistent with the McConnell-Robertson equation's angular part, implying an angle between the distance vector (from the lanthanide to the average positions of these nuclei) and the vector joining the lanthanide to the binding site (assumed colinear with the principal magnetic axis of the LSR) near 54.7°. In 1, there is the possibility of bidentate chelation of the lanthanide by the carbonyl oxygen and the α-amino nitrogen. Such an effect has been discussed for 2 with N,N-diethyl-α-dimethylaminoacetamide (29). LSR applications with some substituted ethanolamines have produced "anomalous" shifts, as for the NCH_3 of phenylpropanolamine (also known as norephedrine) with 2 (30); the NCH_3, CHOH and aryl H of ephedrine with 2 (30); and for the NCH_3 of ephedrine with tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III), $Eu(facam)_3$ (31). The appearance of these upfield shifts with Eu(III) LSR seems to depend on some extremely subtle factors, and may differ with a different LSR, with variation of solvent, or with slight change in substrate structure. It is particularly difficult to evaluate in complex substrates that possess more than one possible LSR binding site, since relative binding site and stoichiometry of the LSR - substrate complex may further vary with molar ratio of LSR to substrate.

The possible role of a bidentate chelation of LSR in defining a favored geometry in the bound complex, thereby increasing the likelihood of observing such "anomalous" shifts,

certainly bears further study. Another analog of 1 has also been studied with LSR by Siddall. With tris(dipivalomethanato)-europium(III), $Eu(dpm)_3$, N-2,6-diisopropylphenylacetamide showed an upfield shift for one of the methyls (32). This substrate resembles 1 in being an N-aryl amide, although the bulky isopropyl substitutents clearly have more steric influence than the 2,6-dimethyl groups of 1; in addition, no bidentate chelation is possible in Siddall's substrate.

We were most interested in the potential for direct optical purity determinations of 1 using the chiral reagent, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III), 3, known as $Eu(hfbc)_3$ or $Eu(hfc)_3$. Increments of 3 were added to a 0.104 molal $CDCl_3$ solution of 1. The unshifted sample showed a clean doublet methyl (^3J = 7.1Hz) for the CH_3 at the chiral center. With added 3, this signal appeared as a double doublet, indicating an enantiomeric shift difference. The enantiomeric shift difference, $\Delta\Delta\delta$, is the difference in chemical shift for the signals of corresponding nuclei in two enantiomers in the presence of a chiral shift reagent. The induced shifts and $\Delta\Delta\delta$ values for 1 with 3 are summarized in Figures 2 and 3, respectively. One difference was observed with regard to shifts induced by 2 and 3, suggesting that changes in geometry in the bound complexes are present depending upon the reagent. With 2, $\Delta\delta$ for the aryl methyls is essentially zero although a definite downfield shift was seen with 3. With either 2 or 3, largest downfield

