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DETERMINATION OF ABSOLUTE CONFIGURATION AND ENANTIOMERIC PURITY OF 2- AND 3-HYDROXYCARBOXYLIC ACID ESTERS[1]

Fujiko Yasuhara and Shozo Yamaguchi*
Department of Chemistry, College of General Education, Tohoku University
Kawauchi, Sendai 980 Japan

Summary: Relative magnitude of lanthanide induced shift of COOMe(LIS_{COOMe}) and methine proton (LIS_{CH}) of (R)-MTPA derivatives of 2- and 3-hydroxycarboxylic acid esters by $Eu(fod)_3$ has been successfully correlated to absolute configuration of the original hydroxy acid. This method also allows simultaneous determination of enantiomeric purity of the original hydroxy acid.

Long chain 2- and 3-hydroxycarboxylic acids (HCA) with straight or branched alkyl group are widely distributed in nature. They are isolated from wool wax, sphingolipids, bacterial lipopolysacchrides and other sources.[2,3] Except for some compounds with short chains, HCA of biological origin occur either as D- or L-enantiomers. Some of them show antimicrobial activity.[4]

A magnitude and a sign of rotation of 2-HCA have been reported[5] to be a solvent, and sometimes even a concentration and a pH dependent. This may cause an uncertainty of determining optical purity and absolute configuration of 2-HCA. On the other hand, most of the previous works of determining absolute configuration and enantiomeric purity of 2-HCA by nmr spectra have been focused on lactic and mandelic acid derivatives, and a difference of induced[6] or noninduced[7,8] chemical shift nonequivalence (Δ LIS or $\Delta\delta$) was generally small.

In the previous papers,[1] we have reported a convenient method for determining enantiomeric, diastereomeric purity and absolute configuration of various carbinols and amino acid derivatives. In this paper, the method was successfully extended to 2- and 3-HCA.

Partially active HCA were prepared by diazotization of the corresponding L-amino acids,[9] and by asymmetric reduction of α-keto-esters with Darvon-$LiAlH_4$ complex.[10] Some of them were resolved by fractional recrystallization of (S)-phenylethylamine salt of the dl-HCA using acetone solvent, which affords more satisfactory results than ether-petroleum ether solvent.[2]

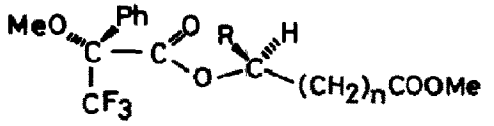
A shift study was carried out on the diastereomeric mixture [(R,R) and (R,S)] of (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid[7] [(R)-(+)-MTPA] esters[1] of partially active 2- or 3-HCA methyl ester with Hitachi R-22 (90MHz) spectrometer in CCl_4 solution. The signals due to the COOMe group and the methine proton of HCA moiety appear only partially resolved ones [$\Delta\delta_{COOMe}$ 0~0.04 ppm, $\Delta\delta_{CH}$ 0~0.04 ppm] in the undoped spectra. These signals, however, gave a sufficient separation by the progressive addition of $Eu(fod)_3$. In the doped spectra, the signal for the COOMe group of HCA moiety appears as a sharper singlet than that for the OMe group of MTPA acid moiety, and the magnitudes of lanthanide induced shifts of COOMe and CH groups [LIS_{COOMe} and LIS_{CH}] are substantially larger than those of MTPA amides of amino acid esters. (Table 1). This enables use of these signals as more suitable probe than OMe signal. Data given in Table 1 strongly suggest that, different from the case of amino acid derivatives,[11] consid-

Table 1. Lanthanide Induced Shift of COOMe and CH group for (R,S)-Diastereomer of Amino and Hydroxy Acid Esters.

