Highly Consistent Correlation between Absolute Configuration of α-Amino Acids and Their Shift induced by the N.M.R. Chiral Shift Reagent Propylenediaminetetra-acetatoeuropium(III) in Aqueous Solution

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A highly consistent correlation was observed between the absolute configuration of α-amino acids and the shift of their α-proton signals induced by the chiral lanthanoid n.m.r. shift reagent for aqueous solution, propylenediaminetetra-acetatoeuropium(III).

Chiral lanthanoid n.m.r. shift reagents with 1,3-diketonate ligands derived from (+)-camphor have been widely used for the determination of the enantiomeric composition of various organic substrates.[1] However, it seems generally accepted that the assignment of absolute configuration by these reagents is not reliable. The correlation of the absolute configuration with the induced shift has been attempted for only a limited number of closely related series of substrates.[2] Nevertheless some exceptions have been observed.[2b,2e]

We now report a highly consistent correlation between the absolute configuration and the lanthanoid induced shift of the α-proton signals of enantiomeric α-amino acids using the europium(III) complex of optically active propylenediamine-tetra-acetate, Na[Eu(*R* or *S*-pdta)$(H_2O)_3$] (**1**), a useful chiral shift reagent for aqueous solution.[3] In 22 examples of wide variety, the H_α signals due to the L-enantiomers always showed larger upfield shifts than those due to the D-isomer in the presence of (*R*)-(**1**) (Tables 1 and 2).†

Table 1. Enantiomeric chemical shift difference (ΔΔδ) and the sense of nonequivalence of H_α signals in the presence of (*R*)-(**1**).[a]

Entry	Amino acid	pH	Molar ratio of (*R*)-(**1**) [(**1**)/amino acid]	ΔΔδ, p.p.m.	Enantiomer with higher field signal
1	Alanine	10.2	0.03	0.08	L
2	Valine	9.7	0.03	0.14	L
3	Leucine[b]	10.2	0.09	0.21	L
4	Isoleucine	9.9	0.04	0.09	L
5	Phenylalanine[b]	9.3	0.04	0.08	L
6	Proline[c]	10.0	0.03	0.08	L[e]
7	Serine	9.4	0.03	0.20	L
8	Threonine	9.3	0.03	0.20	L
9	Methionine	10.1	0.03	0.13	L
10	Djenkolic acid[b]	10.5	0.04	0.16	L
11	Asparagine[b,d]	8.5	0.06	0.03	L
12	Glutamic acid[b]	10.4	0.05	0.19	L
13	Cysteic acid	9.6	0.02	0.03	L[e]
14	Phosphoserine[b,c]	9.9	0.04	0.16	L[e]
15	Ornithine	10.1	0.03	0.10	L[e]
16	Lysine[b]	9.8	0.06	0.13	L
17	Arginine	9.4	0.03	0.09	L
18	Histidine	10.0	0.02	0.21	L[e]

[a] The ^1H n.m.r. spectra were taken for D_2O solutions at 90 MHz under the following conditions unless otherwise stated: conc.: 0.12 M; D/L: 1/2; temp.: 35 °C. [b] Conc. 0.06 M. [c] D/L 1/3. [d] At 50 °C. [e] Because of the signal broadening and/or poor resolution of the signals, the assignment was confirmed by comparing the spectra of partially resolved samples with those of racemic ones.

† Shift data for tyrosine and aspartic acid could not be obtained because of strong broadening of H_α signals by (**1**). For *N*-methyl-leucine the induced shift was small (L.I.S. 0.25) and a distinct enantiomeric chemical shift difference was not observed even at a (**1**): amino acid ratio of 0.7 : 1.

The ^1H n.m.r. spectra were determined for D_2O solutions at pH 8.5—10.5. Addition of a small amount of (*R*)-(**1**) [molar ratio, (**1**)/amino acid <0.1] to a solution of α-amino acid enantiomers shifted the H_α signal upfield, giving separate signals. Unambiguous assignment of the separate signals was attained by use of a non-equimolar mixture of enantiomers.

The substrates examined include acyclic and cyclic amino acids without any additional functional groups (entries 1—6), and those with neutral, acidic, and basic ones (entries 7—11, 12—14, 15—18, respectively).

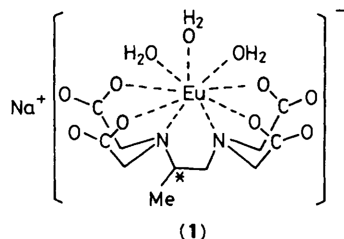
The results summarized in Table 1 indicate that the (*R*)-(**1**) reagent causes a larger upfield shift of the H_α signals of L-α-amino acids than the (*S*)-(**1**) reagent. With the D-amino acids, the results should be reversed. The easy accessibility of (*S*)-(**1**) [prepared by the same procedure as for (*R*)-(**1**) using (*S*)-propylenediaminetetra-acetic acid; see ref. 3] enabled us to examine the correlation with optically pure substrates. The observations (Table 2) on L- and D-alanine, L-alloisoleucine, L-kainic acid, L-glutathione (γ-L-glutamyl-L-cysteinylglycine), and D-glucosaminic acid are consistent with the results in Table 1.

