THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 20

SEPTEMBER 30, 1977

Nuclear Magnetic Resonance Determination of Enantiomeric Compositions of Oxaziridines Using Chiral Solvating Agents

W. H. Pirkle* and P. L. Rinaldi

The Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

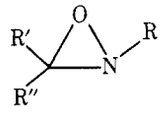
Received March 28, 1977

Addition of chiral arylperfluoroalkylcarbinols to solutions of oxaziridines causes the NMR spectra of the oxaziridine enantiomers to be nonidentical. The resultant chemical shift differences allow direct determination of the enantiomeric composition of the oxaziridine and may ultimately allow assignment of absolute configuration to each enantiomer. Reasons underlying the origin of the spectral nonequivalence are discussed and absolute specific rotations for several oxaziridines are presented.

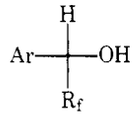
Oxaziridines (1) have attracted considerable stereochemical attention as a consequence of the dissymmetric nitrogen and its appreciable barrier to inversion. Optically active oxaziridines have been prepared by the oxidation of achiral imines with chiral peracids,[1] by the oxidation of chiral imines with achiral peracids,[2] by thermal isomerization in a chiral liquid crystal,[3] and by photochemical synthesis in a chiral solvent.[4] The enantiomeric purities of most chiral oxaziridines have been unknown, since only in select instances have partially resolved oxaziridines been crystallized to enantiomeric purity so that absolute specific rotations might be determined. We now report a method employing chiral solvating agents (CSA) for the rapid and convenient NMR determination of the enantiomeric composition of oxaziridines. This method may ultimately allow determination of oxaziridine absolute configuration as well.

When used as CSA, fluoro alcohols of general structure **2** cause the NMR spectra of oxaziridine enantiomers to differ. This behavior was first noted[5] when oxaziridine **1a**, formed by oxidation of *N-tert*-butylformimine with (*S*)-(+)-monoperoxycamphoric acid (MPCA), was examined by NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-phenylethanol (**2a**) and separate *tert*-butyl singlets and AB patterns were observed for each oxaziridine enantiomer. Simply by comparing the relative signal intensities, the enantiomeric composition of **1a** was determined.

The differential NMR effect of CSA (**2b**) upon the enantiomers of partially resolved oxaziridine **1b** is shown in Figure 1. Results obtained from the NMR spectra of other partially resolved oxaziridines in the presence of (*S*)-(+)-**2b** and **2c** are shown in Table I. In each instance, enantiomeric composition was determined from the relative intensities of the anisochronous resonances of the enantiomers.



1a, R′ = R″ = H; R = *tert*-butyl
b, R′ = H; R″ = CH_3; R = *tert*-butyl



2a, Ar = phenyl; $R_f = CF_3$
b, Ar = 9-(10-methylanthryl); $R_f = CF_3$
c, Ar = 9-anthryl; $R_f = CF_3$
d, Ar = 9-(10-Bromoanthryl); $R_f = CF_3$

Type **2** CSA cause enantiomeric spectral nonequivalence for a wide variety of solutes by forming diastereomeric chelate-like solvates, exemplified by generalizations **3a,b.** These diastereomeric solvates have nonidentical time-averaged NMR spectra owing to the stereochemical dependence of the shielding effect exerted by the aromatic substituent of **2** on R_1 and R_2. Typically R_1 and R_2 show opposite senses of nonequivalence. In alkyl oxaziridines there are but two basic sites, the oxygen and the nitrogen. Because of the opposite senses of nonequivalence observed for the nitrogen and carbon substituents of the nonaromatic oxaziridines, we consider it highly probable that the observed nonequivalence stems from solvation of these oxaziridines by **2** as depicted in **3a,b.** Experience has shown that the hydroxyl proton of **2** hydrogen bonds preferentially to the more basic of the two sites. A priori, it is not known for oxaziridines whether oxygen or nitrogen is the site for primary hydrogen bonding. This is important,

