Preparation of Solutions for Photolysis and Spectral Studies. Dissolution of *trans*-stilbenes in water was generally difficult. A solution of 10^{-6} M (as checked by UV absorption) could be prepared by stirring *trans*-stilbene (20 mg) in 200 mL of water for 24 h. However, solutions of *cis*-stilbene having concentrations $\simeq 10^{-4}$ M were prepared by magnetically stirring 20 mg of *cis*-stilbene in 200 mL of water for 24 h. These solutions after bubbling with nitrogen for 30 min were used for photolysis.

In order to check the possible association of stilbene molecules in water, absorption spectra were recorded (Shimadzu UV-180 spectrophotometer) for aqueous solutions of *cis*-stilbene in the concentration range $(1.1–8.8) \times 10^{-5}$ M. Solutions of these were prepared as follows. A stock solution (1–8 μL) of *cis*-stilbene in methanol (1.1×10^{-2} M) were added to 10-mL portions of water, and the solutions were stirred for 24 h. A plot of optical density vs. concentration indicated a deviation from Beer's law. No attempt was made to carryout such studies with stilbenes **2**–**4**.

β-Cyclodextrin complexes of stilbene **1**–**4** were prepared by the standard procedure.[13] A typical photolysis solution consisted of 20 mg of stilbene, 1.25 g of β-cyclodextrin, and 200 mL of water. An excess of cyclodextrin was required to fully complex the stilbene.

Miceller solutions (SDS) of stilbene under conditions where the occupancy number was less than one were prepared by stirring 10 mg of stilbene in 100 mL of water containing a gram of SDS. The stilbenes (cis and trans) went into aqueous solution rapidly in the presence of SDS.

Photolysis. Aqueous solutions of *trans*-stilbenes **1**–**4** (20 mg in 200 mL of water) were irradiated in Pyrex tubes with a 450-W medium-pressure mercury lamp. Except for a small amount which had gone into solution most of the *trans*-stilbenes were floating as microcrystals during irradiations. Aqueous solutions of *cis*-stilbenes **1**–**4** were also irradiated under similar conditions. Under the conditions these solutions were transparent. The products of photolyses were extracted with chloroform and analyzed by GC (Chemito: Model 3800; 8 ft × $^1/_8$ in. 5% SE-30 column; temperature 170–300 °C programmed at the rate of 10 deg/min). GC and H^1 NMR indicated that the product mixture consisted of *trans*- and *cis*-stilbenes, phenanthrene, and dimers. The absolute yield of the products were measured by using an internal standard, *trans*-2,5-dimethyl-4-methoxystilbene. The material balance was ≃80%, and no products other than the ones mentioned above were seen in GC and H^1 NMR (Brucker WH-270). The structure of the dimers were identified by comparison with authentic samples prepared by irradiating benzene solutions of **1**–**4** (1.0 M) according to the literature reports.[6,14] The two isomeric dimers obtained after purification by column chromatography (silica gel, hexane–chloroform) were identical with the ones obtained from aqueous solution irradiation.[15]

The progress of the photolysis in the case of *cis*-stilbene was monitored by GC. A 10^{-5} M solution of *cis*-stilbene in water was irradiated for 24 h as described above. A small aliquot of the solution was taken out every 30 min, extracted, and analyzed by GC. The results are shown in Figure 1.

In order to assess the importance of association of stilbene molecules in aqueous phase the following experiments were carried out. Five Pyrex tubes consisting of identical concentrations of *cis*-stilbene (10^{-5} M) in water with addends as mentioned below and matched optical densities were irradiated simultaneously with a 450-W medium-pressure mercury lamp in a merry-go-round style. These five Pyrex tubes contained the following solutions: (i) *cis*-stilbene, (ii) *cis*-stilbene and 3 M lithium chloride, (iii) *cis*-stilbene and 3 M guanidinium chloride, (iv) *cis*-stilbene and 1 g of β-cyclodextrin, and (v) *cis*-stilbene and 1 g of SDS. The products were extracted and analyzed by gc. Yields of the dimers are presented in Table I.

