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USE OF SHIFT REAGENT WITH MTPA DERIVATIVES IN ^{1}H NMR SPECTROSCOPY. IV. DETERMINATION OF ABSOLUTE CONFIGURATION AND ENANTIOMERIC PURITY OF AMINO ACID DERIVATIVES.

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Determination of absolute configuration and enantiomeric purity of α-amino acids using chemical shift nonequivalence has been well investigated,[1,2] while little was reported[3] on the successful application correlating the absolute configuration of amino acids with their relative magnitude of lanthanide induced shift (LIS).

In the previous investigation, we have found that the MTPA ester/Eu(fod)$_3$ method for determining absolute configuration and enantiomeric purity of primary and secondary carbinols can be also used for the case where an additional functional group such as OMe is in the carbinyl moiety of the MTPA esters.[4] This observation prompted us to investigate the extention of this method to amino acid derivatives.

A shift study was carried out on a diastereomeric mixture (0.1 mmol) of (R)-(+)- and (S)-(-)-MTPA [α-methoxy-α-trifluoromethylphenylacetic acid, Mosher's Reagent[2]] amides of L-leucine methyl ester [(R,S)/(S,S)=59/41] in the presence of various molar ratio of Eu(fod)$_3$. The methyl proton signals having larger and smaller LIS values were assigned to MeO and COOMe group respectively by comparing the pmr spectra with those of the MTPA amides of alanine methyl and ethyl esters.

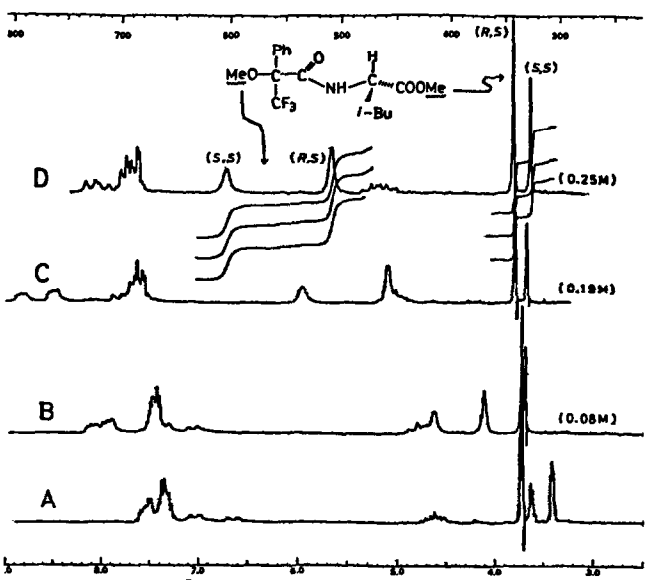


Fig. 1. 90 MHz ^{1}H NMR spectra of (R)-(+)- and (S)-(-)-MTPA amides of L-Leu-OMe[(R,S)/(S,S)=59/41] in CCl_4 containing various molar ratio of Eu(fod)$_3$. A, 0 mol; B, 0.08 mol; C, 0.19; D, 0.25 mol.

In general, the magnitude of LIS_{OMe} is substantially larger than that of LIS_{COOMe} indicating that the Eu(fod)$_3$ coordinates more preferably with both the oxygen atoms from the carbonyl and OMe group[5,6] of MTPA acid moiety than those of COOMe group.

As can be seen from Fig. 1, LIS_{OMe} due to (S,S) pair is larger than that of (R,S) pair. Similar nmr-configurational correlation scheme [$LIS_{OMe}^{(R,R)} > LIS_{OMe}^{(R,S)}$][7] can be observed for all of the amino

Table 1. Lanthanide Induced Shifts of Methoxyl Group in the Acid Moiety for Diastereomeric (R)-(+)-MTPA Amides of Amino Acid Derivatives in the Presence of $Eu(fod)_3$