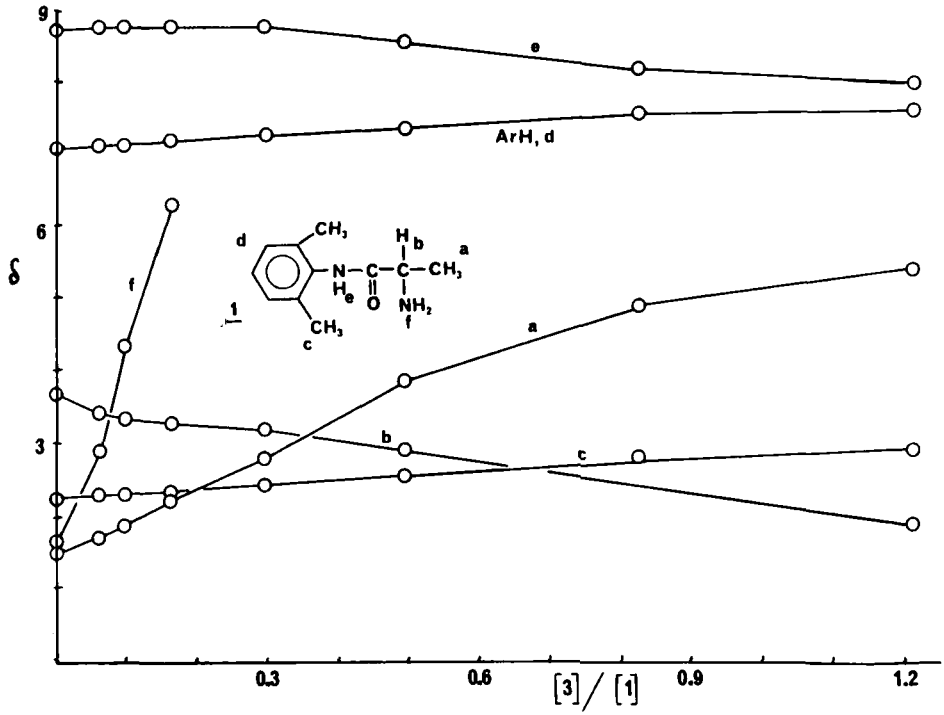


FIG. 2. Variation of chemical shift, δ (in ppm), with molar ratio of 3:1. Where enantiomeric shift differences occur, the average chemical shifts for the optical antipodes are plotted.

shifts are seen for the NH_2, the presumed major binding site, with smaller downfield shifts for the CH_3 at the chiral center. Upfield shifts are seen for the α-CH with both reagents. With 3, a lower concentration of 1 permitted use of higher 3:1 molar ratios without encountering solubility limits, and some upfield shift is clearly apparent for the amide NH at these high 3:1 ratios. Because of the favorable $\Delta\Delta\delta$ values observed for the

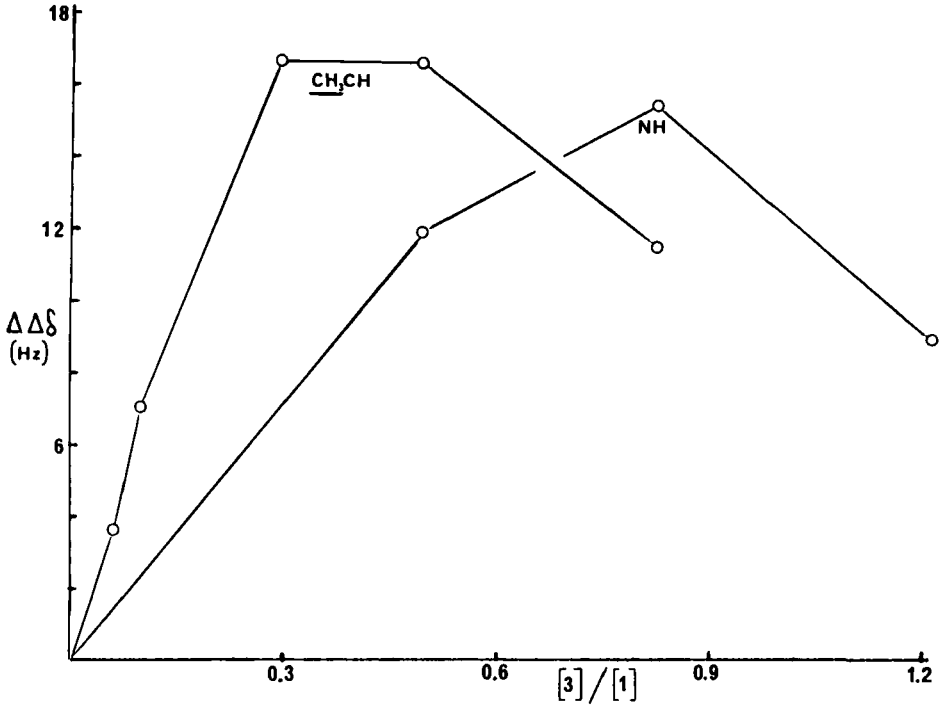


FIG. 3. Variation of enantiomeric shift difference, $\Delta\Delta\delta$ (in Hz), with molar ratio of 3:1.

