Tetrahedron Letters, Vol.32, No.25, pp 2939-2942, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

ELUCIDATION OF THE ABSOLUTE CONFIGURATIONS OF AMINO ACIDS AND AMINES BY THE MODIFIED MOSHER'S METHOD

Takenori Kusumi, Toshiro Fukushima, Ikuko Ohtani, and Hiroshi Kakisawa*

Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

Abstract: Application of the modified Mosher's method to the *N*-MTPA derivatives of several amino acid esters and acyclic amines indicates that this method may be generally used to determine the absolute configurations of the α-carbons of amino compounds of less than 0.1 mg amount.

We have reported the convenient and reliable method, the modified Mosher's method (summarized in Figure 1), which can be used to elucidate the absolute configurations of organic compounds possessing a secondary alcohol moiety.[1-5] This method is widely accepted and has been applied to elucidation of the absolute configurations of some natural products.[6-8] Similar method using *O*-methylmandelates has been developed by Trost.[9] These methodologies depend on the high-field NMR spectroscopy, which has made it possible to assign most of the protons of even big molecules when the modern pulse techniques such as H,H-COSY or HMBC spectra are employed. We herein describe another application of the modified method to the absolute configurations of amines.

The *N*-(+)-(*R*) and (-)-(*S*)-MTPA (2-methoxy-2-phenyl-2-trifluoromethylacetyl) derivatives were prepared by treatment with (+) and (-)-MTPA chlorides in pyridine[10] or the MTPA acids and DCC-DMAP in dichloromethane.[9] The Δδ values (δ_S - δ_R) obtained for these *N*-MTPA-*L*-amino acid esters and *L*-amino alcohols are summarized in Figure 2. As is obvious from the Figure, Δδ values for the protons oriented on the left side of the MTPA plane, are all negative, while those located on the right side of the MTPA plane are positive. These findings are in good agreement with the prediction from Model A (Figure 1), and they have eventually revealed that the idea of MTPA plane was also valid for amines as it is for secondary alcohols.

With respect to the amino acid derivatives, we have noticed other features of the Δδ

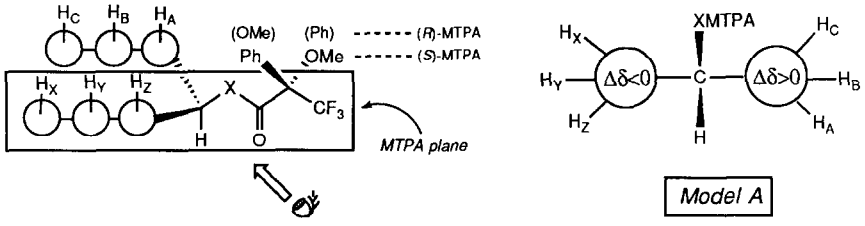

Figure 1. MTPA plane and Model A to predict the absolute configurations of secondary alcohols (X = O) or primary amines (X = NH). $\Delta\delta = \delta_S - \delta_R$.

values: (1) The values for α-protons are positive in all cases.[11] (2) The values for the methoxyl groups of the MTPA moieties are positive and those for the amide protons are negative. Because we have been unable to put a reasonable interpretation on these tendencies thus far, it should be too risky to take these properties as a general rule to tell the *S*-configuration of the α-carbon of amino acids, although these inclinations of the protons have to be consecutively watched in future works.

Typical procedures of the preparation of the *N*-MTPA derivatives are as follows:

Preparation of N-(R)-MTPA-L-valine methyl ester: A solution of *L*-valine methyl ester hydrochloride (100 μg) in pyridine (dried and distilled from CaH_2; 50 μL) was put in a 1-mL microtube. (+)-MTPA chloride (2.2 μL; 20 equivalent) was added *via* a 10-μL syringe, and the mixture was allowed to stand at room temperature for 10 min. *N*,*N*-Dimethyl-1,3-propanediamine (1.5 μL; 20 equivalent) was added to quench the excess chloride, and the pyridine was evaporated on a vacuum evaporator. The residue was subjected to prep TLC (Merck, Kieselgel 60 F_{254}, hexane-EtOAc, 6 : 4). (The bands of the MTPA amides are visible under 254 nm light.) The ^{1}H-NMR spectra (500 MHz) of *N*-(*R*) and (*S*)-MTPA-*L*-valine methyl esters (ca 200 μg each) are shown in Figure 3.