For the sake of comparison, benzene solutions of *trans*- and *cis*-stilbenes of **1**–**4** of the same concentration as employed for aqueous irradiation (matched OD), were irradiated by using a 450-W medium-pressure mercury lamp. GC and H^1 NMR analyses of the reaction mixtures indicated only geometric isomers and phenanthrene. No dimers were obtained.

Acknowledgment. The Council of Scientific and Industrial Research, Government of India is thanked for financial support.

Registry No. (Z)-**1** (X = H), 645-49-8; (E)-**1** (X = H), 103-30-0; (Z)-**1** (X = OMe), 1898-14-2; (E)-**1** (X = OMe), 52805-92-2; (Z)-**2**, 1657-46-1; (E)-**2**, 718-25-2; (Z)-**3**, 1657-45-0; (E)-**3**, 1860-17-9; (Z)-**4**, 14064-68-7; (E)-**4**, 13041-79-7; Dimer A (Ar = *p*-C_6H_4F), 103563-99-1; Dimer A (Ar = *p*-C_6H_4Me), 103564-00-7; Dimer A (Ar = *p*-C_6H_4CN), 103564-01-8; Dimer A (Ar = *o*-C_6H_4OMe), 103564-02-9; Dimer A (Ar = Ph), 54515-63-8; Dimer B (Ar = *p*-C_6H_4F), 103564-03-0; Dimer B (Ar = *p*-C_6H_4Me), 103564-04-1; Dimer B (Ar = *p*-C_6H_4CN), 103564-05-2; Dimer B (Ar = *o*-C_6H_4OMe), 103564-06-3; Dimer B (Ar = Ph), 54515-64-9; SDS, 151-21-3; LiCl, 7447-41-8; phenanthrene (X = F), 440-40-4; phenanthrene (X = Me), 832-71-3; phenanthrene (X = CN), 21661-50-7; phenanthrene (X = OMe), 834-99-1; phenanthrene (X = H), 85-01-8; guanidinium chloride, 50-01-1; β-cyclodextrin, 7585-39-9.

(12) Saltiel, J.; Agostino, J. D.; Megarity, E. D.; Metts, L.; Neuberger, K. R.; Wrighton, M.; Zafiriou, O. C. *Org. Photochem.* **1973**, *3*, 1.

(13) Nageswara Rao, B.; Turro, N. J.; Ramamurthy, V. *J. Org. Chem.* **1986**, *51*, 460. Sharat, S.; Usha, G.; Tung, C. H.; Turro, N. J.; Ramamurthy, V. *J. Org. Chem.* **1986**, *51*, 941. Dasaradha Reddy, G.; Usha, G.; Ramanathan, K. V.; Ramamurthy, V. *J. Org. Chem.*, in press.

(14) Ulrich, H.; Rao, D. V.; Stuber, F. A.; Sayigh, A. A. R. *J. Org. Chem.* **1972**, *35*, 1121.

(15) Spectral details of the dimers are as follows. Dimer of stilbene: ^1H NMR ($CDCl_3$) [dimer A] δ 7.28–7.35 (m, 20 H), 4.45 (s, 4 H), [dimer B] δ 7.36 (m, 20 H), 3.66 (s, 4 H); mass spectrum, (70 eV) *m/e* 360, 180. Dimer of *p*-fluorostilbene: ^1H NMR ($CDCl_3$) [dimer A] δ 7.4–7.2 (m, 18 H), 4.58 (s, 4 H), [dimer B] δ 7.4–7.2 (m, 18 H), 3.78 (dd, 4 H); mass spectrum (70 eV) *m/e* 396, 216, 198, 180. Dimer of *p*-cyanostilbene: ^1H NMR n$CDCl_3$) [dimer A] δ 7.0–7.78 (m, 18 H), 4.58 (s, 4 H), [dimer B] δ 7.0–7.78 (m, 18 H), 3.88 (m, 4 H); mass spectrum, (70 eV), *m/e* 410, 230, 205, 180. Dimer of *p*-methylstilbene: ^1H NMR ($CDCl_3$) [dimer A] δ 7.1–7.88 (m, 18 H), 4.45 (s, 4 H), 1.88 (s, 6 H), [dimer B] δ 7.1–7.88 (m, 18 H), 3.68 (s, 4 H), 1.88 (s, 6 H); mass spectrum, (70 eV) *m/e* 388, 208, 194, 180.