CH_3CH resonance, a "spiking" experiment was performed. A non-racemic sample of 1 was prepared by accurately weighing portions of racemic 1 and of the pure S-(+) enantiomer of 1 (as free bases) into an NMR sample tube. For this sample, as a $CDCl_3$ solution 0.120 molal in total 1, quantitation was attempted at several 3:1 ratios, using both the CH_3CH and amide NH signals. For the racemic 1 (see Figure 3), $\Delta\Delta\delta$ for both the methyl and

amide signals had been shown to go through maxima, decreasing at higher levels of 3. Thus, $\Delta\Delta\delta$ for the $\underline{CH_3}CH$ reached a maximum of about 16.6 Hz for 3:1 ratios of 0.3 - 0.5, and $\Delta\Delta\delta$ for the amide NH was highest (15.4 Hz) at a 3:1 ratio near 0.825. As a result, higher molar ratios of the chiral LSR are undesirable not only because of the expected increase in LSR-induced line broadening, but also because of actual decreases in $\Delta\Delta\delta$. Such non-monotonic variations of $\Delta\Delta\delta$ may reflect changes in the stoichiometry or geometry of the bound complex with varied LSR:substrate ratio. It was clear that for our "spiked" non-racemic sample of 1, optimal determination of optical purity would be based on the $\underline{CH_3}CH$ signal, with 3:1 ratios near 0.5-0.7. Interfering overlaps with the methyl resonance are minimal, $\Delta\Delta\delta$ is substantial and the valley between the doublets of the enantiomers was acceptably low. This valley height was 21%, evaluated with respect to a sloping baseline drawn from the downfield noise floor to the valley between the upfield-most peak of interest, and the adjacent (LSR) peak. Of considerable interest was the observation that the amide NH and $\underline{CH_3}CH$ signals had opposite senses of magnetic nonequivalence, with the methyl of the S-(+) enantiomer of 1 having a downfield sense of nonequivalence and the amide NH having the upfield sense. In applications with chiral LSR, the observation that two different nuclei in an enantiomer have opposite senses of magnetic nonequivalence is often taken to suggest that the enantiomeric

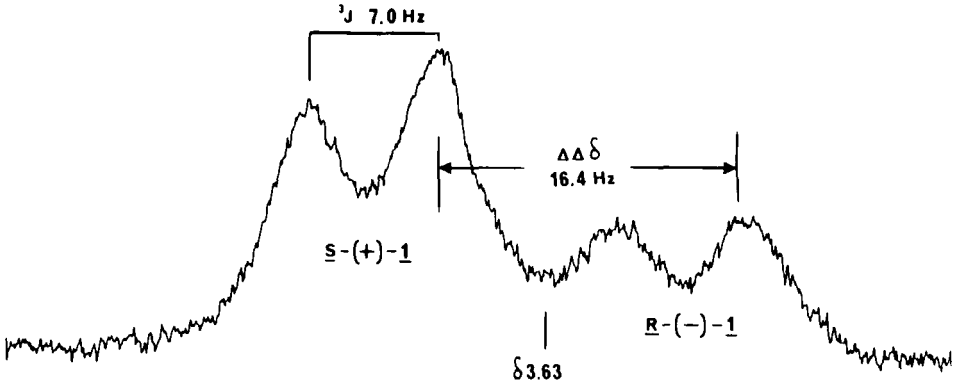


FIG. 4. CH_3CH resonance for a sample of non-racemic 1, 68:32 S-(+):R-(−), 0.120 molal in total 1, with a 3:1 molar ratio of 0.551. The vicinal coupling constant (^3J) and $\Delta\Delta\delta$ are indicated, in Hz. Taken from a scan with 1 ppm sweep width, 2 min. sweep time, 0.1 sec filter, 0.1 mG RF power.

shift differences result from different geometries in the bound complexes of the two enantiomers with the chiral LSR. If the enantiomeric shift differences arose simply from one enantiomer having a greater binding constant to LSR, then it is assumed that all nuclei in the more strongly bound enantiomer would have greater induced shifts and, therefore, have the same sense of magnetic nonequivalence. However, this is true only if all the nuclei are being shifted in the same direction. For 1 with 3, CH_3CH is shifted downfield but the amide NH is shifted upfield. Relative to the chemical shifts without LSR, the same enantiomer, S-(+)-1, has greater magnitudes of induced shifts

Table I. Observed enantiomeric ratios, for "spiked" sample of 1, 68:32 S-(+):R-(-) by weight, 0.120 molal in total 1.

