Chiral Interactions in Aqueous Solution Mediated by Lanthanoid Ions. N.M.R. Spectral Resolution of Enantiomeric Nuclei

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Summary The 1:1 lanthanoid complexes with chiral α-hydroxycarboxylate ligands act as aqueous chiral n.m.r. shift reagents by stereospecifically forming 1:2 complexes, thereby resolving the resonances of enantiomeric mixtures and of enantiotopic protons.

Nuclei in enantiomeric environments are isochronous in n.m.r. spectra. Spectral resolution of enantiomers has been achieved by employing chiral solvents[1] or by applying chiral shift reagents.[2] With the latter the enantiotopic protons of benzyl alcohols have been resolved.[3] It has also been shown that the application of the achiral shift reagents of the Ln(fod)$_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate) type to non-racemic mixtures of enantiomers results in spectral resolution due to the formation of 1:2 adducts.[4] However, these methods have been restricted to non-aqueous media. We here introduce and illustrate the idea of aqueous chiral lanthanoid shift reagents.

As is well documented, the lanthanoid ions in aqueous solution often form complexes of higher than 1:1 stoicheiometry.[5] With bidentate chiral ligands the 1:1 complex will be chiral and will thus provide not only a chiral environment for a second ligand but also, by virtue of the anisotropic magnetic susceptibility of the paramagnetic lanthanoids (except for Gd^{3+}), the means of observing the chiral interaction in the shifted n.m.r. spectrum. This will be so provided the second ligand binds with a stereochemical preference rather than in a random fashion. Similar arguments apply if higher complexes, *e.g.* 3:1 and 4:1, that also form in these systems[5] are considered. This phenomenon of lanthanoid mediated chiral interactions in aqueous solution was observed with α-hydroxycarboxylates as illustrated in the Figure. An excess of D-mandelate [PhCH(OH)CO$_2^-$] was used to resolve the methyl resonances of a racemic mixture of lactate [MeCH(OH)CO$_2^-$] in the presence of EuCl$_3$. Resonance assignments were accomplished by performing a similar experiment with a non-racemic mixture. The methyl protons of D-lactate experience a larger upfield shift than those of L-lactate in the presence of EuCl$_3$ and D-mandelate. The trend was reversed when L-mandelate was employed. As expected, racemic mandelate produces no spectral resolution (*cf.* Figure). Thus, when complexed with D-mandelato-lanthanoids, the lactate enantiomers become diastereomers. Similar experiments were carried out with YbCl$_3$ and D-mandelate. The methyl protons of L-lactate were shifted downfield whereas those of D-lactate experienced a small upfield shift.

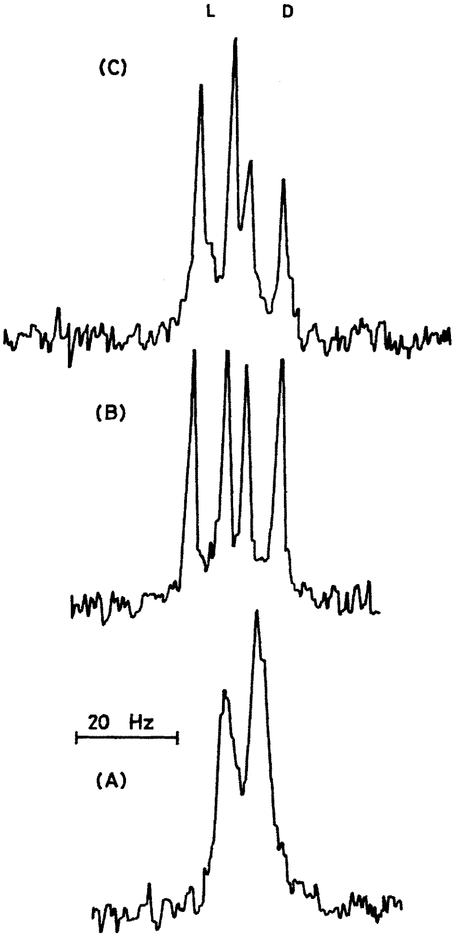

Figure. The methyl proton resonance at 100 MHz of 9·3 mM lactate in the presence of 12·5 mM EuCl$_3$ and 41·2 mM mandelate. (A) Racemic lactate and racemic mandelate; (B) racemic lactate and D-mandelate; (C) excess of L-lactate (L/D=2) and D-mandelate.

The most stringent test of chirality seems to be the ability to resolve enantiotopic protons. The singlet proton resonance of glycolate (HOCH$_2$CO$_2^-$) changes to an AB quartet in the presence of PrCl$_3$ and a molar excess of L-lactate, as a result of the enantiotopic methylene protons becoming diastereotopic. Resolution of the enantiotopic methyl groups of α-hydroxyisobutyrate, Me$_2$C(OH)CO$_2^-$, was also observed with EuCl$_3$ or YbCl$_3$ in the presence of D-mandelate. With YbCl$_3$ one of the resonances was shifted downfield from its original position whereas the other experienced a small upfield shift. This is analogous to the observation with lactate and a stereochemical assignment of the methyl groups of α-hydroxyisobutyrate can now be made.

Mechanisms responsible for these chiral interactions can tentatively be identified. Evidently there is a structural stereospecificity in the formation of 2:1 (or higher) α-hydroxycarboxylato complexes of the lanthanoids. The facts that enantiotopic protons can be resolved and that some lanthanoids (*e.g.* Yb^{3+}) produce shifts in one direction for one enantiomer but in an opposite direction for the other, suggest that one of the mechanisms involves the absence of axial symmetry for the magnetic susceptibility tensor of the central ion. Bidentate co-ordination of the ligands removes the possibility for internal rotations and stereochemical rearrangements of the ligands within the complex, processes that have been suggested as the mechanisms leading to effective axial symmetry in many lanthanoid shift reagent systems.[6] It should be emphasised that these phenomena are observed under conditions of rapid ligand exchange rate relative to the chemical shift difference between complexed and uncomplexed ligands. This is not so, for example, with the chiral ligands of the lanthanoid β-diketonates. The sense of resolution of enantiomeric mixtures (lactate in this example) is a reflection of the absolute configuration at the chiral centre of the ligand (mandelate in this case) used to achieve the resolution. Thus the sense of resolution of non-racemic enantiomeric mixtures of known composition may be used as a 'finger print' of the absolute configuration of the ligand responsible (in the presence of paramagnetic lanthanoids) for that resolution.

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[1] W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, 1969, **91**, 5150 and references cited therein.

[2] G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, 1970, **92**, 6979; 1971, **93**, 5914; H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *ibid.*, p. 5913; H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, *ibid.*, 1974, **96**, 1493; M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *ibid.*, 1972, **94**, 5924.

[3] R. R. Fraser, M. A. Petit, and M. Miskow, *J. Amer. Chem. Soc.*, 1972, **94**, 3253.

[4] K. Ajisaka and M. Kainosho, *J. Amer. Chem. Soc.*, 1975, **97**, 1761.

[5] S. P. Sinha, 'Complexes of The Rare Earths,' Pergamon Press, Oxford, 1966.

[6] J. M. Briggs, G. P. Moss, E. W. Randall, and K. D. Sales, *J.C.S. Chem. Comm.*, 1972, 1180; W. DeW. Horrocks, Jr., *J. Amer. Chem. Soc.*, 1974, **96**, 3022.