Determination of Enantiomeric Purity of Tertiary Amines by ^1H NMR of α-Methoxy-α-(trifluoromethyl)phenylacetic Acid Complexes

Frank J. Villani, Jr.,* Michael J. Costanzo, Ruth R. Inners, Martin S. Mutter, and David E. McClure

Department of Chemical Research, McNeil Pharmaceutical, Spring House, Pennsylvania 19477-0776

Received May 12, 1986

Over the last two decades, several new techniques have been developed for determination of the enantiomeric purity of chiral compounds. In general, these methods are independent of optical rotation and involve the formation of diastereomeric complexes or derivatives for analysis by NMR (^1H, ^{19}F, ^{13}C, ^{31}P)[1] or chromatography.[2] Despite

(1) NMR methods showing the wide utility are α-methoxy-α-(trifluoromethyl)phenylacetic acid derivatives,[3] chiral solvating agents,[4] chiral shift reagents,[5] and other acid derivatives of alcohols and amines.[6]

(2) Chromatographic methods have also employed MTPA and related derivatives[3,6] and the more recently developed chiral stationary phases for direct analysis of enantiomeric purities by HPLC.[7]

(3) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(4) Pirkle, W. H.; Hoover, D. J. *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Wilen, S. H., Eds.; Wiley-Interscience: New York, 1982; p 263 and references therein.

(5) Sullivan, G. R. *Topics in Stereochemistry*; Eliel, E. L.; Allinger, N. L., Eds.; Wiley-Interscience: New York, 1978; p 287.

(6) (a) Raban, M.; Mislow, K. *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley-Interscience: New York, 1967; p 199. (b) Hoyer, G. A.; Rosenberg, D.; Rufer, C.; Seeger, A. *Tetrahedron Lett.* **1972**, 985. (c) Johnson, C. R.; Elliot, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019. (d) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304. (e) Terunuma, D.; Kato, M.; Kamei, M.; Uchida, H.; Nohira, H. *Chem. Lett.* **1985**, 13.

(7) (a) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964. (b) Okamoto, Y.; Okamoto, I.; Yuki, H. *Chem. Lett.* **1981**, 835. (c) Okamoto, Y.; Honda, S.; Okamoto, I.; Yuki, H.; Murata, S.; Norjori, R.; Takaya, H. *J. Am. Chem. Soc.* **1981**, *103*, 6971.

0022-3263/86/1951-3715$01.50/0

Table I. Magnitudes of Nonequivalence and Absolute Configuration[a] for Chiral Amines as Their (+)-MTPA Salts[b]

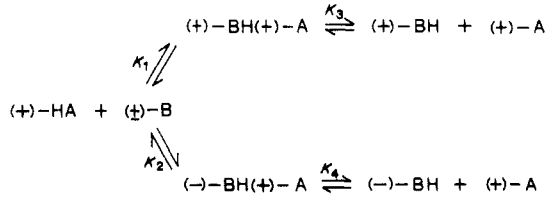
compd	affected proton	$\Delta\delta$[c]	absolute configuration[d]
1	H6′	0.067	3*R*,8a*R*
	H3	0.016	*e*
2	CH_3	0.013	*R*
	H2′	0.052	*R*
3a	H3	0.160	6*R*,10b*S*
	H5	0.120	6*S*,10b*R*
3b	H5	0.13[f]	6*S*,10b*R*
3c	H3	0.156	6*R*,10b*S*
	H5	0.110	6*S*,10b*R*
4	CH_3	0.019	*S*
	H	0.017	*R*
5	H	0.233	*R*
	CH_3	0.070	*R*
	NCH_3	0.020	*S*
6	H2	0.089	*S*
	H6	0.034	*S*
	H6′	0.095	*R*
7	H	0.035[g]	*R*
	H	0.061[h]	*R*
	CH_3	0.007[h]	*R*

[a] References to assignment of absolute configuration are in the Experimental Section. [b] Spectra were obtained in benzene-d_6 unless noted. [c] Difference in chemical shift for the affected proton. [d] Absolute configuration of the enantiomer giving downfield sense of nonequivalence. [e] Not assigned. [f] Measured from a 90-MHz NMR spectrum. [g] Solvent, $CDCl_3$. [h] Solvent, pyridine-d_5.

these substantial advances,[1,2] establishing the enantiomeric purity of chiral tertiary amines remains a problem. In studying various medicinal agents, chemists in our laboratories needed to assay enantiomeric composition of several chiral tertiary amines. We have examined the utility of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) adducts of such amines in the NMR determination of enantiomeric purity and report herein the results of this study.