I. CH_3CH resonance. Method:	Peak height[a]	Peak height[b]	Integrals
3:1 ratio			
0.551	64:36 (N=3, S.D. = 2.5)	64:36 (N=1)	66:34 (N=4, S.D. = 1.0)
0.709	64:36 (N=2, S.D. = 0.64)	———	67:33 (N=4, S.D. = 1.6)

II. NH resonance.	Peak height[c]	Peak height[d]	
0.709	64:36 (N=2, S.D.=2.8)	———	———
0.848	66:34 (N=5, S.D.=2.8)	69:31 (N=4, SD=2.7)	———

Notes:
(a) Ratio of average peak heights for each enantiomer's doublet, measured to a horizontal baseline.
(b) Ratio of average peak heights for each enantiomer's doublet, measured to sloping baseline (see text).
(c) Ratio of peak heights due to each enantiomer, measured to a horizontal baseline.
(d) Ratio of peak heights due to each enantiomer, measured to a sloping baseline (see text).

for both CH_3CH and NH signals. The resulting observed opposite senses of magnetic nonequivalence may in this case simply result from different enantiomer binding constants, and not necessarily different bound complex geometries. The results of the optical purity determinations are shown in Figure 4 and Table 1 and reflect

reasonable accuracy for a chiral LSR technique. Detection of as little as about 7% of the minor enantiomer of 1 in a non-racemic mixture should be feasible. Detection limits would clearly be improved using a higher field NMR spectrometer.

SUMMARY

We have reported the results of achiral and chiral LSR, 2 and 3 respectively, on the ^1H NMR spectra of 1. Anomalous upfield shifts were found for the methine at the chiral center with either LSR, with smaller anomalous shifts seen with either 2 or 3 for the amide NH. The S-(+) enantiomer of 1 has a downfield sense of magnetic nonequivalence for the CH_3CH absorption in the presence of added 3 and the opposite sense for the amide NH. The analytical utility for direct optical purity determinations of 1 with 3 was demonstrated, with optimal 3:1 ratios of about 0.5-0.7.

ACKNOWLEDGMENTS

Samples of racemic tocainide and its enantiomers were kindly provided by Astra Pharmaceutical Products, Inc., Westborough, MA. This work was supported, in part, by the U.S. Department of Education Minority Science Improvement Program (grant no. G008641165), the National Science Foundation Instrumentation and Laboratory Improvement program (grant no. USE-8851684), the Hewlett-Packard Academic Instrument Donation Program, the Sandoz Research Institute and Hoffmann-La Roche Inc.

REFERENCES

1. Kreeger R.W., Hammill S.C. New antiarrhythmic drugs: Tocainide, mexiletine, flecainide, encainide, and amiodarone. Mayo Clin. Proc. 1988; 62(11): 1033-1050.

2. Morganroth J., Nestico P.F. A review of the uses and limitations of tocainide: a class IB antiarrhythmic agent. Am. Heart J. 1985; 110(4): 856-863.

3. Kutalek S.P., Morganroth J., Horowitz L.N. Tocainide: a new oral antiarrhythmic agent. Ann. Intern. Med. 1985; 103(3): 387-391.

4. Alpert J.S., Haffajee C.I., Young M.D. Chemistry, pharmacology, antiarrhythmic efficacy and adverse effects of tocainide hydrochloride, an orally active structural analog of lidocaine. Pharmacotherapy (Carlisle, Mass.) 1983; 3(6): 316-322.

5. Holmes B., Brogden R.N., Heel R.C., Speight T.M., Avery G.S. Tocainide: a review of its pharmacological properties and therapeutic efficacy. Drugs 1983; 26(2): 93-123.

6. Uprichard A.C.C., Allen J.D., Harron D.W.G. Effects of tocainide enantiomers on experimental arrhythmias produced by programmed electrical stimulation. J. Cardiovasc. Pharmacol. 1988; 11(2): 235-241.

7. Block A.J., Merrill D., Smith E.R. Stereoselectivity of tocainide pharmacodynamics in vivo and in vitro. J. Cardiovasc. Pharmacol. 1988; 11(2): 216-221.

8. Sheldon R.S., Cannon N.J., Nies A.S., Duff H.J. Stereospecific interaction of tocainide with the cardiac sodium channel. Mol. Pharmacol. 1988; 33(3): 327-331.

9. Hoffman K.J., Renberg L., Baeaernhielm C. Stereoselective disposition of RS-tocainide in man. Eur. J. Drug Metab. Pharmacokinet. 1984; 9(3): 215-222.

