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Consistent Correlation between Absolute Configuration of α-Hydroxy Carboxylic Acids and Lanthanoid Induced Shift by an NMR Chiral Shift Reagent in Aqueous Solution

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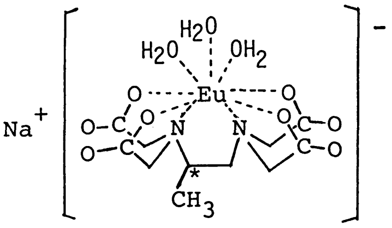
The absolute configuration of various α-hydroxy acids, including those with polar substituent(s) on the side chain, have been consistently correlated with the relative position of α-proton or α-methyl signals due to their enantiomers in ^{1}H NMR in the presence of the chiral shift reagent for aqueous solution, 1,2-propanediaminetetraacetatoeuropium (III).

The chiral lanthanoid NMR shift reagents with 1,3-diketonate ligands have been used for the determination of enantiomeric purity, whereas they have not been used for the determination of absolute configuration. Although several workers attempted to correlate the lanthanoid induced shift with absolute configuration, no remarkable success has been reported.1)

We recently reported,2) however, that 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 new chiral shift reagent Na[Eu^{III}(R- or S-pdta)$(H_2O)_3$] [(R)- or (S)-1, pdta = 1,2-propanediaminetetraacetate]3) for aqueous solution. This result clealy indicates that 1 can be a useful reagent for determining the absolute configuration of α-amino acids. In this letter we wish to report that 1 is also useful for determining the absolute configuration of α-hydroxy acids 2, which frequently occur as chiral moieties of natural products.4) The present method can be applicable to the substrates having polar substituents on their side chains, to which no simple method for determining the absolute configuration has been reported.5,6)



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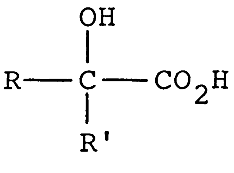

$R-C(OH)(R')-CO_2H$

2

Table 1. Enantiomeric chemical shift difference (ΔΔδ) and the sense of nonequivalence of H_α signals of 2 in the presence of (R)-1a)

2b)	R	R'	pH	Molar ratio of (R)-1 ([1]/[2])	ΔΔδ (ppm)	Enantiomer with higher field signal
2a	H	H	3.9	0.11	0.09	
2b	CH_3	H	4.0	0.11	0.18	S
					0.09c,d)	R
2c	$CH(CH_3)_2$	H	3.8	0.11	0.14	S
2d	$CH_2CH(CH_3)_2$	H	4.1	0.07	0.13	S
2e	$CH(CH_3)C_2H_5$	H	4.0	0.11	0.19e)	S
2f	$C(CH_3)_3$	H	4.1	0.11	0.06	S
2g	C_6H_5	H	4.0	0.05	0.10	S
					0.03f)	R
2h	$CH_2C_6H_5$	H	4.1	0.11	0.13	S
2i	CH_2OH	H	4.0	0.07	0.05	S
2j	CH_2CH_2OH	H	4.5	0.11	0.19	S
2k	$C(CH_3)_2CH_2OH$	H	3.5	0.21	0.03	S
2l	CH_2COOH	H	3.4	0.09	0.13g)	S
2m	CH_2CH_2COOH	H	5.8	0.11	0.20	S
2n	CH(OH)COOH	H	10.0h)	0.25	0.11i)	S
2o	$CH(COOH)CH_2COOH$	H	4.0	0.12	0.15e)	S
2p	$[CH(OH)]_3CH_2OH$	H	3.8	0.07	0.04j)	S
2q	CH_3	CH_3	4.0	0.11	0.10c,d)	
2r	CH_2CH_3	CH_3	4.2	0.11	0.10c,d)	S
2s	C_6H_5	CH_3	4.1	0.11	0.08c,d)	S
2t	CH_2COOH	CH_3	5.0	0.11	0.22c,d)	S

a) The ^1H NMR spectra were taken for 0.1 M D_2O solution at 90 MHz, 35 °C, using t-butyl alcohol or dioxane as an internal standard unless otherwise stated. Upfield shift of H_α signals was usually observed for both enantiomers. b) (2S)-isomers were used except for the followings. 2g: [R]/[S] = 1/2, 2i: (R), 2k: (R), 2l: [R]/[S] = 1/3, 2n: [R]/[S] = 1/3, 2o: (2R,3S), 2p: (2R,3S,4R,5R), 2r: [R]/[S] = 2.1/1, 2s: [R]/[S] = 3/2, 2t: [R]/[S] = 2.8/1. c) α-CH_3 signal. d) Two α-CH_3 signals shifted upfield and downfield, respectively. e) Downfield shift was observed for (R)-isomer. f) Ph signal. g) at 0.12 M. h) The H_α signal was not separated under acidic condition. i) at 0.15 M. j) determined at 400 MHz.