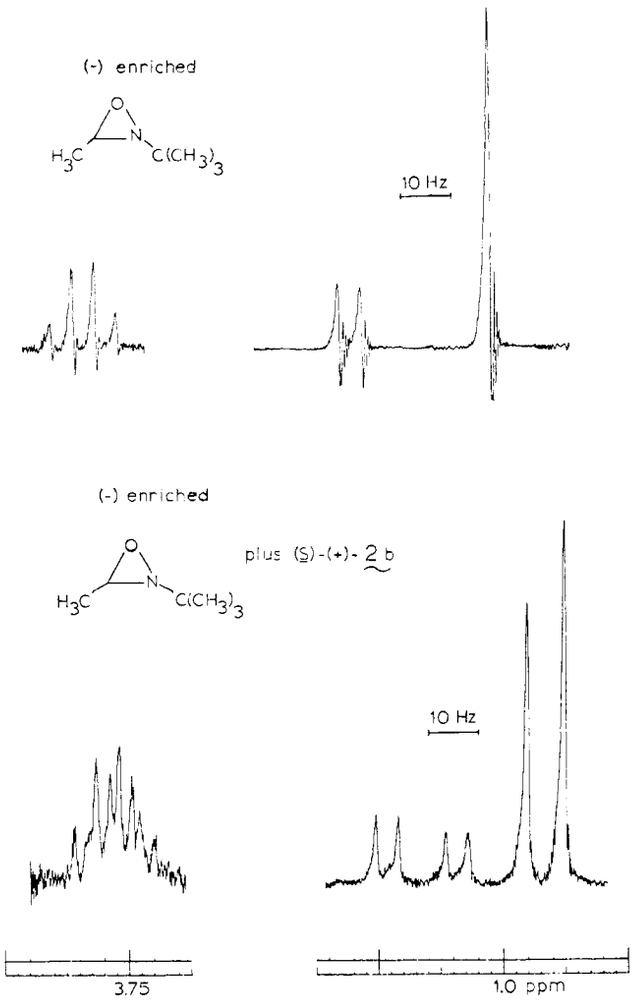
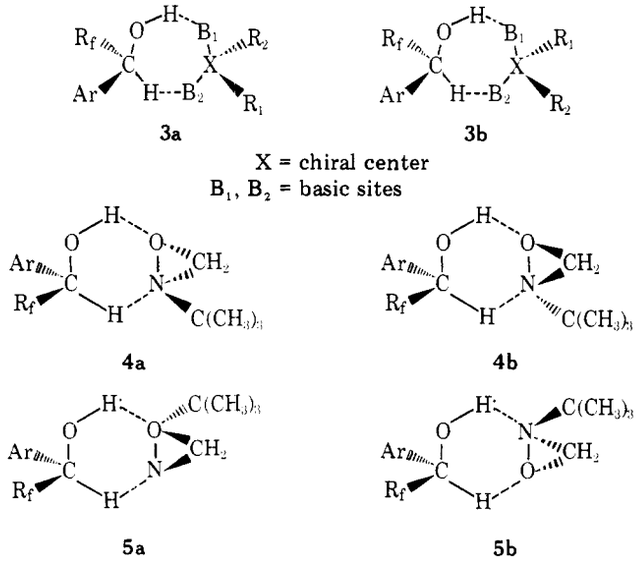


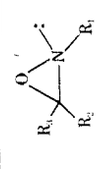
Figure 1. 100-MHz NMR spectrum of (−)-enriched **1b** in the absence (top) and in the presence (bottom) of (*S*)-(+)-**2b.**

since formation of diastereomeric solvates of the type illustrated by **4a,b** as opposed to those illustrated by **5a,b** would



invert the prediction of nonequivalence sense for a given absolute configuration. It is this uncertainty that prevents us from assigning absolute configurations to the oxaziridines in Table I based upon the observed senses of nonequivalence and the known absolute configurations of **2b,c.**

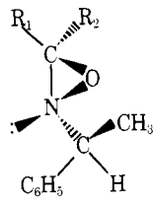
Table I. Properties of Oxaziridines from Percamphoric Acid Oxidation of Imines

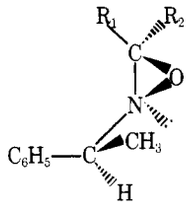


	Registry no.	R_1	R_2	R_3	Chemical shifts, δ CCl_4 R_1	R_2	R_3	Nonequivalence,[a] Hz[b]/sense[c] R_1	R_2	R_3	CSA	Registry no.	% enantiomeric excess by NMR	$[\alpha]^{27}_D$,[d] deg	$[\alpha]^{27}_D$ max, deg
1a	63017-52-7	*t*-Bu	H	H	1.03	3.62 AB	3.62	9.0/H	35.0/H	30.0/L	2b		6	−2.07	−34.5
1b	62107-41-9	*t*-Bu	H	CH_3	1.07	4.00 q	1.37 d	7.5/H	3.0/L	15.0/L	2c	60646-30-2	14[f]	−5.19[g]	−37.1
1c	63017-53-8	CH_3	$-(CH_2)_5-$		2.43	1.3–2.0		11.0/H			2b	63017-54-9	14	−5.39[g]	−38.5
1d	63087-57-0	*t*-Bu	H	C_6H_5	1.05	4.63 s	7.1–7.6	6.7/L	0		2b		21[f]	−22.3	−85.6
1e	40264-03-7	CH_3	H	C_6H_5[e]	2.80	4.25 s	7.27	2.5/L	1.5/H		2c		40[f]		
1f	39345-63-1	CH_3	C_6H_5	H[e]	2.34	5.02 s	7.32	8.5/H		12.0/L	2c		12		
1g	59905-68-9	*t*-Bu	H	*p*-$NO_2C_6H_4$	1.14	4.62 s	7.84	3.5/L	0	3.0/L	2c		25	−30.9	−124