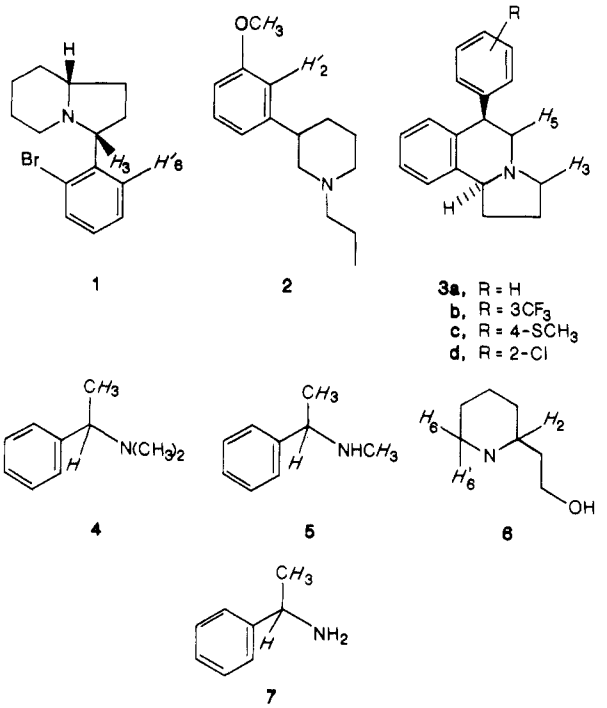
Results and Discussion

Differentiation of Enantiomers. The primary factor contributing to NMR nonequivalence of enantiomeric resonances is the formation of diastereomeric complexes. Differences in the association constants of the contributing equilibria (i.e., eq 1; $K_1 \neq K_2$ and/or $K_3 \neq K_4$) play a key role in the magnitude of nonequivalence, as does the presence of highly polarized or anisotropic groups in the complexing agent. Selection of complexing agent and



solvent can greatly influence the overall results. We reasoned that MTPA should form stable salts with a wide spectrum of amines, because of its acid strength, and afford desirable polar (OMe, CF_3) and aromatic (Ph) elements for optimizing chemical shift nonequivalence.[8]

Chart I



The compounds investigated are shown below, and the results from experiments involving (*R*)-(+)-MTPA and racemic mixtures of these amines are collected in Table I.[11] Certain ^1H NMR resonances exhibited sufficient chemical shift differences (nonequivalence) to allow integration and quantitation of enantiomeric composition. In general, the largest chemical shift differences are observed for protons adjacent to the nitrogen atom. In most cases, several protons more distant from nitrogen also showed spectral nonequivalence; however, many were not sufficiently resolved to permit accurate integration. Nonequivalence was also observed by ^{13}C NMR but for the purpose of integration, ^1H NMR is more convenient. No nonequivalence was observed for the MTPA component by ^1H, ^{13}C, or ^{19}F NMR.

The NMR spectra of the pure enantiomers, as their (+)-MTPA salts, were also examined to assign enantiomeric resonances and correlate the sense of nonequivalence with absolute configuration. Different protons within the same molecule can exhibit an opposite sense of nonequivalence. For example, one of the 3-position protons of the 6*S*, 10b*R* enantiomer of **3a** (Chart I) resonates upfield, while one of the **5** protons resonates downfield, relative to the other enantiomer.[9] Analogues **3b** and **3c** demonstrated a comparable sense and magnitude of nonequivalence, but the 2-chloro compound **3d** failed to show any nonequivalence under similar conditions. Although benzene-d_6 was the typical solvent employed for our nonequivalence experiments, $CDCl_3$ was used for the temperature studies discussed below and comparable nonequivalences for **1** were observed. Spectral nonequivalence of MTPA–amine salts is, of course, not restricted to ter-

