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ABSOLUTE CONFIGURATION AT CHIRAL NITROGEN IN OXAZIRIDINES
CONFIGURATIONAL CORRELATIONS BY NMR SPECTROSCOPY IN OPTICALLY ACTIVE SOLVATING AGENTS

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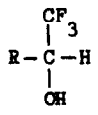
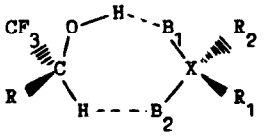
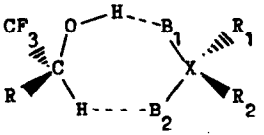
In recent years, chiral solvating agents have been extensively used in NMR spectroscopy to make assignment of absolute configuration for many systems of dissymmetric compounds. Experiences, conducted with solvents of type (1) and of known absolute configuration, have shown that one fundamental model accounts for the nonequivalence observed for the enantiomers of a variety of solute types.[1] In these cases, the hydroxyl proton of (1) is expected to intermolecularly hydrogen bonds to the more basic site B_1 of the solute, while the weaker but intramolecular bonding between the carbinyl hydrogen of (1) and a second basic site B_2 in the solute is postulated to afford chelatelike conformations exemplified by (2,a) and (2,b).[1] Clearly, configurational correlations by using models of type (2) can not be made for systems which present uncertainty about what centre of the molecule has to be considered as B_1 or B_2 site.



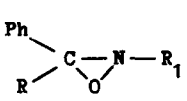
(1)



(2,a)



(2,b)



(3)

a; R = Ph

b; R = α-naphthyl

X = Chiral centre

B_1, B_2 = Basic sites

R = H,Ph

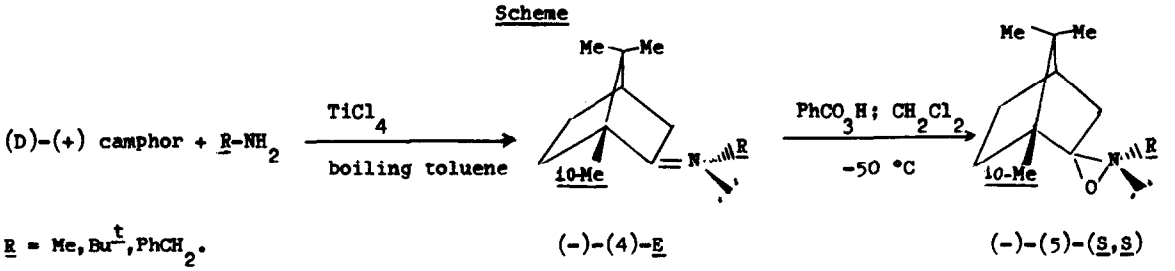
R_1 = Me,Et,Pro^{i},Bu^{t}, $CH(CH_3)Ph$.

Optically active oxaziridines, containing the stable chiral nitrogen, are characterized by having two basic sites: the oxygen and the nitrogen atoms of the three membered ring. Since a priori it is not known which of these two centres is responsible for primary hydrogen bonding, one may try to go round this kind of problem by using closely related series of optically active substrates of known absolute chirality. In a previous work we studied the opportunity of making configurational correlations for chiral oxaziridines of type (3), by comparing the NMR behaviour of partially resolved oxaziridines of known absolute configuration, [R = Ph; R_1 = $CH(CH)_3Ph$][2], with the spectra of optically active oxaziridines of unknown chirality, (R = H,Ph; R_1 = Me,Et,Pro^{i}, Bu^{t}).[3] In many cases, the addition of chiral alcohol (1,a) caused the NMR spectra of oxaziridine enantiomers to be nonidentical.[4] Nevertheless, we could not observe a regular and interpretable

pattern of the nonequivalence for corresponding diastereotopic protons of the compounds examined.[4] This behaviour was attributed to the presence of the aromatic ring(s) directly linked to the carbon atom of the cycle, which can influence the diastereotopic protons of the dissymmetric oxaziridines much more than does the phenyl group of the chiral solvent.[5]

In order to use chiral oxaziridines of known absolute configuration at nitrogen but not containing aryl substituents at the carbon of the cycle, we oxidized with peroxybenzoic acid imines of type (4), obtained from condensation of methylamine, t-butylamine and benzylamine with (D)-(+) or racemic camphor. NMR spectra and t.l.c. revealed that both imine synthesis and subsequent asymmetric oxidation are highly stereoselective: in every case we obtained a much higher proportion (> 95%) of one isomer. The reported stereochemistry for many reactions of compounds containing the 1,7,7-trimethylbicyclo[2,2,1]heptane structure,[6] molecular model analyses and NMR spectra suggest that, independently of whether N-methyl, t-butyl, or benzyl substituent is used, the configurations of major imine and oxaziridine isomer obtained are as depicted in Scheme: i.e., imine (4) and oxaziridine (5) with E configuration and (S,S) absolute chirality at carbon and nitrogen, respectively.[7]

Scheme



R = Me, Bu^t, $PhCH_2$. (-)-(4)-E (-)-(5)-(S,S)

When ^1H NMR spectra of partially optically active (-)-(5) were registered in the presence of chiral (1,a) or (1,b) of known absolute configuration, we obtained the results reported in Table. Doubling of the resonances of the enantiotopic R substituents and C-10 methyl protons is clearly observed. The values of the enantiomeric chemical shift differences ($\Delta\delta$) are generally high and can easily allow direct determination of the enantiomeric compositions of the oxaziridines examined.

