A europium(III)–*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-(*R*)-propylenediamine complex as a new chiral lanthanide NMR shift reagent for aqueous neutral solution

Ryoichi Hazama,[a] Keisuke Umakoshi,[a] Chizuko Kabuto,[b] Kuninobu Kabuto*[c] and Yoichi Sasaki*[a]

[a] *Division of Chemistry, Graduate School of Science, Hokkaido University, Kita-ku, Sapporo 060, Japan*
[b] *Instrumental Analysis Center for Chemistry, Faculty of Science, Tohoku University, Aoba, Aramaki, Aoba-ku, Sendai 980-77, Japan*
[c] *Department of Chemistry, Graduate School of Science, Tohoku University, Kawauchi, Aoba-ku, Sendai 980-77, Japan*

A new chiral lanthanide shift reagent [Eu^{III}Cl$_2${(*R*)-tppn}]ClO$_4$ which is structurally characterized by X-ray crystallography, resolves the enantiomer signals of α-amino acids in neutral aqueous solution and affords a good relation between the relative signal position of enantiomers and their absolute configurations.

Direct determination of the absolute configuration of underivatized organic compounds is an intriguing subject. Chiral lanthanide shift reagents, if they are properly designed, can provide a useful approach for such purpose.[1] During our continuing studies on chiral lanthanide shift reagents suitable for such purpose, we have found a novel europium complex, [Eu^{III}Cl$_2${(*R*)-tppn}]ClO$_4$ **1** [tppn = *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)propylenediamine], which resolved the enantiomer signals of α-amino acids in aqueous solution even at neutral pH. This property of **1** has not been seen in other reagents and is considered advantageous to avoid possible undesired change of substrates under alkaline conditions usually employed for other shift reagents.[2]

Complex **1** was obtained as a pale brown precipitate† by refluxing a 1:1 mixture of $EuCl_3 \cdot 6H_2O$ and (*R*)-tppn[3] in methanol and subsequent addition of 3 equiv. of $NaClO_4 \cdot H_2O$ in methanol. Complex **1** is soluble in water and stable at neutral pH.‡

The structure of **1** was determined by an X-ray analysis at 150 K on a single crystal obtained by recrystallization from acetonitrile§ and an ORTEP view is shown in Fig. 1. The Eu^{3+} ion is eight-coordinate with six nitrogen donor atoms from the tppn ligand and two chloride ions. The coordination geometry is best described as a distorted dodecahedron.¶ The angle [N(11)–Eu–N(41)] formed by Eu and two pyridine nitrogens adjacent to Cl(2) is large (150.9°), while the angle [N(21)–Eu–N(31)] formed by the other two pyridine nitrogens opposite Cl(2) is small (73.6°). Another characteristic feature is the deviation from co-planarity of four coordinated pyridine nitrogen atoms [N(11), N(21), N(31), N(41)] which form a trapezoid when viewed from the direction of Cl(1)–Eu: deviations from the mean plane are 0.135, −0.226, 0.233 and −0.143 Å respectively [minus indicating the opposite side of the mean plane relative to Cl(1)]. The Eu is displaced by −0.286 Å from the mean plane. The mean value of the dihedral angles between two sets of triangles dividing the trapezoid square is 21.4°. Similar but less marked non-planarity (av. 12.2°)‖ was observed for the four coordinated carboxyl oxygen atoms of sodium(propylenediaminetetraacetato)europium(III) **2** in a hexameric structure.[4] These non-planarities can be ascribed to a *gauche* conformation of the propylenediamine moiety [torsion angle of N(1)–C–C–N(2) in **1**: 53.4°]. As for **2**, the direction of