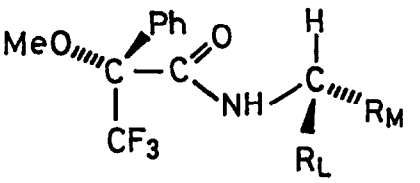
Entry	MTPA Amides[a] of Amino Acid Derivatives	$LIS_{OMe}^{(R,R)}$	$LIS_{OMe}^{(R,S)}$	ΔLIS_{OMe} $[LIS_{OMe}^{(R,R)} - LIS_{OMe}^{(R,S)}]$	Config. of Amino Acid with larger LIS_{OMe}
1	Ala-OMe	9.7	8.5	1.2	(R)
2	Ala-OEt	8.0	7.1	0.9	(R)
3	Ala-OBu-t	8.0	7.3	0.7	(R)
4	Val-OMe	10.0	7.4	2.6	(R)
5	Val-OMen[b]	12.1	9.0	3.1	(R)
6	Val-(NH_2)	11.0	2.7	8.3	(R)
7	Leu-OMe	12.4	9.1	3.3	(R)
8	Met-OMe	10.1	9.8	0.3	(R)
9	Phe-OMe	7.1	8.8	-1.7	(S)
10	Phe-OBzl	6.9	8.4	-1.5	(S)
11	Phe-OBu-t	7.9	10.2	-2.3	(S)
12	Phe-OMen[b]	9.3	10.3	-1.0	(S)
13	Tyr(Me)-OMe	7.5	9.8	-2.3	(S)
14	Trp-OMe	8.9	10.8	-1.9	(S)
15	Asp(Me)-OMe	7.2	6.4	0.8	(R)
15	Glu(Me)-OMe	2.7	2.0	0.7	(R)
17	Ile-OMe	12.0	8.8	3.2	(R)
18	Thr(Bzl)-OBzl	13.1	9.4	3.7	(R)
19	aIle-OMe	14.5	10.5	4.0	(R)
20	L-Ile-OMe (2S,3S) D-aIle-OMe(2R,3S)	14.7	10.8	3.9	(R)
21	Abu-OMe	10.0	8.4	1.6	(R)
22	Nva-OMe	7.8	6.2	1.6	(R)
23	Nle-OMe	11.5	9.9	1.6	(R)
24	Phgly-OMe	9.8	7.9	1.9	(R)
25	$PhCH_2CH_2CH(NH_2)COOMe$[c]	6.9	6.1	0.8	(R)
26	$PhCH_2CH_2CH_2CH(NH_2)COOMe$[d]	8.9	8.0	0.9	(R)
27	βAbu-OMe[e]	10.4	9.7	0.7	(R)
28	βPhe-OMe[f]	8.6	8.0	0.6	(R)

[a]The amides were purified by preparative TLC(SiO_2-Benzene/Et_2O=5/1, or n-Hexane/EtOAc=4/1),if necessary. [b]OMen: ℓ-Menthyl ester. The spectra were taken on the mixture of specified molar ratio of the (R)-(+)-MTPA amides from ℓ-menthyl ester of L- and D-amino acids. [c]A. Tanaka, and N. Izumiya, Bull. Chem. Soc. Jpn., 31, 529 (1958). [d]T. Ueno, T. Nakashima, and H. Fukami, Agric. Biol. Chem., 39, 1115 (1975); Y. Shimohigashi, S. Lee, and N. Izumiya, Bull. Chem. Soc. Jpn., 49, 3280 (1976). [e]K. Balenovic, D. Cerar, and Z. Fuks, J. Chem. Soc., 3316 (1952). [f]S. G. Cohen, and S. Y. Weinstein, J. Am. Chem. Soc., 86, 725 (1964).

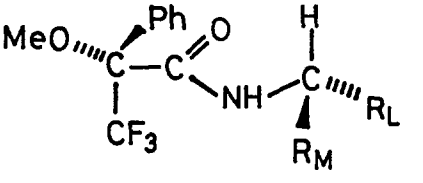
acids tested except for the case where the substituent on the α-carbon atom is benzyl group or its analogs (Table 1. entries 9~14).[8] Therefore, if one may tentatively assume that the repulsive interaction (including polar effect) between the coordinating $Eu(fod)_3$ and the substituents (R_L, R_M) on the chiral center of the amino acid moiety decreases in the order of,

$ArCH_2 > COOR > Ph, PhCH_2CH_2, PhCH_2CH_2CH_2, CH_2CH_2COOMe$, Alkyl ; $COOMe > Ph > CH_2COOMe > CH_3$

the diastreomeric (R)-(+)-MTPA amides with the larger LIS_{OMe} will have configuration (A), while the alternate diastereomer with the smaller LIS_{OMe} will have configuration (B).



A



B

If an original amino acid ester is partially active, the diastereomeric mixture of MTPA amides [(R,R) and (R,S)] may be prepared by acting excess (R)-MTPA on the amino acis ester for quantitative acylation. The enantiomeric purity of original amino acid can be determined from the ratio of peak areas of the well separated OMe signals.[9] The experimental deviations from those obtained by the measurement of specific rotations were within ± 2%.

