Comments on the Use of Nuclear Magnetic Resonance Spectroscopy to Assign Absolute Configurations of Diastereomeric Salts

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Summary Because of chemical shift perturbations by ion-pair aggregation, the sense of n.m.r. spectral nonequivalence observed for diastereomeric salts may not be readily correlated with the relative (or absolute) configurations of the diastereomers.

MIKOŁAJCZYK *et al.*[1] have recently assigned the absolute configurations of several phosphorus thio-acids by correlating the senses of n.m.r. spectral nonequivalence of the salts of the acids and chiral α-phenylethylamine with that observed for a similar diastereomeric pair of salts of known configuration. While this correlation technique has proved quite reliable for the diastereomeric solvates formed by enantiomeric solutes in chiral solvents,[2] caution should be exercised in applying the method to diastereomeric salts.

Consider the case of weakly basic enantiomeric solutes, B_R and B_S in a weakly acidic chiral solvent, HA_S. The following equilibria are established; all are rapid on the n.m.r. time scale.

$$B_R + HA_S \overset{k_1}{\rightleftharpoons} B_RHA_S \overset{k_2}{\rightleftharpoons} B_RH^+ + A_S^-$$

$$B_S + HA_S \overset{k_3}{\rightleftharpoons} B_SHA_S \overset{k_4}{\rightleftharpoons} B_SH^+ + A_S^-$$

Now, n.m.r. spectral nonequivalence may be observed either because the diastereomeric solvates have dissimilar spectra, because $k_2 \neq k_4$ (assuming the solvate and the solute cation have dissimilar spectra), or because $k_1 \neq k_3$ (assuming the solvated and nonsolvated solutes have dissimilar spectra). If one is dealing with weak acids and/or bases, the ionic dissociation of the solvates is negligible (*i.e.*, $k_2 \approx k_4 \approx 0$). Moreover, by using an excess of HA_S, both solvation equilibria may be shifted essentially to completion so that differences in k_1 and k_3 are irrelevant. Under these conditions, any enantiomeric spectral nonequivalence observed arises from dissimilarity in the spectra of the diastereomeric solvates. Prior work[2] has demonstrated that these dissimilarities can occur when the chiral solvent contains a moiety possessing high diamagnetic anisotropy (usually an aryl group) and appropriate solvent–solute interactions obtain. These rather specific interactions result in conformations which give rise to enantiomeric spectral nonequivalence, the sense of which is diagnostic of absolute configuration.

When dealing with solutions of diastereomeric salts, the situation is rather different.[3] First, these salts are ionic and, when dissolved in comparatively nonpolar n.m.r. solvents, exist as aggregates of ion pairs. It is well established that the composition of ion-pair aggregates can affect the chemical shifts of salts.[4] Hence, in principle, the magnitudes *and senses* of nonequivalence observed for the diastereomeric salts are influenced not only by the intrinsic spectral nonequivalence of the diastereomers but also influenced by the composition (and possibly the size) of the aggregate. Other factors can, in principle, affect the magnitudes and senses of nonequivalence shown by diastereomeric salts. Using the equations above to refer to strong acids and strong bases, one may assume that $k_1 \approx k_3 \approx \infty$. However k_2 need not equal k_4. Since dissociation of an ion pair may bring about spectral shifts, differential dissociation may contribute to the observed nonequivalence. Accordingly, one expects (and finds) that the magnitude (and perhaps sense) of nonequivalence observed is rather solvent and concentration dependent. Mikołajczyk *et al.*[1] report that the magnitude of nonequivalence observed for the diastereomeric (−)-α-phenylethylamine salts of (I) varied from 9·2 to 2·5 Hz *depending*

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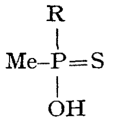
upon which isomer was in preponderance. Changing the sense of preponderance must change the composition and perhaps the size of the aggregate. The sense of the chemical shift perturbation attendant with this change may either reinforce, diminish, or over-ride the intrinsic nonequivalence of the diastereomeric molecules. It is not obvious, within a series of configurationally related diastereomeric salts of similar structure, that one can confidently expect uniformity in the observed sense of nonequivalence.



$$\mathrm{Me{-}\overset{\displaystyle R}{\underset{\displaystyle OH}{P}}{=}S}$$

(I) R = Ph
(II) R = Pr^{i}O

Consider, for example, the observation by Mikołajczyk *et al.*[1] that the (—)-α-phenylethylamine salts of (*R*)-(+)-(I) and of (*R*)-(—)-(II) show their *P*-methyl resonances at lower field than do their diastereomers [*i.e.* the (—)-α-phenylethylamine salts of (*S*)-(+)-(I) and (*S*)-(—)-(II). However, (*R*)-(I) is *not* configurationally similar to (*R*)-(II); substitution of isopropoxy for phenyl in (*R*)-(I) affords (*S*)-(II). Until further work is done in this area, absolute configurations assigned *via* the sense of nonequivalence of diastereomeric salts must be regarded as speculative.

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[1] M. Mikołajczyk, M. Para, A. Ejchart, and J. Jurczak, *Chem. Comm.*, 1970, 654.
[2] W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, 1969, **91**, 5150 and references therein.
[3] I. P. Guette, L. Lacombe, and A. Horeau, *Compt. rend.*, 1968, **267**, *C*, 166.
[4] R. L. Buckson and S. G. Smith, *J. Phys. Chem.*, 1964, **68**, 1875.