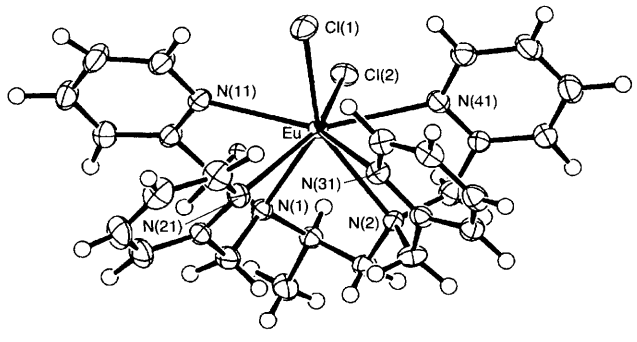

Fig. 1 ORTEP drawing of **1**. Perchlorate is not shown for clarity. Selected bond lengths (Å) and angles (°) are as follows. Eu–Cl(1) 2.653(1), Eu–Cl(2) 2.672(1), Eu–N(1) 2.603(3), Eu–N(2) 2.621(3), Eu–N(11) 2.628(3), Eu–N(21) 2.546(4), Eu–N(31) 2.602(3), Eu–N(41) 2.593(4), Cl(1)–Eu–Cl(2) 99.0, Cl(1)–Eu–N(11) 80.0, Cl(1)–Eu–N(21) 96.1, Cl(1)–Eu–N(31) 84.4, Cl(1)–Eu–N(41) 83.9, Cl(2)–Eu–N(1) 82.5, Cl(2)–Eu–N(2) 90.1, Cl(2)–Eu–N(11) 83.5, Cl(2)–Eu–N(41) 75.3, N(1)–Eu–N(2) 68.1, N(1)–Eu–N(11) 66.2, N(1)–Eu–N(21) 67.5, N(2)–Eu–N(21) 95.1, N(2)–Eu–N(31) 67.8, N(2)–Eu–N(41) 66.3, N(31)–Eu–N(41) 64.6, e.s.d.s (angles) 0.0–0.1(°).

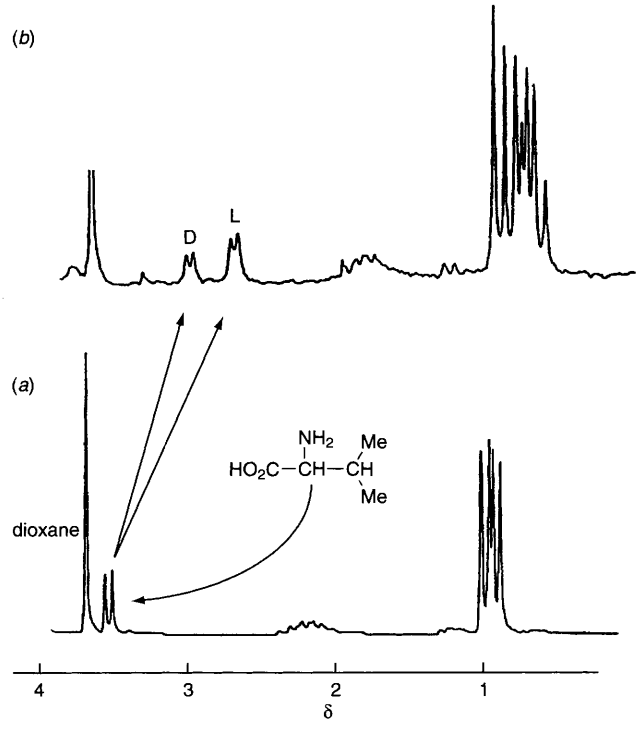

Fig. 2 ^{1}H NMR spectra (90 MHz) of 0.06 mol dm^{-3} valine (D:L = 1:2) in D_2O: (*a*) [**1**]/[valine] = 0, pH 6.9; (*b*) [**1**]/[valine] = 0.44, pH 7.5

Table 1 Chemical shift non-equivalence of the enantiomer signals of amino acids and related compounds in the presence of **1**[a]

Entry	Compound	pH	Molar ratio [Reag.]/[Subst.]	Signal	ΔΔδ/ppm	Enantiomer with upfield signal
1	alanine	7.7	0.46	H_α	0.20	L
				CH_3	0.41	D
2	valine	7.5	0.44	H_α	0.30	L
3	isoleucine	7.1	0.18	H_α	0.19	L
4	phenylalanine	7.0	0.16	H_α	0.07	L
5	methionine[b]	7.2	0.28	H_α	0.19	L
				H_γ	0.22	D
				SCH_3	0.11	D
6	threonine[c,d]	6.9	0.16	H_α	0.11	L
				CH_3	0.04	D
7	asparagine[b,e]	6.4	0.13	H_α	0.05	L
8	proline[f]	7.0	0.28	H_α	0.13	L
9	lysine[b]	7.4	0.20	H_α	0.10	L
10	*N*-acetylalanine[d,g]	7.0	0.15	CH_3CO	0.05	D
				CH_3	0.03	D
11	glycylvaline[d,g]	6.9	0.34	H_α	0.09	L
				H_2NCH_2	0.07	D
12	2-aminoisobutyric acid	7.5	0.18	CH_3	0.27	—
13	2-hydroxyisobutyric acid[g]	7.4	0.28	CH_3	0.13	—
14	isobutyric acid[g]	5.5	0.24	CH_3	0.12	—