[a] Nonequivalence was caused by adding ca. a threefold excess of (*S*)-(+)-**2b** or (*S*)-(+)-**2c** to a dilute CCl_4 solution of oxaziridine. [b] At 100 MHz and 25 °C. [c] H refers to high-field sense, L to low-field sense. [d] Rotations were taken in CCl_4 using concentrations of ca. 5%. [e] Obtained as a 1.2:1 mixture of trans/cis isomers. [f] Recrystallized MPCA used. [g] Rotations were taken of the neat liquid.

One approach to the determination of the site of the primary interaction (O vs. N) would be to examine partially resolved oxaziridines of known absolute configuration so as to see which primary interaction site accounted for the observed nonequivalence senses. There are but five oxaziridines (**6–10**)





6, R_1, R_2 = C_6H_5
7, R_1 = p-BrC_6H_4; R_2 = H
8, R_1 = H; R_2 = p-BrC_6H_4

9, R_1 = H; R_2 = p-BrC_6H_4
10, R_1 = p-BrC_6H_4; R_2 = H

of known absolute configuration[10,11] and, while partially resolved samples of these all show nonequivalence in the presence of **2d**, no consistent or interpretable pattern of nonequivalence was observed. This was not altogether unexpected, since the aromatic rings on these oxaziridines introduce two complications.[12] First, phenyl rings can act as additional "secondary" basic sites, and give rise to solvation modes other than **4a,b** or **5a,b**. For instance, styrene epoxides are known[13] to show nonequivalence in the presence of chiral type **2** alcohols, the senses of nonequivalence being explained best by a solvate in which the epoxide oxygen acts as the primary basic site, while the phenyl ring acts as the secondary basic site. The second complication attending the aromatic groups in **6–10** is that the anisotropy of the phenyl rings could possibly give rise to nonequivalence stemming from different conformational behavior of these groups in one diastereomeric solvate than in the other. In this event, "internal" nonequivalence would stem from shielding (or deshielding) by the aryl groups *of the oxaziridine* rather than by the "external" anthryl substituent of **2d**. The time-averaged result of such contributions cannot be predicted.

It is evident that enantiomeric compositions of a wide variety of oxaziridines may now be directly determined[14] by using chiral type **2** fluoro alcohols as CSA. The method also appears to have excellent potential for the determination of oxaziridine absolute configuration, although such assignments are presently premature. Determination of the primary site of interaction between oxaziridines and type **2** fluoro alcohols should make such assignments feasible.

Experimental Section

NMR spectra were obtained with Varian Associate A60-A, EM-390, HA-100, and HR-220 spectrometers. Optical rotations were determined in a Zeiss visual polarimeter using a 1.0-dm tube. For nonequivalence measurements spectra were determined at 100 MHz and 27 °C using CCl_4 solutions 0.1–0.2 M in oxaziridine with a one- to twofold excess of **2a, 2b,** or **2c**.

(*S*)-(+)-Monopercamphoric Acid. This compound was prepared by the method of Miles and McAlevy;[16] a viscous syrup was obtained, which was dissolved in CH_2Cl_2 and titrated for active oxygen by iodometry.

Oxaziridines. Oxaziridines were prepared from the corresponding imines using either the procedure illustrated below or by oxidation at −78 °C in a 3:1 $CHCl_3$–CH_2Cl_2 solution using monopercamphoric acid purified by recrystallization. The use of the purified peracid generally leads to a greater degree of asymmetric induction than does use of the mixed percamphoric acid isomers.[17] Oxaziridines so obtained are designated in Table I.

Synthesis of *trans*-2-*tert*-Butyl-2-phenyloxaziridine (1d). A solution of *N*-*tert*-butylbenzaldimine (8.05 g, 0.05 mol) in CH_2Cl_2 (50 mL) was cooled in a dry ince–acetone bath and monopercamphoric acid (11.9 g, 0.055 mol) in 80 mL of CH_2Cl_2 was added dropwise (30 min) to the stirred solution. The bath and the immersed reaction vessel were allowed to slowly warm to room temperature after stirring overnight. The reaction mixture was extracted once with 100 mL of saturated sodium sulfite, then twice with 10% aqueous potassium carbonate. The organic layer was dried over anhydrous potassium carbonate, the solvent removed under vacuum, and the residual oil purified by molecular distillation to afford a clear liquid: $[\alpha]^{25}_D$ = −22.3° (*c* 10, CCl_4); NMR δ CCl_4 7.1–7.6 (m, 5 H, Ar), −4.63 (s, 1 H, CH), 1.05 (s, 9 H, *tert*-butyl).

