Determination of the enantiomeric composition of *N*,*N*-dimethyl-α-ferrocenylethylamine by ^{1}H NMR spectroscopy

N. A. Kataeva,[a] Yu. K. Grishin,[b] and V. V. Dunina[b]★

[a]*N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 31 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 954 1279*
[b]*Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie Gory, 119899 Moscow, Russian Federation. Fax: +7 (095) 932 8846. E-mail: dunina@org.chem.msu.ru*

A new method for the determination of enantiomeric composition of *N*,*N*-dimethyl-α-ferrocenylethylamine by ^{1}H NMR spectroscopy using (*S*)-mandelic acid as a chiral protonating agent was proposed.

Key words: *N*,*N*-dimethyl-α-ferrocenylethylamine, enantiomeric purity, chiral protonation, (*S*)-mandelic acid, ^{1}H NMR spectroscopy.

N,*N*-Dimethyl-α-ferrocenylethylamine (**1**) is widely used for the synthesis of planar-chiral enantioselective catalysts.[1—3] However, the enantiomeric purity of this compound and similar ferrocenylalkylamines was determined hitherto by HPLC using expensive and not always available chiral columns[4—6] or by polarimetry.[7—9] The latter method has some drawbacks[10] aggravated in the case of amine **1** by its low optical activity ($[\alpha]_D$ ±14.4)[7—9] in combination with intense light absorption in the range close to the D-line of Na. The goal of the present work was to develop a simple and convenient method for the reliable determination of enantiomeric composition of *N*,*N*-dimethyl-α-ferrocenylethylamine by ^{1}H NMR spectroscopy.

Results and Discussion

The initial attempts to use various homochiral palladacycles for the conversion of enantiomers of amine **1** to spectrally discernible diastereomers failed because of a low capability of tertiary amines for coordination with palladium[11] and a low resistance of the ferrocenyl fragment to oxidation. Nor solvation of amine **1** with an excess of methyl ester of (*S*)-*N*-(3,5-dinitrobenzoyl)phenylalanine followed by its protonation with L-tartaric acid gave a noticeable dispersion of signals of the resulting diastereomers.

Insofar as (*S*)-mandelic acid (**2**)[12] and its derivatives[13,14] are known to be more efficient as chiral protonating agents for the determination of enantiomeric purity of amines than other similar reagents, including Mosher's acid,[12,15] we estimated its applicability for the solution of our problem.

The resolution of signals for diastereomeric salts (*R*,*S*)-**3**/(*S*,*S*)-**3** was estimated by protonating samples of scalemic ferrocenylethylamine **1** in $CDCl_3$ *in situ* with (*S*)-mandelic acid (*S*)-**2** in an NMR tube (Scheme 1).

Scheme 1

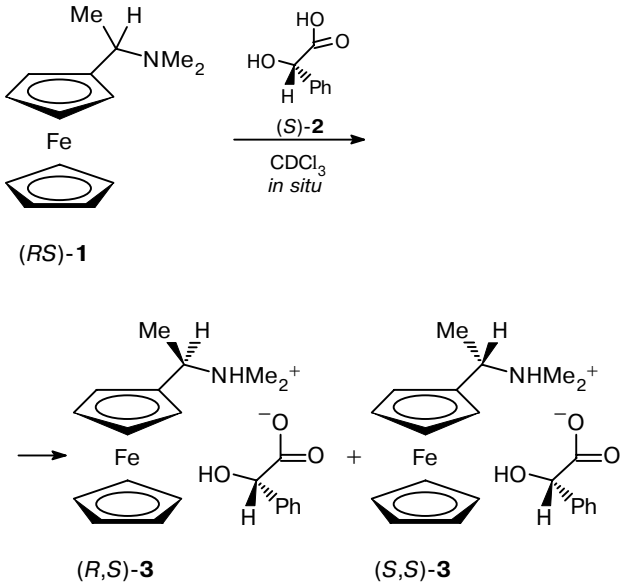

Figure 1 displays fragments of the ^{1}H NMR spectra of three specimens of *N*,*N*-dimethyl-α-ferrocenylethyl-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1260—1262, July, 2001.