(8) A few reports utilizing NMR of diastereomeric salts for determination of enantiomeric purity of amines exist; see: (a) ref 9 and 10. (b) Baxter, C. A. R.; Richards, H. C. *Tetrahedron Lett.* **1972**, 3357. (c) Dyllick-Brenzinger, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 1166. (d) Jochims, J. C.; Taigel, G.; Seeliger, A. *Tetrahedron Lett.* **1967**, 1901. (e) Mannschreck, A.; Jonas, V.; Kolb, B. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 583.

(9) A preliminary application of our method has been reported by our colleagues: Maryanoff, B. E.; McComsey, D. F. *J. Heterocycl. Chem.* **1985**, *22*, 911.

(10) (a) Mikolajczyk, M.; Omelanczuk, J.; Leitloff, M.; Drabowicz, J.; Ejchart, A.; Jurczak, J. *J. Am. Chem. Soc.* **1978**, *100*, 7003 and references therein. (b) Ejchart, A.; Jurczak, J.; Bankowski, K. J. *Bull, Acad. Pol. Sci.* **1971**, *19*, 731.

(11) We thank our colleagues at McNeil for contributing data for Table I: **2**, Dr. Chih Yung Ho; **3a-c**, David F. McComsey; **6**, Philip M. Pitis.

Table II. Effects of Concentration on Nonequivalence for Proton H6′ in (±)-1 with (+)-MTPA

conc, M	nonequiv, ppm[a]
1.0	0.038
0.5	0.055
0.1	0.066
0.05	0.068
0.01	0.071
0.005	0.068
0.001	0.061

[a] In benzene-d_6, ±0.0003 ppm.

Table III. Dependence of Nonequivalence on Molar Equivalents of MTPA for Proton H6′ in (±)-1 with (+)-MTPA

MTPA amine ratio	nonequiv, ppm[a]
0.1	0.018
0.3	0.037
0.4	0.045
0.5	0.049
0.6	0.056
0.7	0.059
0.9	0.066
1.0	0.067
2.0	0.071

[a] In benzene-d_6, ±0.0003 ppm.

tiary amines as supported by the large nonequivalences exhibited by secondary amines **5** and **6**.[8] The benzene-insoluble MTPA salt of compound **7** showed small nonequivalence in $CDCl_3$, but in pyridine-d_5 both the α-H and methyl enantiomeric resonances were well resolved. In contrast, a pyridine-d_5 solution of **1**·MTPA showed no spectral nonequivalence under similar conditions.

Nature of the Complexes. A strong interaction between tertiary amines and MTPA in nonpolar solvents such as benzene is supported by the concentration data in Table II. The magnitude of nonequivalence is markedly insensitive to dilution, varying only slightly over the typical NMR concentration range of 0.1–0.005 M. In highly concentrated solutions, the magnitude of nonequivalence decreased. Such behavior may be attributed to a high degree of aggregation.[12] These studies are consistent with those of Mikolajczyk et al.,[10a] in that aggregation of the ion pairs of diastereomeric salts does not affect the sense of nonequivalence, only the magnitude.

Molar-equivalency studies support a strong ion-pair interaction and rapid exchange[10e] of MTPA anion. Although experiments were usually performed with 1 equiv of MTPA, significant nonequivalence (0.018 ppm) was observed with compound **1** and as little as 0.1 mol equiv of MTPA (Table III). In contrast to earlier studies,[13] addition of excess MTPA (2 mol equiv) led to a slight increase in nonequivalence. This probably relates to displacement of the dissociation equilibrium.

Dissociation equilibria are of some concern when measuring enantiomeric purity of diastereomeric salts by NMR spectroscopy. Since the diastereomeric complex is responsible for the observed nonequivalence, dissociation can reduce the magnitude of nonequivalence. Also, since the dissociation constants need not be equal, the magnitude of nonequivalence can change with variations of enantiomeric purity. This phenomenon has been observed in other diastereomeric salt systems.[14] However, in monitoring classical resolutions of compounds **1**, **3** and **6** with our MTPA method, we failed to detect such a relationship. This implies that the dissociation constants for the two diastereomeric complexes are small or that related constants are nearly equal (i.e., eq 1; $K_1 \simeq K_2$ or $K_3 \simeq K_4$).

