The Europium(III)–(*R*)-Propylenediaminetetra-acetate Ion: a Promising Chiral Shift Reagent for ^{1}H N.M.R. Spectroscopy in Aqueous Solution

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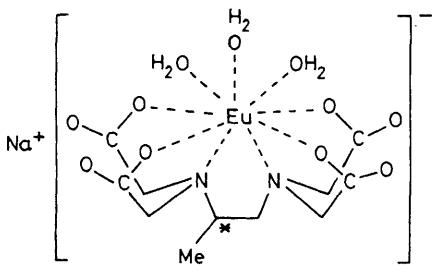
The title ion is shown to be a useful chiral shift reagent in the ^{1}H n.m.r. spectroscopy of hydroxy-, amino-, and carboxylic-acids in aqueous solution.

Chiral lanthanoid shift reagents are widely used to determine enantiomeric purities of various types of organic compounds in organic solvents.[1] There have been only two reports,[2,3] however, of chiral shift reagents for use in water which is the appropriate solvent for many chiral natural products. Europium(III) α-hydroxycarboxylate derivatives can be prepared only *in situ* and are effective when they are used in excess of the substrates.[2] The recently reported Eu^{III}– and Yb^{III}–(*S*)-carboxymethyloxysuccinate complexes showed in the 200 MHz n.m.r. spectrum *ca.* 0.05 p.p.m. separation of the enantiomeric protons of alanine.[3] We report herein our preliminary results with europium(III)–(*R*)-propyl-



(1)

Table 1. Separation of the ^1H n.m.r. signals of enantiomers in the presence of (**1**).[a]

Compound	Mol ratio [(**1**) : Substrate]	Signal observed	ΔΔδ (p.p.m.)	Enantiomer with higher field signal
Lactic acid	0.11	Me	0.19[b]	*R*
		CH	0.30[b]	*S*
Mandelic acid	0.04	CH	0.12	*S*
Atrolactic acid[c]	0.09	Me	0.11	*S*
Alanine	0.12	Me	0.13[b]	*R*
		CH	0.32[b,d]	*S*
Valine	0.04	CH	0.13	*S*
Isoleucine	0.04	CH	0.09[e]	*S*
Threonine	0.13	Me	0.17	*R*
		CH	0.6[d]	*S*
2-Phenylpropionic acid[f]	0.20	Me	0.03	*S*
		CH	0	—
Isobutyric acid	0.13	Me	0.03	—

[a] Spectra (90 MHz) were run in D_2O at 35 °C using $Me_4N^+I^-$ (δ 3.19) (ref. 5) as an internal standard under the following conditions unless otherwise stated. Concentration of substrate 0.4—0.6 M; ratio of enantiomers, *R* : *S* = 1 : 2; pH for hydroxy acids, 3.8—4.0, for amino acids, 11.5—11.8, and for carboxylic acids, 5.0—5.2; pH adjusted using a solution of NaOD. [b] Data at 31 °C. [c] 21% e.e. for the *R*-enantiomer. [d] Distinct line broadening was observed. [e] Concentration of substrate = 0.2 M. [f] 30% e.e for the *R*-enantiomer.

enediaminetetra-acetate (*R*-pdta) which shows that it is very promising as a chiral shift reagent in aqueous solution.

The europium(III) complex, $Na[Eu(R\text{-pdta})(H_2O)_3]\cdot 2H_2O$ (**1**), was prepared from Eu_2O_3 and (*S*)-propylenediaminetetra-acetic acid, by a similar method to that used for the corresponding ethylenediaminetetra-acetate (edta) complex.[4] The effects of (**1**) on the n.m.r. spectra of some hydroxy-, amino-, and carboxylic-acids are summarized in Table 1. Addition of (**1**)† to a solution of lactic acid resolved both the H_α and Me signals (Figure 1). The magnitudes of the shift differences between the enantiomers (ΔΔδ) were sufficient to determine the enantiomeric purity even on a 90 MHz n.m.r. instrument.

The ΔΔδ values show a strong pH dependence. The separation of signals of lactic acid was optimum at pH *ca.* 4 and was not observed at pH *ca.* 12. Conversely, good separation of the H_α and α- and β-Me signals of amino acids was attained even at high pH (*ca.* 12).§ All of the H_α signals of the (*S*)-enantiomers of the amino acids were shifted by a larger amount than those of the (*R*)-isomers, which suggests a possible configurational determination of amino acids using (**1**).