(R)-MTPA Derivatives of (S)-Amino and (S)-Hydroxy Acid Esters	$LIS^{(R,S)}_{COOMe}$		$LIS^{(R,S)}_{CH}$		$LIS^{(R,S)}_{COOMe}/LIS^{(R,S)}_{OMe}$	
	X=OH	$X=NH_2$	X=OH	$X=NH_2$	X=OH	$X=NH_2$
X-CH(Me)-COOMe	4.4	0.49	7.6	5.0	0.69	0.06
X-CH(i-Pr)-COOMe	2.5	0.40	5.4	2.7	0.32	0.05
X-CH(n-Bu)-COOMe	2.3	0.50	5.3	3.8	0.31	0.05
X-CH(Ph)-COOMe	1.3	0.30	3.1	2.4	0.37	0.04
X-CH(Me)-CH_2COOMe	5.2	1.6	7.8	12.2	0.90	0.16

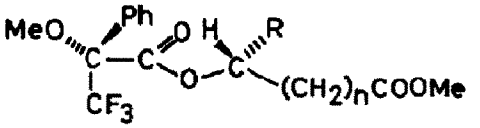
erable amount of added $Eu(fod)_3$ coordinate with the COOMe group of HCA moiety as well as the OMe group of MTPA moiety because of weaker basicity of the ester carbonyl group than the amide carbonyl group. This is also supported by the fact that LIS_{COOMe}/LIS_{OMe} for MTPA derivatives of HCA are substantially larger than those of amino acid derivatives.

As can be seen from Table 2, for all of the 28 HCA esters including lower and higher homologs tested, $LIS^{(R,S)}_{COOMe}$ and $LIS^{(R,S)}_{CH}$ due to the (R,S) isomers are consistently larger than those of the (R,R) isomers [$LIS^{(R,R)}_{COOMe}$ and $LIS^{(R,R)}_{CH}$] allowing absolute configuration assignment of the original HCA; the diastereomeric (R)-(+)-MTPA ester with a larger LIS_{COOMe} and LIS_{CH} will have structure (A) whereas the alternate diastereomer with a smaller ones will have structure (B). Relative



A

n = 0 or 1



B

peak area of the well separated COOMe signals affords enantiomeric purity of the original HCA. For example, enantiomeric purity of partially active $n\text{-}C_7H_{15}CH(OH)COOMe$ $[\alpha]_D^{25}$ + 6.84 (C 1.1, $CHCl_3$), was determined as 62 % e.e. Therefore, absolute rotation of this ester (entry 14) whose value has not been reported was estimated to be $[\alpha]_D^{25}$ + 11.0 ± 0.4 (C 1.1, $CHCl_3$).

Recently, several types of asymmetric synthesis of 3-HCA have been reported.[12,13] Meyers and Knaus observed that determination of enantiomeric purities of partially active 3-HCA (entries 24~26) with various chiral lanthanide shift reagents was unsuccessful.[13] As can be seen from Table 2, the present method provides a satisfactory results for these 3-HCA allowing the simultaneous assignment of the absolute configuration. (22, 27),[14] (24~26).[15]

Chemical shift nonequivalence of the OMe signal for the (R)-MTPA acid moiety in the undoped spectra is also correlated to absolute configuration of 2-HCA. Several representative examples are tabulated in Table 3 along with those of secondary carbinols. Although difference of chemical shift nonequivalence of OMe group ($\Delta\delta_{OMe}$) is considerable small, the OMe signal due to the (R,R) diastereomer of 2-HCA ester generally appears at lower field than that of the (R,S) isomer. If one may assume that (1) in the absence of $Eu(fod)_3$, the major conformation for the (R,R) diastereomer is similar to that proposed by Mosher[7] in which the COOMe group is preferentially oriented towards the OMe group and (2) the COOMe group exhibits a deshielding effect to the facing OMe group, the above stereochemical correlation scheme can be reasonably interpreted by Mosher model.[7] Data cited in Table 3 clearly indicate that the OMe signals for the (R,R) diastereomers

Table 2. Relative Magnitudes of LIS_{COOMe} and LIS_{CH} for (R)-(+)-MTPA Derivatives of 2- and 3-Hydroxycarboxylic Acid Esters in the Presence of $Eu(fod)_3$.

