Tetrahedron Letters, Vol.31, No.47, pp 6867-6868, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ENANTIOMERIC PURITY OF MOSHER'S ACID

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Abstract: Several commercial samples of 2-methoxy-2-phenyl-3,3,3-trifluoropropionic acid (Mosher's acid, MTPA) were investigated for enantiomeric purity by capillary gas chromatography with octakis(3-O-butyryl-2,6-di-O-pentyl)-γ-cyclodextrin as a chiral stationary phase. Enantiomeric purities were found between 97.89 % and 99.80 %.

The spectacular advancements in the preparation of enantiomerically pure compounds by asymmetric syntheses and biotechnological methods in recent years has increased the demand for sensitivity and precision of analytical procedures for ascertaining the enantiomeric excess (ee). For the determination of the enantiomeric composition of chiral hydroxy compounds and amines Mosher et al.[1] have proposed the formation of diastereomeric esters or amides, respectively, by using (+)- or (-)-2-methoxy-2-phenyl-3,3,3-trifluoropropionic acid or its chloride as a chiral reagent. The diastereomeric derivatives could be quantified by gas or liquid chromatography[2] or by NMR investigations[3], depending on the type of compound. These techniques have been widely accepted, although it is obvious that accurate results can only be expected, if 1. the formation of diastereomers proceeds to completion (without kinetic enrichment of one of the diastereomers) and 2. the chiral reagent is 100 % pure or its enantiomeric composition is known. In a recent publication Svatos et al.[4] demonstrated that large deviations from the theoretical 50:50 value may occur in the proportion of diastereomers if racemic alcohols are esterified with MTPA, corresponding to ee-values of up to 22 % and with MTPA chloride, corresponding to ee-values of up to 10 %, depending on the structure of the alcohols investigated. This problem could only partly be overcome by optimizing the reaction conditions. Precise values of enantiomeric purity of commercial MTPA reagents are usually not supplied by the producers.

We have investigated MTPA from 4 major suppliers by enantioselective capillary gas chromatography. Using a capillary column with the chiral stationary phase octakis(3-O-butyryl-2,6-di-O-pentyl)-γ-cyclodextrin[5,6] we succeeded in the direct separation of the enantiomers of MTPA methyl ester[7] (figure 1). ee-Values between 97.89 % and 99.80 % were found with a relative standard deviation of 0.29 % (10 consecutive measurements with an electronic integrator[8]). This result not only clearly

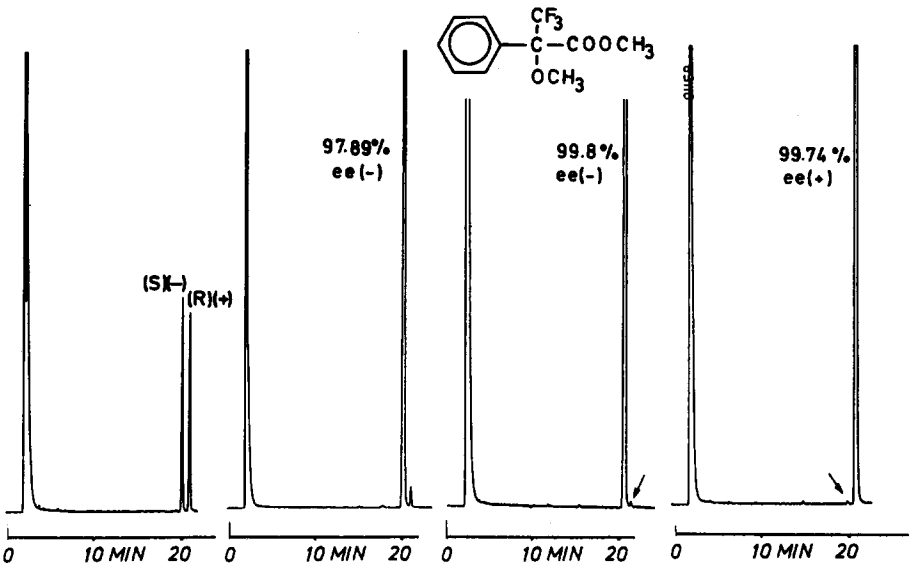

Figure 1
Gas chromatographic enantiomer separation of MTPA methyl ester and determination of enantiomeric purity of 3 commercial samples. 30 m Pyrex glass capillary column with octakis(3-O-butyryl-2,6-di-O-pentyl)-γ-cyclodextrin. Column temperature 130°C; carrier gas 0.7 bar hydrogen.

demonstrates the sensitivity and precision achieved by enantioselective gas chromatography, it also proves that accurate values of enantiomeric composition can not be expected if MTPA of insufficient enantiomeric purity is used (the relative error in the determination of ee of an optically active alcohol would be 2.11 % if MTPA of an enantiomeric purity of only 97.89 % ee is used).

These consequences must be generally considered for analytical procedures involving the formation of diastereomeric derivatives.

Acknowledgments
We thank the Deutsche Forschungsgemeinschaft, the Bundesminister für Forschung und Technologie and the Fonds der Chemischen Industrie for financial support.

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6. Fused-silica capillary columns with this chiral phase are available from Macherey-Nagel, D-5160 Düren, FRG.
7. MTPA samples of 1 mg were methylated with an excess of diazomethane in diethylether.
8. A Merck-Hitachi chromato-integrator model 2000 was used.

(Received in Germany 19 September 1990)