The potential ability of (**1**) in differentiating enantiomers was also shown for simple carboxylic acids. The Me signal of 2-phenylpropionic acid was resolved into a set of doublets with 0.03 p.p.m. separation at a mol ratio of (**1**) : 2-phenylpropionic acid 0.20. Furthermore, the enantiotopic Me signals of isobutyric acid were separated in the presence of (**1**). Complex (**1**) is the first lanthanoid shift reagent that has been reported to resolve the n.m.r. signals due to enantiomers and enantiotopic groups of carboxylic acids.

† The ^1H n.m.r. spectrum of (**1**) in D_2O showed broad signals at δ 7.0, 5.4, 3.1, and 1.0. Other signals range from δ −2 to −5.5. Although the signals are small under the usual conditions of the shift measurement, care must be taken in accurate determinations of enantiomeric purity of substrates.

‡ Distinct line broadening was observed for the H_α signals at a mol ratio of (**1**) : (amino acid) > 0.1. However, less broadening occurred at higher temperature.

§ Addition of (**1**) to a neutral solution of alanine gave some precipitation.

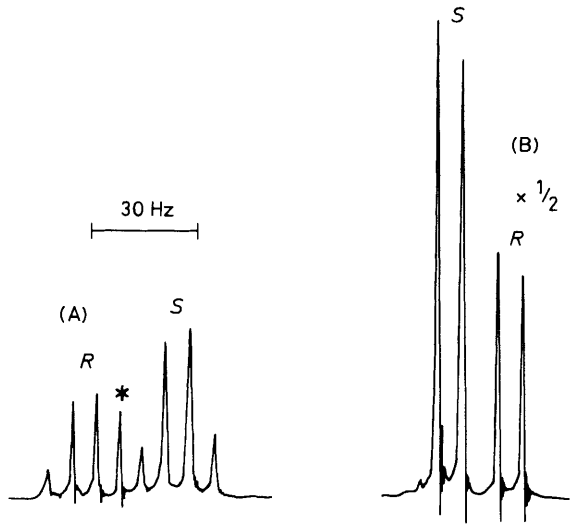


Figure 1. ^1H N.m.r. (90 MHz) spectrum of 30 mg lactic acid (*R* : *S* = 1 : 2) in D_2O in the presence of (**1**) [mol ratio (**1**) : lactic acid = 0.11] at pH 4.0 (31 °C). (A) H_α signals, the asterisk indicates a peak with a side band due to H_2O. (B) Methyl signals.

The Me signals of both enantiomers of alanine were shifted to higher field by (**1**), whereas those of lactic acid were moved to higher and lower field for (*R*)- and (*S*)-isomers, respectively. These two structurally similar substrates would co-ordinate to (**1**) differently. Circular dichroism[6] and circularly polarized luminescence studies[7] indicated that structural change of (**1**) occurs on increasing the pH beyond *ca.* 10—11, and that *R*-pdta is retained in the co-ordination sphere over the pH range 1.5—13.0. The suggested high pH species is a hydroxo complex of (**1**). Structural change in (**1**) is probably responsible for the different shift behaviour of the two substrates.

Complex (**1**) has the following favourable features as a chiral shift reagent in aqueous solution. Its stability constant could be as high as 10^{15}—10^{20} $mol^{-1}\,dm^3$, judging from those of lanthanoid–edta complexes.[8] The substrates probably interact with (**1**) at the sites normally occupied by water molecules or hydroxide ions. Substrate exchange should be

rapid on the n.m.r. time scale,[9] and furthermore, the flexibility of the co-ordination geometry of lanthanoid complexes can create an asymmetric environment in the exchanging sites upon co-ordination of *R*-pdta.[10]

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References

1 G. R. Sullivan, 'Topics in Stereochemistry,' vol. 10, John Wiley and Sons, New York, 1978, p. 287.
2 J. Reuben, *J. Chem. Soc., Chem. Commun.*, 1979, 68; *J. Am. Chem. Soc.*, 1980, **102**, 2232.
3 J. A. Peters, C. A. M. Vijverberg, A. P. G. Kieboom, and H. van Bekkum, *Tetrahedron Lett.*, 1983, **24**, 3141.
4 A. Merbach and F. Gnagi, *Chimia*, 1969, **23**, 271.
5 J. K. M. Sanders, S. W. Hanson, and D. H. Williams, *J. Am. Chem. Soc.*, 1972, **94**, 5325.
6 S. Misumi, T. Isobe, and H. Furuta, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 421.
7 H. G. Brittain and K. H. Pearson, *Inorg. Chem.*, 1983, **22**, 78.
8 'Stability Constants,' Special Edition No. 17, The Chemical Society, 1964, p. 634.
9 R. V. Southwood-Jones and A. E. Merbach, *Inorg. Chim. Acta*, 1978, **30**, 138.
10 *Cf.* K. Z. Suzuki, Y. Sasaki, S. Ooi, and K. Saito, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1288.