Several additional observations can be made from the Table 1: (1) A change of steric bulk of the ester group in the amino acid moiety does not alter the sense of the correlation scheme. (entries 2, 3, 5, 10~12, 18). (2) The presence of additional chiral center(s) in the amino acid moiety does not interfere with the application of this method. (entries 5, 12, 17~19). Consequently, the method may provide a versatile direct way for determining a sense and an extent of asymmetric induction for diastereoselective amino acid synthesis.[10] (3) The present technique can be also useful for the diastereomeric mixture of the amino acid (entry 20) as has been observed for those of secondary carbinols.[11] (4) The method affords a reliable result for α-amino acid amide and acidic amino acid esters. (entries 6, 15, 16). It is interesting to note that the magnitudes of LIS of β- or γ-COOMe of the (R,R) diastereomers [$LIS^{\beta(\gamma)}_{COOMe}$] are considerably larger than that of α-COOMe group [LIS^{α}_{COOMe}]. (Table 2).[12] The ratios of LIS value, $LIS_{OMe}/LIS^{\beta(\gamma)}_{COOMe}$ and $LIS^{\alpha}_{COOMe}/LIS^{\beta(\gamma)}_{COOMe}$, decrease with increasing distance between the OMe group and the β- or γ-COOMe group, suggesting that preferential coordination of $Eu(fod)_3$ to the OMe and the carbonyl group of the MTPA acid moiety prevents a coordination of the second $Eu(fod)_3$ molecule to the neighboring COOMe group. A similar phenomenon was also observed for the (R,S) diastereomers.

Table 2. LIS of α-and β(γ)-COOMe of (R,R) Diastereomer

Amino Acid Ester	LIS_{OMe}	LIS_{COOMe} α	LIS_{COOMe} β(γ)
Asp(Me)-OMe	7.2	0.24	1.0
Glu(Me)-OMe	2.7	0.19	(5.4)
Glu(Et)-OMe	3.9	0.88	(7.9)
Ala-OMe	9.7	0.32	$-CH_2Me$

Further advantages of the present procedure

over those in the literature are that (1) only one of the enantiomeric pair of amino acids is necessary for the configurational assignment, whereas a pair of enantiomers is required for the previous method,[3] and (2) the magnitude of LIS_{OMe} is substantially larger than that observed for the case of enantiomer-chiral solvent.[1(a)]

Since the sign and the magnitude of ΔLIS_{OMe} value are governed primarily by the steric requirement of R_L and R_M group alone, the present method may be, in principle, generally applicable for α-, β- (entries 25~28), and other amino acids (γ-, δ-, ····) regardless of substituent on the chiral carbon atom.

Further investigation is underway to explore the limitation of the present technique.

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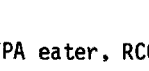
6. The magnitude of LIS_{OMe} of the (R)-(+)-MTPA eater, RCOO-CHPh(Et) [R: ], is substantially larger than that of RCH_2O-COCHPh(Et). This observation strongly suggests that the carbonyl group in the MTPA acid moiety plays an important role in coordination of the $Eu(fod)_3$. (S. Yamaguchi, and K. Kabuto, Unpublished results).
7. For the sake of clarity of presentation in the discussion and Table 1, we will represent all the spectra as though they were taken on a mixture of (R,R) and (R,S) diastereomer, whereas in fact, (S,S) and (R,S) diastereomeric mixture have been used. The nmr spectra, in an achiral measurement conditions, of (R,R) and (R,S) enantiomers are identical, as are those of the (S,S) and (S,R) isomers.
8. Shift studies for MTPA amides of certain amino acid esters such as DOPA(Me)-OMe, MePhe-OMe Lys(Ts)-OMe did not afford satisfactory results because of rapid line broadening or complication of the spectra upon addition of $Eu(fod)_3$.
9. Sometimes, COOMe signals are also available for this purpose.
10. It has been reported that unfavorable fractionation or racemization of amino acid happens during the purification or removal process of chiral handle preventing the correct evaluation of asymmetric bias in the diastereoselective amino acid synthesis. (K. Matsumoto, K. Harada, J. Org. Chem., 31, 1956 (1966); K. Harada, K. Matsumoto, ibid., 32, 1794 (1967).
11. S. Yamaguchi, and F. Yasuhara, Tetrahedron Lett., 89 (1977).
12. Assgnmemt of signals due to the α-, and γ-COOMe was done by comparing the spectra of MTPA amides of Glu(Me)-OMe and Glu(Et)-OMe.