The most critical test for the use of the lanthanoid shift reagent seems to be to examine the consistency for substrates with a functional group on the side chain because this may provide additional interaction[4] with (**1**) and invert the correlation of the configuration with the induced shift. It is, therefore, important to note that no exceptions have been observed within such substrates so far examined. Thus, the use

Table 2. Lanthanoid induced shifts (L.I.S.) of H_α signals of optically pure amino acids by (*R*)- and (*S*)-(**1**).[a]

Amino acid	pH	L.I.S., p.p.m. (*R*)-(**1**)[b]	L.I.S., p.p.m. (*S*)-(**1**)[b]
L-Alanine	10.3	6.00	3.69
D-Alanine	10.3	3.27	6.06
L-Alloisoleucine	9.8	6.02	0.44
L-Kainic acid	10.1	3.09	1.76
L-Glutathione	10.3	5.87[c]	2.40[c]
L-Glucosaminic acid	9.6	6.17	8.39

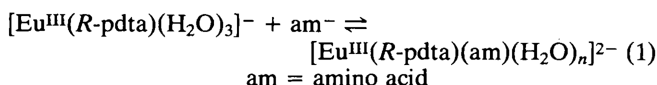
[a] Slope of the induced shift plots *vs.* molar ratio of the reagent [(**1**)/amino acid <0.15], determined for 0.1 M solutions at 90 MHz, 35 °C, using t-butyl alcohol or dioxane as an internal standard. [b] These reagents were prepared using (*R*)- and (*S*)-propylenediaminetetra-acetic acid monohydrates: {(*R*)-pdta$H_4 \cdot H_2O$, $[\alpha]_D^{20}$ −43.1° (*c* 0.52, H_2O); (*S*)-pdta$H_4 \cdot H_2O$, $[\alpha]_D^{20}$ + 41.7° (*c* 0.52, H_2O)}; *cf.* F. P. Dwyer and F. L. Garvan, *J. Am. Chem. Soc.*, 1959, **81**, 2955. [c] Value for the H_α signal of the glutamic acid moiety.



(1)

of (**1**) is highly promising for the determination of the absolute configuration of α-amino acids[5] in underivatized form.‡

The induced shift is mainly the result of the establishment of the rapid equilibrium (1).[4] The induced shift is much smaller for a monodentate substrate such as acetate ion.§ Thus the amino acids should co-ordinate to the europium(III) complex in the chelate form.[4,6] The difference in the formation constants for diastereoisomeric amino acid complexes for D- and L-isomers is probably responsible for the observed separation of enantiomer signals.¶



$$[Eu^{III}(R\text{-pdta})(H_2O)_3]^- + am^- \rightleftharpoons [Eu^{III}(R\text{-pdta})(am)(H_2O)_n]^{2-} \quad (1)$$

am = amino acid

‡ The use of this reagent is not suitable for the analysis of enantiomeric composition of the substrates. In many cases, insufficient separation of enantiomer signals and/or distinct line broadening caused by the reagent prevented accurate integration of the enantiomer signals. It is, however, possible to estimate an approximate value for the enantiomeric composition for most substrates used here (see also footnote e of Table 1).

§ The following L.I.S. values were obtained for acetate and glycinate. L.I.S.($CH_3CO_2^-$): 0.21 p.p.m. (0.12 M, pH 10.1), L.I.S.(H_2N-$CH_2CO_2^-$): 8.21 p.p.m. (0.12 M, pH 10.1).

¶ The signals of the enantiotopic protons of glycinate were not resolved. Therefore, the intrinsic chemical shift difference of H_α signals between the diastereoisomeric complexes of (**1**) with the D- or L-isomer is probably not important for the enantiomeric shift difference; *cf.* ref. 1(b), p. 289.

The inconsistent correlation between absolute configuration and induced shift by the shift reagents with tris-diketonate ligands has been ascribed to many of the factors responsible for enantiomeric chemical shift differences,[7] including the ambiguity about the structure of the reagent in solution. The structure of (**1**) should be retained in solution since the stability constant is extremely high[3] and the interactions with the substrates are restricted at the sites where water molecules are usually located. Such simple structural characteristics contribute to the consistent correlation of the absolute configuration with the shift induced by (**1**).

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