1066-5285/01/5007-1323 $25.00 © 2001 Plenum Publishing Corporation

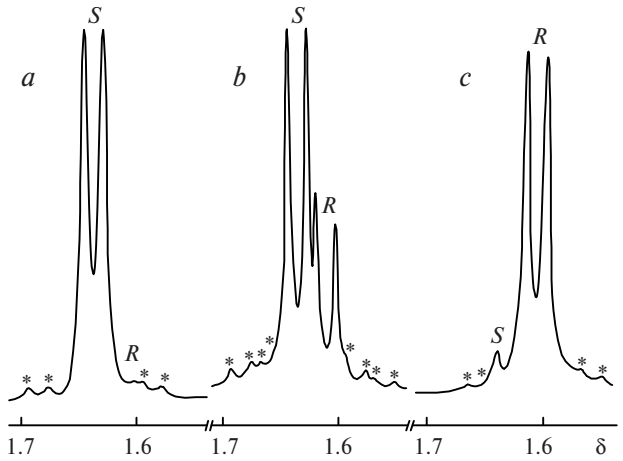

Fig. 1. Fragments of the ^{1}H NMR spectra in the range of α-Me proton resonance of *N*,*N*-dimethyl-α-ferrocenylethylamine protonated with (*S*)-mandelic acid in $CDCl_3$ (*in situ*): (*a*) the (*S*)-enantiomer, (*b*) a scalemic sample, and (*c*) the (*R*)-enantiomer. "Satellite" lines owing to rotation are asterisked.

amine **1** protonated with approximately equimolar amounts of (*S*)-mandelic acid, namely, specimens with high (*a*) (*S*)-*ee* or (*c*) (*R*)-*ee* and (*b*) a specimen containing comparable amounts of the two enantiomers.

The ^{1}H NMR spectrum of a protonated scalemic amine **1** shows two doublets with $\Delta\delta = 0.025$ ppm in the region of the α-Me proton resonance (see Fig. 1, *b*). Such dispersions of the signals for diastereomeric salts should be regarded as quite satisfactory for this type of compounds. Thus chiral protonation of *N*,*N*-dimethyl-α-methylbenzylamine with methoxy(trifluoromethyl)phenylacetic acid gives $\Delta\delta = 0.019$ ppm[15] for the α-Me protons.

The ratio of the integral intensities of two doublets for the α-Me group of the above sample was refined by signal deconvolution to give the value of 2.56 : 1. The corresponding enantiomeric purity of the amine is 43.8±1.5% *ee*, while that calculated from the specific rotation of this sample ($[\alpha]_D^{20}$ −4.0±2.7) equals 27.8±18.5% *ee*.

Analogous processing of the ^{1}H NMR spectra of the salts derived from (*S*)- and (*R*)-enantiomers of amine **1** ($[\alpha]_D^{20}$ −10.7±2.7 and +10.8±0.7, respectively) gave 93.2±2.0% *ee* and 83.4±1.5% *ee*. These values differ significantly from those found from specific rotation (74.1±18.5% *ee* and 75.0±4.2% *ee*, respectively). An additional recrystallization of L-tartrates of these amines afforded individual enantiomers (*S*)-**1** and (*R*)-**1** (the ^{1}H NMR spectra of the samples protonated with (*S*)-mandelic acid contain one doublet).

In a representative series of 15 differently enriched specimens of amine **1**, it was found that the chemical shifts of the Me groups of salts of its enantiomers vary in narrow and non-overlapping regions (δ 1.635—1.645 and 1.605—1.619 for (*S*)- and (*R*)-enantiomers, respectively). This makes it possible to estimate the absolute configuration of amine **1** together with the solution of an analytical problem.

In spite of a comparatively small dispersion of signals from diastereomeric salts, the proposed method for the determination of the enantiomeric composition of *N*,*N*-dimethyl-α-ferrocenylethylamine has some advantages over the other methods. These are a simple procedure of *in situ* derivatization, for which there is no need to strictly observe the stoichiometry of the reactants; the use of available and inexpensive (*S*)-mandelic acid, which virtually does not complicate a highfield ^{1}H NMR spectral pattern; and the possibility of estimating the absolute configuration of the amine.

Experimental

^{1}H NMR spectra were recorded on a Varian VXR-400 spectrometer (400 MHz) in $CDCl_3$; signals were assigned from the results of homonuclear double resonance. The chemical shifts were measured with respect to signals from the residual protons of the solvent and are referenced to Me_4Si. Specific rotation at the D-line of Na was measured on an A1-EPO automated polarimeter (VNIEKIProdmash). (*S*)-Mandelic acid with $[\alpha]_D^{20}$ +152.4 (*c* 5.0, water) and $CDCl_3$ (Aldrich) were used without additional purification.

Racemic *N*,*N*-dimethyl-α-ferrocenylethylamine (1) was synthesized[8] and resolved[7—9] by the known methods. To remove oxidation products,[16,17] it was purified by "dry column" chromatography[18] (5.5×2.9 cm, neutral Al_2O_3) in benzene—acetone mixtures of increasing polarity immediately before recording NMR spectra. ^{1}H NMR, δ: 1.455 (d, 3 H, α-Me, J = 6.9 Hz); 2.086 (s, 6 H, NMe_2); 3.624 (q, 1 H, $C_\alpha H$, J = 6.9 Hz); 4.101 (s, 5 H, C_5H_5); 4.092 (m, 1 H, C_5H_4); 4.119 (m, 2 H, C_5H_4); 4.139 (m, 1 H, C_5H_4).