The ^1H NMR relative field position of R and C-10 methyl protons reported in Table represents the most important result of this work. When (+)-(S)-(1,a) was used as chiral solvating agent, we observed high for R and low relative field position for C-10 methyl protons respectively. This trend is inverted when NMR spectra of (5) are registered in the presence of (-)-(R)-(1,b). The NMR behaviour observed for alkyl oxaziridines, (R = Me, Bu^t), is not modified by the presence of the aromatic ring of the N-benzyl substituent (R = $PhCH_2$).

Opposite senses of nonequivalence for groups on either side of the chiral centre and the same senses for all protons within a given group, have been reported as typical for dissymmetric systems for which models (2) can be applied.[1] In these cases, it is assumed that shielding ef-

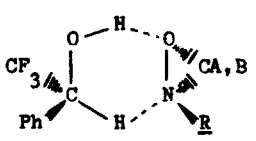
fect of the aromatic R substituent causes the resonances of the R_1 substituent(s) to occur at higher field for the enantiomer incorporated in (2,a) than for that incorporated into (2,b). The converse situation holds for the resonances of R_2 substituents located on the other side of the chiral centre,(see model 2).

Table

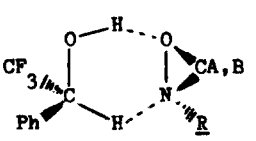
Enantiomeric chemical-shift differences and correlation of ^{1}H NMR relative field position with (S) absolute configuration at Nitrogen for optically active oxaziridines (-)-(5).[a]

Substituent	Δδ, Hz [b] (relative field position)			
	with (S)-(+)-(1,a) [c]		with (R)-(-)-(1,b) [d]	
R	R	10-Me	R	10-Me
Me	3.5 (high)	2.1 (low)	2.2 (low)	2.1 (high)
Bu^t	- --	0.7 (low)	- -	- --
$PhCH_2$	2.3 (high) 1.6 (high)	0.9 (low)	1.5 (low) 1.5 (low)	- --

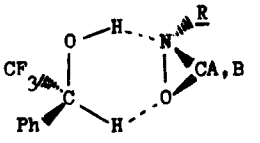
[a] (-)-(5),ca. 70% o.p., were prepared by mixing oxaziridines (5) obtained from reactions carried out with optically active and racemic camphor; [b] ^{1}H NMR spectra were measured on a JEOL-C60-HL spectrometer at 25 °C using samples composed of 2:1:ca. 3 Mol. ratios of alcohol: oxaziridine:CCl_4, respectively; [c] 100 o.p.; [d] 76% o.p., obtained by asymmetric reduction of the corresponding ketone by actively fermenting yeast.[8]



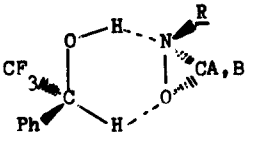
(6,a) S,R solvate



(6,b) S,S solvate



(7,a) S,R solvate



(7,b) S,S solvate

By taking into account that the oxygen and the nitrogen atoms of the oxazirane ring are the most basic sites of molecules (5), we can now apply model (2) to our systems, as represented by structures (6,a) and (6,b) or by (7,a) and (7,b). In these models the oxygen and the nitrogen of the cycle are considered as B_1 and B_2 or B_2 and B_1 sites respectively. Clearly, the prediction of nonequivalence sense for a given absolute configuration is inverted in structures (6) with respect to (7), and if we want to apply NMR spectroscopy for configurational correlations of chiral oxaziridines , we have to choose between these opposite conformations of the diastereoisomeric solvates.

The results of the Table, obtained for oxaziridines (-)-(5) of (S) absolute configuration at

nitrogen, can be accounted for by assuming that interactions between chiral 2,2,2-trifluoro derivatives (1) and oxaziridine enantiomers are controlled by a primary hydrogen bonding between the hydroxyl proton and the nitrogen B_1 basic site of the oxazirane cycle, and by a second bonding between the carbinyl hydrogen of (1) and the oxygen B_2 basic site of the solute, to give structures (7,a) and (7,b). In fact, from these models and not from (6,a) and (6,b), we can predict that Ph or α-naphthyl ring of chiral (S) alcohol causes the resonances of the N-R substituent to occur at higher field for the enantiomer of (S) configuration at nitrogen,[(S,S)-(7,b) solvate], than for that of (R) configuration,[(S,R)-(7,a) solvate]. The opposite situation can be postulated for the resonances of A,B, (in our case 10-Me), substituents located on the other side of the chiral nitrogen centre.

In our opinion, present configurational correlations can be extended at least to optically active dialkyl oxaziridines which, in the presence of chiral alcohols of type (1), have been reported to give NMR results wich are very similar to those obtained in this work.[9]

Acknowledgements.

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3) I. Moretti, F. Montanari, and G. Torre, Gazzetta, 103, 681 (1973).

4) I. Moretti and G. Torre, unpublished results.

5) During the completion of present work, Pirkle and Rinaldi have reported very similar results. Also these Authors, having used oxaziridines of type (3) as reference compounds, were unable to see which primary interaction site of the oxazirane ring accounted for the observed nonequivalence senses.[9]

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7) A. Forni, I. Moretti, and G. Torre, to be published.

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