Table IV. Effects of Temperature on Nonequivalence for Proton H6′ in (±)-1 with (+)-MTPA

temp, °C	nonequiv, ppm[a]
18	0.096
0	0.128
−15	0.152
−30	0.174
−45	0.206

[a] In $CDCl_3$, ±0.0003 ppm.

The effect of lower temperature on the magnitude of nonequivalence can be striking.[15] Compound **1**·MTPA gave a twofold increase in the magnitude of nonequivalence when the probe temperature was lowered from ambient to −45 °C (Table IV). These increases in nonequivalence probably result from stabilization of specific conformations of the diastereomeric complexes rather than a decrease in the dissociation constants.[4]

Compounds **3a–c** exhibited a consistent sense of nonequivalence as did compound **1** with variations in concentration, temperature, and MTPA molar equivalents. These findings supplement reports of other diastereomeric salt systems in that the sense of nonequivalence can be used to correlate absolute configuration within a related series. However, this series must be cautiously defined. The reversal in the sense of the α-methyl group nonequivalence within the 1-phenylethylamines **4**, **5**, and **7** would lead to an incorrect assignment of absolute configuration and exemplifies a limitation of this method.

In conclusion, determinations of enantiomeric purity of amines (particularly tertiary amines) by NMR spectroscopy of MTPA diastereomeric salts are convenient and accurate and augment the use of chiral solvating agents and chiral shift reagents for these analyses.

Experimental Section

Proton NMR spectra were recorded on either a Varian EM-390 (90 MHz) spectrometer using standard conditions or in Fourier transform mode on a Bruker AM-360 WB (360.13 MHz) spectrometer. Typical FT parameters were as follows: 3-μs pulse (39° flip angle), with a 6.36-s recycle time; spectral window was ±8.3 ppm, with a digital resolution of 0.18 Hz. Benzene-d_6 or $CDCl_3$ (low-temperature studies) were used as solvent and internal standard. Methanol (100%) was used for temperature calibration. The temperature was maintained at ±1 °C by using the Bruker temperature unit. The detection limit for the assay of enantiomeric purity using this method was determined to be <2%. Preparation of racemic compounds **1**,[17] **2**,[18] and **3**[19] have been reported, and racemic compounds **4–7** and (*R*)-(+)-**4**, **5**, and **7** were obtained commercially (Aldrich). Resolutions and absolute configurations of **2**,[18] **3a**,[9] and **6**[20] and have been reported.

(12) Buckson, R. L.; Smith, S. G. *J. Phys. Chem.* **1964**, *68*, 1875.
(13) Ejchart, A.; Jurczak, J. *Bull. Acad. Pol. Sci.* **1970**, *18*, 445.
(14) (a) Mikolajczyk, M.; Ejchart, A.; Jurczak, J. *Bull Acad. Pol. Sci.* **1971**, *19*, 721. (b) Ejchart, A.; Jurczak, J. *Bull. Acad. Pol. Sci.* **1971**, *19*, 725.
(15) This has been previously demonstrated by other workers for chiral solvating agents[4,15] and diastereomeric salts.[13a]
(16) Jochims, J. C.; Taigel, G.; Seeliger, A. *Tetrahedron Lett.* **1967**, 1901.
(17) Carson, J. C.; Carmosin, R. J. U.S. Pat. 4 582 836.
(18) Wikstrom, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 1030 and references therein.
(19) (a) Maryanoff, B. E.; McComsey, D. F.; Costanzo, M. J.; Setler, P. E.; Gardocki, J. F.; Shank, R. P.; Schneider, C. R. *J. Med. Chem.* **1984**, *27*, 943. (b) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.
(20) (a) Toy, M. S.; Price, C. C. *J. Am. Chem. Soc.* **1960**, *82*, 2613. (b) Kostyanovsky, R. G.; et al. In *Atlas of Stereochemistry*; Klyne, W., Buckingham, J., Eds.; Oxford University: New York 1978; Vol. 2, p 5.