Chiral protonation of *N*,*N*-dimethyl-α-ferrocenylethylamine with (*S*)-mandelic acid. (*S*)-Mandelic acid (**2**) (0.0142 g, 0.093 mmol) was added to a solution of amine **1** (0.024 g, 0.093 mmol) in $CDCl_3$ (~0.3 mL). After dissolution of the acid, the reaction mixture was transferred to an NMR tube. The volume of the solution was brought to 0.5 mL with an additional amount of $CDCl_3$ (0.2 mL) before recording ^{1}H NMR spectra.

The ^{1}H NMR spectrum of a salt with amine (*S*)-**1** of low optical purity, $[\alpha]_D^{20}$ −4.0±2.7 (*c* 0.73, EtOH): amine **1**, δ: 1.613 (d, 0.84 H, α-Me, J = 7.0 Hz); 1.638 (d, 2.16 H, α-Me, J = 6.9 Hz); 2.377 (s, 6 H, NMe_2); 4.256 (q, 1 H, C(α)H, J = 6.9 Hz); 4.155 (s, 5 H, C_5H_5); 4.17—4.25 (m, 4 H, C_5H_4); acid **2**, δ: 4.978 (s, 1 H, C(α)H); 7.239 (tt, 1 H, H_p arom., ^3J = 7.4 Hz, ^4J = 1.6 Hz); 7.322 (m, 2 H, H_m arom., J = 7.4 Hz); 7.531 (dd, 2 H, H_o arom., ^3J = 7.4 Hz, ^4J = 1.5 Hz). The spectrum recorded in C_6D_6 shows a very broad signal at δ 9.33 (s, 1 H, $\Delta\nu_{1/2}$ = 255 Hz), which may be assigned to the OH or $Me_2N\underline{H}^+$ proton.

References

1. T. Hayashi and M. Kumada, *Acc. Chem. Res.*, 1982, **15**, 395.

2. A. Togni, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1475.
3. Ch. J. Richards and A. J. Locke, *Tetrahedron: Asymmetry*, 1998, **9**, 2377.
4. Y. Matsumoto, A. Ohno, Sh.-j. Lu, T. Hayashi, N. Oguni, and M. Hayashi, *Tetrahedron: Asymmetry*, 1993, **4**, 1763.
5. A. Ohno, M. Yamane, and T. Hayashi, *Tetrahedron: Asymmetry*, 1995, **6**, 2495.
6. D. W. Armstrong, J. T. Lee, and L. W. Chang, *Tetrahedron: Asymmetry*, 1998, **9**, 2043.
7. D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, and I. Ugi, *J. Am. Chem. Soc.*, 1970, **92**, 5389.
8. G. W. Gokel and I. K. Ugi, *J. Chem. Educ.*, 1972, **49**, 294.
9. G. W. Gokel, D. Marquarding, and I. K. Ugi, *J. Org. Chem.*, 1972, **37**, 3052.
10. D. Parker, *Chem. Rev.*, 1991, **91**, 1441.
11. S. Y. M. Chooi, P.-H. Leung, Ch. Ch. Lim, K. F. Mok, G. H. Quek, K. Y. Sim, and M. K. Tan, *Tetrahedron: Asymmetry*, 1992, **3**, 529.
12. Sc. C. Benson, P. Cai, M. Colon, M. A. Haiza, M. Tokles, and J. K. Snyder, *J. Org. Chem.*, 1988, **53**, 5335.
13. D. Parker and R. J. Taylor, *Tetrahedron*, 1987, **43**, 5451.
14. G. Prestat, A. Marchand, J. Lebreton, A. Guingant, and J.-P. Pradere, *Tetrahedron: Asymmetry*, 1998, **9**, 197.
15. Fr. J. Villani, M. J. Constanzo, R. R. Inners, M. S. Mutter, and D. E. McClure, *J. Org. Chem.*, 1986, **51**, 3715.
16. R. F. Winter and G. Wolmershauser, *J. Organomet. Chem.*, 1998, **570**, 201.
17. H.-B. Kraatz, *J. Organomet. Chem.*, 1999, **579**, 222.
18. J. T. Sharp, I. Gosney, and A. G. Rowley, *Practical Organic Chemistry*, Chapman and Hall, London—New York, 1989, Ch. 4.2.2d.

Received January 19, 2001;
in revised form March 28, 2001