Preparation of (R)-MTPA amide of L-phenylalaninol: A mixture of *L*-phenylalaninol (15 mg) and CH_2Cl_2 (1 mL) was treated with DCC (25 mg) and (+)-MTPA acid (28 mg), and the mixture was stirred for 30 min. The reaction mixture containing the precipitates of urea was concentrated and the residue was separated by prep TLC, affording the (*R*)-MTPA amide (31 mg; 86 %). Under these conditions the hydroxyl group was not esterified at all.

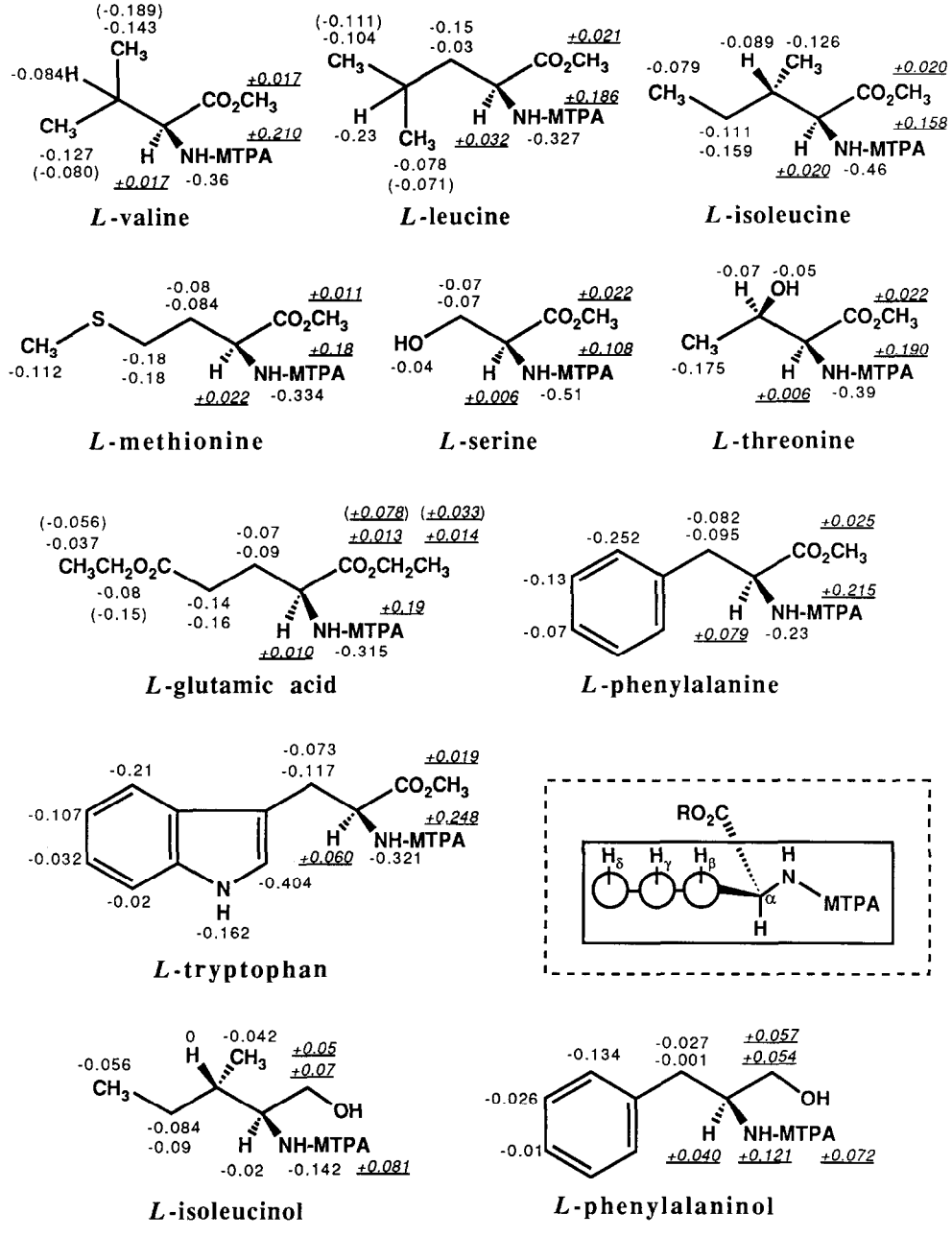

Figure 2. Δδ values (ppm) obtained for (*R*) and (*S*)-MTPA amides of amino compounds. For the protons which could be interchanged with other protons (e.g. α-CO_2Et *vs* γ-CO_2Et in *L*-glutamic acid), two possible values, one in parenthesis, are assigned. The data are obtained from the spectra measured on a Bruker AM 500 spectrometer using $CDCl_3$ as a solvent. The assignments are based on decoupling experiments and H,H COSY spectra. For the assignments of the aromatic protons of *L*-phenylalanine and *L*-tryptophan MTPA amides, NOESY spectra were used.

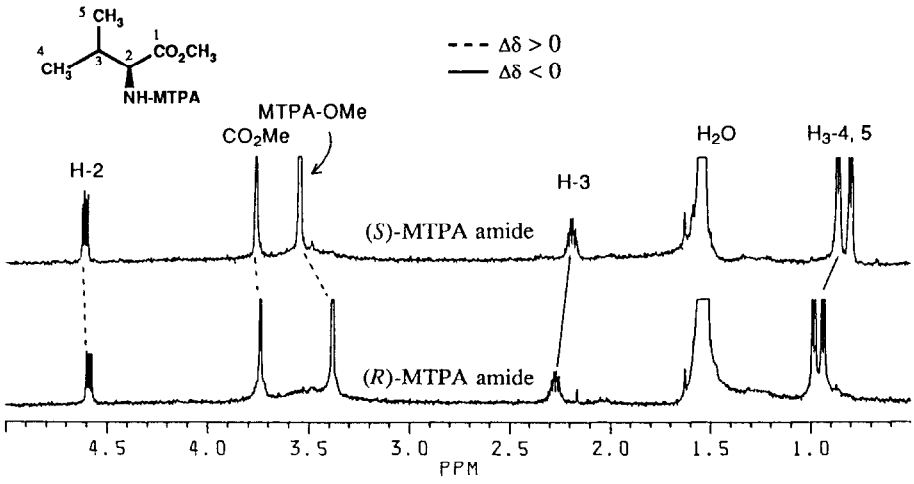

Figure 3. ^{1}H NMR ($CDCl_3$; 500 MHz) spectra of 2 mM solutions of the *N*-(*S*)-MTPA (above) and (*R*)-MTPA (below)-*L*-valine methyl esters.

References and Notes

1 Kusumi, T.; Ohtani, I.; Inouye, Y.; Ishitsuka, O. M.; Kakisawa, H. 16th IUPAC International Symposium on the Chemistry of Natural Products (Kyoto), May-June, 1988, Abstr. Pa17.

2 Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731.

3 Ohtani, I.; Kusumi, T.; Ishitsuka, O. M.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147.

4 Ohtani, I.; Kusumi, T.; Kashman, Y; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296.

5 Ohtani, I.; Kusumi, T.; Kashman, Y; Kakisawa, H. *J. Am. Chem. Soc.* in press.

6 Kobayashi, M.; Kawazoe, K.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 4149.

7 Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710.

8 Hundt, A. F.; Burger, J. F. W.; Steynberg, J. P.; Steenkamp, J. A.; Ferreira, D. *Tetrahedron Lett.* **1990**, *31*, 5073.

9 Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.

10 Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

11 The chemical shift of the proton on the carbon bearing an MTPA amide group should be affected more by the carbonyl group of the MTPA moiety than from the phenyl group.

(Received in Japan 22 January 1991)