The Direct Resolution of DL-*Aspartic Acid by the Use of an Optically Active Amine*[1]

By Kaoru HARADA

(Received April 9, 1964)

N-Acyl DL-amino acids have been used in most cases for the chemical and enzymatic resolution of DL-α-amino acids. However, for acidic amino acids, various other methods of resolution have been employed. DL-Glutamic acid was resolved by seeding,[2] by an optically-active amine[3] and by lysine[4] without using its *N*-acyl derivative. DL-Aspartic acid was resolved from its supersaturated copper complex solution by seeding it with L- or D-aspartic acid copper complexes.[5] DL-Aspartic acid was resolved by preferential crystallization with optically-active glutamic acid[6] and by the direct salt formation of optically-active lysine.[4] DL-Aspartic acid was also partially resolved on a starch column.[7]

In this report, the direct resolution of DL-aspartic acid by the use of optically-active α-methylbenzylamine[8] will be described. The optically-active amine has been used in several stereospecific syntheses of α-amino acids.[9-12] The use of D(−)α-methylbenzylamine ($[\alpha]_D^{27} = -40.6°$) resulted in the crystallization of L-aspartic acid D-amine salt ($[\alpha]_D^{27} = -9.7°$) from the reaction mixture. L(+)Amine ($[\alpha]_D^{27} = +39.3°$) resulted in D-aspartic acid L-amine salt ($[\alpha]_D^{27} = +10.9$). These salts were dissolved in water, and the pH was adjusted to about 2.8 to precipitate L- or D-aspartic acid. Optically-pure L-aspartic acid ($[\alpha]_D^{27} = +25.0°$) and almost pure D-aspartic acid ($[\alpha]_D^{27} = -23.0°$) were obtained. Optically-impure D- and L-aspartic acid (optical purity 50~60%) were isolated from the mother liquors of crystallization. D-Aspartic acid D-amine salt was prepared in order to compare it with its diastereomer. The solubility of the salt in the resolution solvent was much higher than that of its diatereomer. The optically-active amine could not be applied for the resolution of free DL-glutamic acid.

Experimental

Standard Aspartic Acid Amine Salts. — *(L-Aspartic Acid D-Amine) Salt.* — L-Aspartic acid (0.67 g., 0.005 mol.) was dissolved in a mixture of 2.0 ml. of water and 0.66 g. (0.005 mol.) of D(−)-methylbenzylamine ($[\alpha]_D^{27} = -40.6°$ in benzene). To this, 10 ml. of methanol and 5 ml. of acetone were added, and the mixture was kept in a refrigerator overnight. The (L-aspartic acid D-amine) salt crystallized; m. p. 260~263°C (decomp.), $[\alpha]_D^{27} = -9.9°$ (*c* 2.04, water). Found: C, 56.48; H, 7.34; N, 11.23. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02%.

(D-Aspartic Acid L-Amine) Salt. — The salt was obtained from D-aspartic acid ($[\alpha]_D^{27} = -24.3°$) and L(+) amine, $[\alpha]_D^{27} = +10.5°$ (*c* 2.13 water). Found: C, 56.43; H, 7.14; N, 11.18%.

(D-Aspartic Acid D-Amine) Salt.—The salt did not crystallize under the above conditions, but it did crystallize upon the addition of an extra 10 ml. of acetone to the salt solution; m. p. 258~263°C (decomp.), $[\alpha]_D^{27} = +9.2°$ (*c* 1.04, water). Found: C, 56.66; H, 7.17; N, 10.92%.