We have examined the relation between the absolute configuration of α-hydroxy acids and the lanthanoid induced shift of their α-proton (H_α) signals for fifteen substrates. The ^1H NMR shift study was conducted for D_2O solution (0.1 M, pH ca. 4) of the substrates at 90 MHz. When the sample was a non-equimolar mixture of enantiomers, the relative position of their H_α signals and the enantiomeric chemical shift difference (ΔΔδ) was directly determined by use of (R)-1. When only one enantiomer was available, two separate measurements were conducted using

(R) and (S)-1[2)] under the same condition. Since the interaction on one enantiomer at hand with (S)-1 must be the same as that of the other isomer with (R)-1, the shift data of the pair of enantiomers by (R)-1 were indirectly obtained. The results are summarized in Table 1.

The consistent correlation was observed between the absolute configuration and the induced shift of H_α signals; the H_α signals of (S)-isomers always appear at higher field than those of corresponding (R)-isomers in the presence of (R)-1. This relation is the same as that observed for α-amino acids.[2)] It is important to note that the regularity holds for the substrates (2i-2p) having functional group(s) on their side chain which might invert the correlation through its additional interaction with Eu^{3+}. Even the four additional hydroxyl groups on the side chain of sugar-related gluconic acid 2p did not invert the correlation. The $\Delta\Delta\delta$ was usually larger than 0.05 ppm at the molar ratio 0.11 of 1. Only exception was 2k, which showed the small separation of 0.03 ppm even at the molar ratio 0.21. This unusually small $\Delta\Delta\delta$ probably originates from some combined effects of the β-dimethyl and the γ-hydroxyl groups, since the shift behavior of 2f and 2j, which have either of the two, was normal.

The consistent correlation was also observed for α-methyl (α-CH_3) signals. The α-CH_3 signal due to (R)-2b appeared at higher field than that of (S)-isomer and the same was observed for the α-Ph signal (singlet) of 2g. On the contrary, the signals due to the methyl groups on the quaternary α-carbons of the (S)-isomers of 2r, 2s, and 2t appeared at higher field. Since the position of α-CH_3 in the (R)-isomers of these compounds corresponds to that of (S)-2b, all the results are consistent. The relations between the induced shift and the absolute configuration observed for both H_α and α-CH_3 signals are summarized in Fig. 1. This relation must be useful for the facile determination of the absolute configuration of α-hydroxy acids of wide variety.

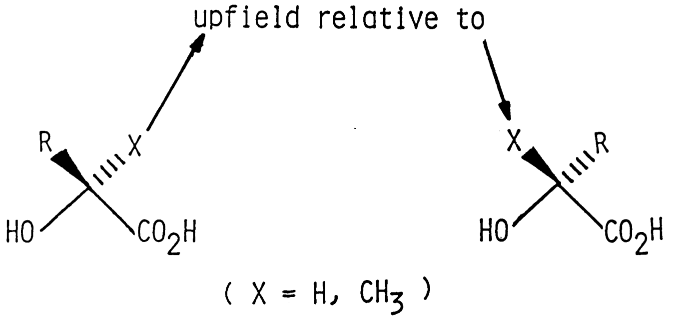

Fig. 1. Relative position of enantiomer signals in the presence of (R)-1.

The differentiation of the H_α and α-CH_3 signals of the enantiomers must be perfomed through chelating coordination of the substrates with Eu^{3+} by the carboxyl and the α-hydroxy groups because fairly larger induced shifts were obsereved for α-hydroxy acids than for monodentate substrates such as acetic acid.[7)]

It is apparent that the intrinsic chemical shift difference between the two diastereomeric complexes[8)] formed from 1 and the substrate enantiomers is important for the observed enantiomeric chemical shift difference since separations of the signals due to the enantiotopic H_α and α-CH_3 groups were observed for 2a and 2q, respectively (Table 1).

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