[a] The ^1H NMR spectra were taken for D_2O solutions at 90 MHz under the following conditions unless otherwise stated: c = 0.06 mol dm^{-3}, D:L = 1:2; T = 35 °C; internal standard: dioxane (δ 3.76 from TSP). [b] Internal standard: Bu^{t}OH (δ 1.25 from TSP). [c] D:L = 2:1; 80 °C. [d] Internal standard: dichloromethane (δ 5.47 from TSP). [e] 85 °C; because of the signal broadening and insufficient separation of the signals, the assignment was confirmed by comparing the spectra with those of the racemic sample. [f] At 270 MHz; 25 °C. [g] 50 °C.

the twisting, which is related to the chirality of the propylenediamine moiety, plays an important role in differentiating enantiomer signals through different bound shifts and different formation constants.[2c]

The most significant feature of **1** as a chiral lanthanide shift reagent is that it can resolve the enantiomer signals of α-amino acids under netural conditions. This is in contrast to reported reagents such as **2** which are effective only under alkaline or acidic condition.[1,2] As a typical example, the spectral changes of valine (D:L = 1:2) at neutral pH upon the addition of **1** is shown in Fig. 2. The signal due to the α-proton is shifted upfield and is resolved into a pair of enantiomeric signals with the α-proton of the L-isomer at higher field. This relation between the sense of non-equivalence of enantiomeric α-proton signals and their absolute configurations holds without exception for the common α-amino acids examined (Table 1, entries 1–9).

In contrast, signals from α-methyl, γ-proton and β-methyl groups show reversed correlation (entries 1, 5, 6). Although the results are preliminary, the use of **1** for assignment of absolute configuration of α-amino acids at neutral pH appears promising.

The positive charge of **1** probably plays an important role in the interaction with a substrate. Complex **1** is monopositive and may be di- or tri-positive in aqueous solution as coordinated Cl^- is likely to dissociate. Cationic **1** would interact more strongly with the carboxyl group of amino acids than would an anionic complex such as **2**. Complex **1** is also effective towards *N*-acyl α-amino acids (entries 10, 11), which have not previously shown resolved signals with other reagents in aqueous solution. Furthermore, the result of entry 11 encourages the application of **1** in the assignment of oligopeptides.

The resolution of signals due to enantiotopic methyl groups by **1** is good for 2-aminoisobutyric acid, but more significant signal broadening was observed for 2-hydroxyisobutyric acid and isobutyric acid. The interaction between these substrates and **1** at ambient temperature is too strong to give well-resolved signals. **1** does not work as a shift reagent in acetonitrile, probably because the Cl^- ligands are retained in the coordination sphere so preventing interaction with the substrates. We are investigating further to find conditions to use **1** as a shift reagent in organic solvents.

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Footnotes

† Elemental analysis. Calc. for $C_{27}H_{30}EuCl_3N_6O_4$: C, 42.62; H, 3.97; N, 11.05. Found: C, 42.13; H, 3.92; N, 10.92%. **1** is soluble in water and acetonitrile but insoluble in common NMR solvents such as chloroform or benzene.

‡ The formation constant of a similar Eu–tpen complex [tpen = *N,N,N′,N′*-tetrakis(2-pyridylmethyl)ethylenediamine] in neutral aqueous solution is reported to be $10^{5.7}$ dm^3 mol^{-1}.[5] The ^1H NMR spectrum of **1** in D_2O showed broad signals at δ −0.1, 3.3, 4.8–5.0 and 6.0–9.5 at pH 7. The ^1H NMR signals of **1** became distinct around pH 5, indicating some decomposition of **1** occurred. At pH 10 a colourless solid precipitated.

§ *Crystal data*: $C_{27}H_{30}Cl_3EuN_6O_4$, M_r = 760.89, a = 15.873(1), b = 24.137(4), c = 7.720(1) Å, U = 2950.8(6) Å^3, space group = $P2_12_12$ (no. 18), Z = 4, D_c = 1.713 g cm^{-3}, μ(Mo-Kα) = 24.44 cm^{-1}. Data collection; T = 150 K, 45 kV, 200 mA, 6707 measured reflections ($2\theta_{max}$ = 68°). The final R factor was 0.0262 (R_w = 0.0282) for 5936 reflections with $F_o > 6\sigma(F_o)$. Details of the crystallography have been submitted elsewhere. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

¶ The four coordinated pyridine nitrogens and Cl(2) are approximately on a plane and form a pentagon. The coordination of Cl(1) is almost perpendicular to this plane. The two nitrogens of diamine are located on the other side of the plane.

‖ The angle (12.2°) was calculated using the data for **2**; see ref. 3.

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