The Resolution of DL-Aspartic Acid. — DL-Aspartic acid (6.65 g., 0.05 mol.) was dissolved in a mixture of 200 ml. of water and 6.10 g. (0.05 mol.) of D(−)α-methylbenzylamine ($[\alpha]_D^{27} = -40.6°$ in benzene) and filtered. To this, 50 ml. of methanol and 60 ml. of acetone were added, and the flask was rubbed with a glass rod (or preferably seeded with L-aspartic acid D-amine salt) and kept overnight in a refrigerator. The product, 4.70 g. (71%) of (L-aspartic acid D-amine) salt, was recrystallized by dissolving it in 12 ml. of water and precipitated with 15 ml. of methanol and 35 ml. of acetone. Pure salt (3.60 g.) was obtained; m. p. 260~263°C (decomp.), $[\alpha]_D^{27} = -9.7°$ (*c* 2.18, water). Found: C, 56.68; H, 6.97; N, 11.01. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02%.

In the same way, (D-aspartic acid L-amine) salt was isolated by the use of L(+)-α-methylbenzylamine ($[\alpha]_D^{27} = +39.3°$ in benzene); 4.50 g. of salt was thereby isolated. After recrystallization, 3.48 g. of pure salt was obtained; m. p. 260~263°C

1) Contribution number 31 of the Institute for Space Biosciences, Florida State University.
2) Japanese Pat. 2972 (1956), *Chem. Abstr.*, **51**, 2135 (1957).
3) F. H. Radke, R. B. Fearing and S. W. Fox, *J. Am. Chem. Soc.*, **76**, 2801 (1954).
4) British Pat. 773653, *Chem. Abstr.*, **51**, 14, 794.
5) K. Harada and S. W. Fox, *Nature*, **194**, 768 (1962).
6) British Pat. 773660, *Chem. Abstr.*, **51**, 17984; U. S. Pat. 2790001, *Chem. Abstr.*, **51**, 13910.
7) German Pat. 1016713, *Chem. Abstr.*, 541344.
8) W. Theilacker and H. Winkler, *Chem. Ber.*, **87**, 690 (1954); B. Helberich and W. Portz, ibid., **86**, 1034 (1953); A. W. Ingersoll, "Organic Syntheses," Coll. Vol. II, 506 (1943).
9) J. C. Sheehan and R. E. Chandler, *J. Am. Chem. Soc.*, **83**, 4791 (1961).
10) R. G. Hiskey and R. C. Northrop, ibid., **83**, 4798 (1961).
11) K. Harada, *Nature*, **200**, 1201 (1963).
12) K. Harada and S. W. Fox, *Naturwissenschaften*, **51**, 106 (1964).

(decomp.), $[\alpha]_D^{27} = +10.9°$ (*c* 2.08, water). Found: C, 56.63; H, 7.03; N, 11.13%.

Optically-Active Aspartic Acid. — *L-Aspartic Acid.*—Three grams of (L-aspartic acid D-amine) salt was dissolved in 15 ml. of water, and the pH was adjusted to about 2.8 by the addition of 3 N hydrochloric acid. Then 15 ml. of ethanol was added, and the mixture was kept in a refrigerator overnight. The crystallized L-aspartic acid was filtered and washed with cold water and absolute alcohol. L-Aspartic acid (1.35 g.) was obtained; $[\alpha]_D^{27} = +25.0°$ (*c* 1.97, 6 N HCl). Found: C, 36.25; H, 5.39; N, 10.48. Calcd. for $C_4H_7NO_4$: C, 36.09; H, 5.30; N, 10.52%. From the mother liquor, optically-impure D-aspartic acid (1.50 g.) was obtained, $[\alpha]_D^{27} = -12.3°$ (*c* 1.07, 6 N HCl). Found: C, 36.21; H, 5.43; N, 10.34%.

D-Aspartic Acid. — D-Aspartic acid L-amine salt (1.20 g.) was treated in the way described above. D-Aspartic acid (0.53 g.) was isolated; $[\alpha]_D^{27} = -23.0°$ (*c* 2.30, 6 N HCl). Found: C, 35.88; H, 5.45; N, 10.37%.

The author is indebted to Professor Sidney W. Fox of this Institute for his helpful discussions. This work was supported by National Aeronautics and Space Administration Grant Number NsG-173-62.

Institute for Space Biosciences
and Department of Chemistry
Florida State University
Tallahassee, Florida, U. S. A.