Chiral Solvating Agents (2). The fluoro alcohols used in this study were synthesized and resolved by a procedure analogous to that reported previously for **2c**.[18] The syntheses, resolutions, and assignments of absolute configuration of **2a–d** have been reported by Pavlin.[19]

Acknowledgments. This work was partially supported by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—$R_2R_3C{=}NR_1$(R_1 = Bu-*t*; R_2, R_3 = H), 13987-61-6; $R_2R_3C{=}NR_1$ (R_1 = Bu-*t*; R_2 = H; R_3 = CH_3), 7020-80-6; $R_2R_3C{=}NR_1$ (R_1 = CH_3; R_2, R_3 = $-(CH_2)_5-$), 6407-35-8; $R_2R_3C{=}NR_1$ (R_1 = Bu-*t*; R_2 = H; R_3 = Ph), 6852-58-0; $R_2R_3C{=}NR_1$ (R_1 = CH_3; R_2 = H; R_3 = Ph), 622-29-7; $R_2R_3C{=}NR_1$ (R_1 = Bu-*t*; R_2 = H; R_3 = $NO_2C_6H_4$) 718-36-5; (*S*)-(+)-monoperoxycamphoric acid, 20696-10-0; **2a**, 10531-50-7.

References and Notes

(1) (a) D. R. Boyd, *Tetrahedron Lett.*, 4561 (1968); (b) F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 1964 (1968); (c) D. R. Boyd and R. Graham, *ibid.*, 2648 (1969); (d) J. Bjorgo, D. R. Boyd, R. M. Campbell, N. J. Norris, and W. B. Jennings, *J. Chem Soc., Perkin Trans. 2*, 606 (1976).
(2) C. Belzecki and D. Mostowicz, *J. Chem. Soc., Chem. Commun.*, 244 (1975).
(3) W. H. Pirkle and P. L. Rinaldi, *J. Am. Chem. Soc.*, **99**, 3510 (1977).
(4) D. R. Boyd and D. C. Neill, *J. Chem. Soc., Chem. Commun.*, 51 (1977).
(5) R. L. Muntz, Ph.D. Thesis, University of Illinois, 1972.
(6) A full description of this general model is being published elsewhere. Specific instances of this type solvation for sulfoxides,[7a-c] amine oxides,[8] and sulfinates[9] have been reported.
(7) (a) W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **90**, 6250 (1968); (b) W. H. Pirkle, S. D. Beare, and R. L. Muntz, *Tetrahedron Lett.*, 2295 (1974); (c) W. H. Pirkle and D. L. Sikkenga, *J. Org. Chem.*, **40**, 3430 (1975).
(8) W. H. Pirkle and R. L. Muntz, *J. Am. Chem. Soc.*, **93**, 2817 (1971).
(9) W. H. Pirkle and M. S. Hoekstra, *J. Am. Chem. Soc.*, **98**, 1832 (1976).
(10) M. Bucciarelli, I. Moretti, G. Torre, G. D. Andretti, G. Bocelli, and P. Sgarabotto, *J. Chem. Soc., Chem. Commun.*, 60 (1976).
(11) M. Bogueka-Ledoehowsk, A. Konitz, A. Hempel, Z. Dauter, E. Borowski, C. Belzecki, and D. Mostowicz, *Tetrahedron Lett.*, 1025 (1976).
(12) The departure of the C-aryl-substituted oxaziridines in Table I from the "opposite sense of nonequivalence" generalization made for C and R substituents presumably has its origin in such effects.
(13) (a) F. Montanari, I. Moretti, and G. Torre, *Gazz. Chim. Ital.*, **104**, 7 (1974); (b) F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 135 (1969).
(14) A referee has raised the question of the precision of NMR determinations of enantiomeric purity. The precision with which the relative intensities of two NMR signals may be determined will be influenced by experimental parameters such as signal to noise ratio, instrument stability, and chemical shift differences between the signals. We routinely attain precision of ±1%. The accuracy of the enantiomeric purity measurements cannot yet be independently checked for oxaziridines. Such checks have been made, however, for methyl esters of α-amino acids and agreements of ±1–2% were observed.[15]
(15) W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **91**, 5150 (1969).
(16) N. A. Miles and A. McAlevy, *J. Am. Chem. Soc.*, **55**, 349 (1933).
(17) W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.*, **42**, 2080 (1977).
(18) W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977).
(19) M. S. Pavlin, Ph.D. Thesis, University of Illinois, 1977.