Resolution of 1[21] and **3b**,**c**[22] and assignment of absolute configuration will be reported separately.

General Procedure. A mixture of the racemic or partially resolved amine (25 mmol) and 25 mmol (+)-MTPA[23] was dissolved in 0.5 mL of benzene-d_6 (or $CDCl_3$) and the NMR spectrum recorded.

Acknowledgment. We are grateful to our colleagues at McNeil for contributing data for Table I and especially Dr. Bruce E. Maryanoff and David F. McComsey for constructive conversations. We also thank Professor Harry S. Mosher for helpful discussion of MTPA applications. The use of the facilities at the South Carolina Nuclear Magnetic Resonace Spectroscopy Center, funded by the National Science Foundation Grant CHE78-18723, is acknowledged.

Registry No. (±)-1, 103729-18-6; 1·(+)-MTPA, 103639-53-8; (±)-2, 86562-23-4; 2·(+)-MTPA, 103639-54-9; (±)-3a, 90390-52-6; (6*R*,10b*S*)-3a·(+)-MTPA, 103729-10-8; (6*S*,10b*R*)-3a·(+)-MTPA, 103729-15-3; (±)-3b, 90390-54-8; 3b·(+)-MTPA, 103729-12-0; (±)-3c, 90390-64-0; (6*S*,10b*R*)-3c·(+)-MTPA, 103729-17-5; (6*R*,10b*S*)-3c·(+)-MTPA, 103729-14-2; (±)-4, 7398-61-0; (+)-(*R*)-4, 19342-01-9; (*S*)-4·(+)-MTPA, 103639-55-0; (*R*)-4·(+)-MTPA, 103639-60-7; (±)-5, 42882-26-8; (+)-(*R*)-5, 5933-40-4; (*R*)-5·(+)-MTPA, 103639-56-1; (*S*)-5·(+)-MTPA, 103639-61-8; (±)-6, 103729-19-7; (*S*)-6·(+)-MTPA, 103639-58-3; (*R*)-6·(+)-MTPA, 103639-62-9; (±)-7, 618-36-0; (*R*)-(+)-7, 3886-69-9; 7·(+)-MTPA, 103639-59-4; (*S*)-(−)-MTPA, 17257-71-5; (*R*)-(+)-MTPA, 20445-31-2.

(21) Carson, J. R.; Carmosin, R. J.; Costanzo, M. J.; Villani, F. J., Jr., unpublished results.
(22) Maryanoff, B. E.; McComsey, D. F.; Costanzo, M. J., manuscript in preparation.
(23) Use of (*S*)-(−)-MTPA of course gives opposite sense of nonequivalence, which can be useful for examining partially obscured resonances.

Differentially Protected α-Aminoglycine

Mark G. Bock,* Robert M. DiPardo, and Roger M. Freidinger

Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

Received May 15, 1986

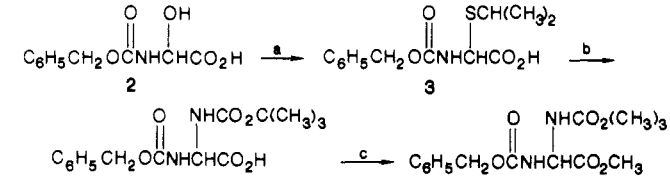
A number of methods have been devised to stabilize biologically active peptides against metabolic degradation and to study their structure–activity relationships.[1] Among these is the preparation of partially modified retro-inverso-peptide structures.[2] Implicit in this approach is the notion that the requisite α,α-diamino residues are readily accessible and that these species can be incorporated into the desired peptide sequence in standard fashion.[3] Recent additional interest in α,α-diamino compounds derives from their possible application in the study of peptide carrier systems designed with the intent of transporting therapeutically useful compounds into microbial cells.[4] There are thus several applications[5] for which one would like to have an α,α-diamino residue available for use in peptide synthesis. In this connection, we report the preparation of α-aminoglycine (**1**), in protected form, which complements existing methodology,[3a-c,4] and demonstrate its manipulation in the synthesis of simple dipeptides.