Entry	R-CH(COOMe)(O-MTPA-(R))	$LIS_{COOMe}^{(R,R)}$	$LIS_{COOMe}^{(R,S)}$	$LIS_{CH}^{(R,R)}$	$LIS_{CH}^{(R,S)}$
1	Me	3.0	4.4	6.4	7.6
2	Me(Et ester)			7.5	8.7
3	Et	1.8	3.0	5.2	6.1
4	i-Pr	1.6	2.5	4.4	5.4
5	n-Bu	1.4	2.3	4.2	5.3
6	sec-Bu	1.2	2.1	4.3	5.0
7	i-Bu	1.1	1.9		
8	t-Bu	1.0	1.7	4.1	5.0
9	Ph	0.8	1.3	2.7	3.1
10	Ph(ℓ-Menthyl ester)			3.4	4.6
11	$PhCH_2$	2.0	3.1	5.4	6.6
12	$PhCH_2CH_2$	1.2	2.0	4.3	5.3
13	$n\text{-}C_6H_{13}$	1.4	2.3	4.9	5.4
14	$n\text{-}C_7H_{15}$ (R)-(-)[a,c]	1.5	2.5	4.6	5 4
15	$n\text{-}C_{10}H_{21}$	1.5	2.4	4.3	5.3
16	$n\text{-}C_{12}H_{25}$	1.5	2.4	3.8	5.0
17	$n\text{-}C_{14}H_{29}$	1.5	2.5	3.8	5.6
18	$n\text{-}C_{16}H_{33}$	1.4	2.3	4.0	4.9
19	$MeOOCCH_2$	1.6	2.1		
20	Panthoyl lactone			5.0	6.2
	R-CH(CH_2COOMe)(O-MTPA-(R))				
21	Me	4.5	5.2	5.7	7.8
22	Et (R)-(-)[a,b]	4.2	4.7	7.7	8.6
23	i-Pr	4.1	4.5	7.9	9.1
24	t-Bu (R)-(-)[a,c]	2.6	3.7	10.4	11.1
25	$n\text{-}C_6H_{13}$ (R)-(+)[a,c]	4.3	4.7	7.7	8.7
26	Cyclohexyl (R)-(-)[a,c]	3.9	4.3	8.4	9.6
27	$n\text{-}C_7H_{15}$ (R)-(-)[a,d]	4.1	4.4	7.5	8.4
28	$n\text{-}C_{11}H_{23}$	4.1	4.6	6.8	8.0

[a]Configurations have not been reported in the literature. These configurations are assigned based on the method described in this paper. Rotations are taken in [b]EtOH, [c]$CHCL_3$, [d]MeOH solution.

of 2-HCA and of alkylphenylcarbinols appear at lower and higher fields respectively than those of dialkylcarbinols in which no chemical shift nonequivalence is observed($\Delta\delta_{OMe}$ zero). These results unequivocally illustrate that the COOMe group exhibit a deshielding effect for the OMe group in the (R,R) diastereomer.

Table 3. Chemical Shift of OMe Group in the (R)-(+)-MTPA Esters of sec-Carbinols and 2-Hydrox Carboxylic Acid Esters

$R_1 > CHO$-MTPA-(R)

R_1	R_2	δ OMe(ppm) (R,R)	(R,S)	$\Delta\delta^{(R,R)-(R,S)}_{OMe}$ (ppm)
Me	COOMe	3.60	3.52	+ 0.08
Et	COOMe	3.61	3.53	+ 0.08
i-Pr	COOMe	3.63	3.56	+ 0.07
n-C_6H_{13}	COOMe	3.64	3.55	+ 0.09
n-$C_{14}H_{29}$	COOMe	3.64	3.54	+ 0.10
Ph	COOMe	3.72	3.56	+ 0.16
Me	Ph	3.43	3.53	- 0.10
Et	Ph	3.43	3.54	- 0.11
i-Pr	Ph	3.42	3.52	- 0.10
Me	Et	3.53		0.0
Me	i-Pr	3.52		0.0
n-Pr	i-Pr	3.53		0.0

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