10. Pillai G.K., Axelson J.E., Kerr C.R., McErlane K.M. Stereospecific salivary excretion of tocainide enantiomers in man. Res. Commun. Chem. Pathol. Pharmacol. 1984; 43(2): 209-221.

11. Sedman A.J., Bloedow D.C., Gal J. Serum binding of tocainide and its enantiomers in human subjects. Res. Commun. Chem. Pathol. Pharmacol. 1982; 38(1): 165-168.

12. Gal J., French T.A., Zysset T., Haroldsen P.E. Disposition of RS-tocainide. Some stereoselective aspects. Drug Metab. Dispos. 1982; 10(4): 399-404.

13. Sedman A.J., Gal J. Simultaneous determination of the enantiomers of tocainide in blood plasma using gas-liquid chromatography with electron capture detection. J. Chromatogr. 1984; 306: 155-164.

14. Gyllenhaal O., Lamm B., Vessman J. Enantiomer separation of tocainide and some of its analogs and derivatives on a Chirasil-Val capillary column. J. Chromatogr. 1987; 411: 285-295.

15. Antonsson A.M., Gyllenhaal O., Kylberg-Hanssen K., Johansson L., Vessman J. Monitoring of S- and R-tocainide in human plasma after heptafluorobutyrylation, separation on Chirasil-Val and electron capture detection. J. Chromatogr, 1984; 308: 181-187.

16. McErlane K.M., Pillai G.K. Gas-liquid chromatographic resolution and assay of tocainide enantiomers using a chiral capillary column and study of their selective disposition in man. J. Chromatogr. 1983; 274: 129-138.

17. Schill G., Wainer I.W., Barkan S.A. Chiral separation of cationic drugs on an α_1-acid glycoprotein bonded stationary phase. J. Liq. Chromatogr. 1986; 9(2-3): 641-666.

18. Schill G., Wainer I.W., Barkan S.A. Chiral separations of cationic and anionic drugs on an α_1-acid glycoprotein-bonded stationary phase. (Enantio-Pac). II. Influence of mobile phase additives and pH on chiral resolution and retention. J. Chromatogr. 1986; 365: 73-88.

19. Schulze J., König W.A. Enantiomer separation by high performance liquid chromatography on silica gel with covalently bound monosaccharides. J. Chromatogr. 1986; 355(1): 165-175.

20. Fraser, R.R. Nuclear magnetic resonance analysis using chiral shift reagents. Asymmetric Synth. 1983; 1: 173-196.

21. Rinaldi P.L. The determination of absolute configuration using nuclear magnetic resonance techniques. Progr. Nucl. Magn. Reson. Spectrosc. 1982; 15: 291-352.

22. 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.

23. Sullivan G.R. Chiral lanthanide shift reagents. In: Eliel E.L., Allinger N.L. eds. Topics in Stereochemistry, vol. 10, New York: John Wiley - Interscience 1978: 287-329.

24. Kutal C. Chiral shift reagents. In: Sievers R.E., ed. Nuclear Magnetic Resonance Shift Reagents, New York: Academic Press 1973: 87-98

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

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

27. Aboul-Enein H.Y. NMR methods for optical purity determinations of pharmaceuticals. Anal. Lett. 1988; 21(12) in press.

28. McConnell H.M., Robertson R.E. Induced chemical shifts from both contact and dipolar interactions. J. Chem. Phys. 1958; 29: 1361-1369.

29. Gutierrez M.A., Martins M.A.P., Rittner R. NMR chemical shift substituent effects 3; alpha-monosubstituted N,N-diethylacetamides; bifunctional compounds in LSR experiments. Org. Magn. Reson. 1982; 20(1): 20-25.

30. Hatzis A., master's thesis no. 666, John Jay College of Criminal Justice, City University of New York, June 1986, pp. 106-116.

31. Dewar G.H., Kwakye J.K., Parfitt R.T., Sibson R. Optical purity determination by NMR: use of chiral lanthanide shift reagents and a base line technique. J. Pharm. Sci. 1982; 71(7): 802-806.

32. Siddall, III T.H. An upfield magnetic resonance shift induced by tris(dipivalomethanato)europium. J. Chem. Soc. Chem. Commun. 1971; (9)452-453.

Date Received: 01/31/89
Date Accepted: 03/03/89