$H_2NCH(NH_2)CO_2H$
1

The synthetic process is summarized in Scheme I. 2-Propanethiol is amidoalkylated with α-hydroxy-*N*-(benzyloxycarbonyl)glycine (**2**) according to the method of Ben-Ishai to give the crystalline α-isopropylthio derivative **3**.[6] The second amino group is then introduced via a mercuric ion mediated displacement of the isopropylthio moiety with *tert*-butyl carbamate. In this way, protected α-aminoglycine **4** is accessible in 70% overall yield from **2** as a stable solid which can be stored in the refrigerator indefinitely. The acyl imine which is presumably the intermediate in the alkylthio displacement can be intercepted with other primary carbamates as well, for example, ethyl carbamate. However, treatment of **3** with ammonia and mercury salts to give monoprotected α-aminoglycine (cf. **8a**) was found not be an efficient process.

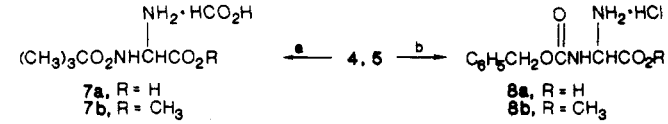
The differentially protected **4** is poised for further elaboration at both the amino and carboxy termini, in either order. Accordingly, the coupling of **4** with L-alanine methyl ester in the presence of common carbodiimide reagents afforded the corresponding dipeptide **6**, as a mixture of diastereomers, 86% yield. Alternatively, esterification of **4** leads to **5**, which is stable indefinitely at room temperature and which can be further modified as outlined in Scheme II. No difficulty is encountered in selectively removing the amino protecting groups of **4** or **5** as either the benzyloxycarbonyl (Cbz) or *tert*-butyloxycarbonyl (Boc) groups are readily cleaved to give **7** and **8**, respectively. These compounds are also stable materials (0 °C, dry) although we have found it advisable to use **7a** and **7b** as soon as they are generated. As a further illustration of their application in peptide synthesis, **7b** was coupled with

Scheme I[a]



[a] (a) $(CH_3)_2CHSH$, H_2SO_4 (catalyst), HOAc; (b) $(CH_3)_3CCO_2N-H_2$, Hg^{2+}, THF; (c) CH_3I, K_2CO_3, DMF.

Scheme II



[a] (a) Pd/C, HCO_2H–H_2O, CH_3OH. (b) HCl(g), EtOAc.

(1) Veber, D. F.; Freidinger, R. M. *Trends NeuroSci. (Pers. Ed.)* **1985**, *8*, 392 and references cited therein.
(2) (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1. (b) Goodman, M.; Chorev, M. *Perspectives in Peptide Chemistry*; Eberle, A., Geiger, R., Wieland, T., Eds.; Karger: Basel, 1981; p 283.
(3) (a) Chorev, M.; Willson, C. G.; Goodman, M. *J. Am. Chem. Soc.* **1977**, *99*, 8075. (b) Chorev, M.; Goodman, M. *Int. J. Pept. Protein Res.* **1983**, *21*, 258. (c) Pallai, P.; Goodman, M. *J. Chem. Soc., Chem. Commun.* **1982**, 280. (d) Chorev, M.; Shavitz, R.; Goodman, M.; Minick, S.; Guillemin, R. *Science (Washington, D.C.)* **1979**, *204*, 1210. (e) Pallai, P. V.; Richman, S.; Struthers, R. S.; Goodman, M. *Int. J. Pept. Protein Res.* **1983**, *21*, 84. (f) Fuller, W. D.; Goodman, M.; Verlander, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 5821. (g) Loudon, G. M.; DeBons, F. E. *J. Org. Chem.* **1980**, *45*, 1703.
(4) Kingsbury, W. D.; Boehm, C. J.; Mehta, R. J.; Grappel, S. F.; Gilvarg, C. *J. Med. Chem.* **1984**, *27*, 1447.
(5) For a recent application in heterocyclic synthesis, see: Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M., submitted for publication in *Tetrahedron Lett.*
(6) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863.

0022-3263/86/1951-3718$01.50/0