Tetrahedron Letters No. 40, pp 3813 - 3816.
©Pergamon Press Ltd. 1978. Printed in Great Britain.
0040-4039/78/1001-3813$02.00/0

MUTUAL RESOLUTION OF (±)-EPHEDRINE AND Z-DL-AMINO ACID INDUCED BY SEEDING CHIRAL SALT

Chi-Huey Wong and Kung-Tsung Wang*

Institute of Biological Chemistry, Academia Sinica
P. O. Box 23-106, Taipei, Taiwan, Republic of China

The diastereomeric salt-forming acid-base reaction is one of the most convenient methods of optical resolution. It is always carried out with one optically pure resolving agent to form a mixture of diastereomeric salts whose separation depends on solubility differences. The enantiomers to be resolved are then recovered from the salts after acid or base decomposition[1,2].

An interesting new method for the mutual resolution by salt forming process between (±)-ephedrine and Z-DL-amino acid was found in our laboratory during the preparation of D-amino acid derivatives, using ephedrine as resolving agent, <u>via</u> "reciprocal" resolution[3,4,5].

Reciprocal Resolution

$$(-)A + (\pm)B \longrightarrow (-)A\cdot(+)B \quad + \quad (-)A\cdot(-)B$$

$$(+)A + (\pm)B \longrightarrow (+)A\cdot(-)B \quad + \quad (+)A\cdot(+)B$$

$$(-)B + (\pm)A \longrightarrow (+)A\cdot(-)B \quad + \quad (-)A\cdot(-)B$$

$$(+)B + (\pm)A \longrightarrow (-)A\cdot(+)B \quad + \quad (+)A\cdot(+)B$$

Mutual Resolution

$$(\pm)A + (\pm)B \longrightarrow \begin{matrix} (+)A\cdot(-)B & + & (+)A\cdot(+)B \\ (-)A\cdot(+)B & + & (-)A\cdot(-)B \\ \text{Less soluble} & & \text{More soluble} \end{matrix}$$

A: Z-Ala, Z-Val, Z-Met, Z-Phe

B: Ephedrine

Both the compound being resolved and the resolving agent we used are racemic. After dissolving both racemic compounds in a suitable solvent with suitable concentration, the resolution was induced by seeding the desired chiral salt. The precipitates formed in a few hours were collected by filtration and the mother liquid was kept for another chiral salt precipitation. Thus, optical resolution of the two pairs of racemic compounds, resulting in preparation of four optically pure substances, was succeeded simultaneously. In theory, the solution is an equilibrium mixture of the 4 isomeric salts before seeding with (+)A·(-)B, and the precipitation of (+)A·(-)B left only (-)A·(+)B in the solution. So, we can not observe the formation of (+)A·(+)B and (-)A·(-)B in solution. The Figure summarized the relationship between "reciprocal" resolution and "mutual" resolution.

The experiment of this mutual resolution was performed by dissolving equivalent amounts of racemic Z-amino acid and (±)-ephedrine in ethyl acetate. The concentration of each racemic compound was around 0.5M. The salt precipitation was then initiated at room temperature by adding traces of optically pure diastereomeric salt as seed. The mixture was kept without disturbing for 5 hr and then at $0^{o}C$ for 1 hr. The solution was filtered to collect the first precipitates which showed predominantly the same as the added seed when the optical rotation was measured. After recrystallization from ethyl acetate followed by acid decompositon, optically pure (Ca. 90-95%) Z-amino acid and ephedrinium chloride were recovered in chemical yields ranging 70-80%. The filtrate obtained from filtering the first precipitates as described above was kept in cooling over night and the second precipitates were collected, which showed essentially the antipode salt of first precipitate. After recrystallization and decomposition, optically pure (Ca. 100%) enantiomers of Z-amino acid and ephedrine were obtained in chemical yields of about 90%, respectively. The results with Z-DL-Ala, Z-DL-Val, Z-DL-Met and Z-DL-Phe as examples were illustrated in the Table.

Other amino acid derivatives such as Z-DL-Ile, Z-DL-Asp(OMe), and Z-DL-Ser(Z) which can be resolved reciprocally with ephedrine will be tested with the same method.

The results of the "reciprocal" resolution between ephedrine and Z-amino acid reported previously concluded that Z-amino acids with a β-methyl side group, as well as Ala, precipitated to afford predominantly salts of the L-isomers of amino acids with (+)-ephedrine, and D-isomers of amino acids with (-)-ephedrine. Entirely opposite results were obtained when amino acid derivatives without a β-methyl side group, as well as Phe, were used. However, in spite of which compound, Z-amino acids or ephedrine, being resolved the resolving agent used was optically pure.

Table. Physical constants of resolved acids and bases

Starting Acid and (±)-Ephedrine	1st ppt[a] (%)	$[\alpha]_D$[b] Acid (lit) Base (lit)	2nd ppt (%)	$[\alpha]_D$[b] Acid (lit) Base (lit)
Z-DL-Ala	Z-D-Ala· (-)-Ephedrine (71)	-12.8(-14.2)[3] -31.0(-34.5)[3]	Z-L-Ala· (+)-Ephedrine (90)	+14.6(+14.5)[3] +34.5(+34.59)[3]
Z-DL-Ala	Z-L-Ala· (+)-Ephedrine (74)	+12.1 +30.8	Z-D-Ala· (-)-Ephedrine (88)	-14.3 -34.0
Z-DL-Val	Z-L-Val· (-)-Ephedrine (70)	+24.4(+29.5)[4] -31.1	Z-D-Val· (+)-Ephedrine (86)	-28.1(-28.3)[4] +34.5
Z-DL-Val	Z-D-Val· (+)-Ephedrine (72)	-25.3 +32.1	Z-L-Val· (-)-Ephedrine (82)	+27.4 -32.1
Z-DL-Met	Z-L-Met· (+)-Ephedrine (76)	+20.1(+23.4)[4] +30.2	Z-D-Met· (-)-Ephedrine (86)	-22.1(-26.0)[4] -30.1
Z-DL-Met	Z-D-Met· (-)-Ephedrine (70)	-21.0 -30.1	Z-L-Met· (+)-Ephedrine (82)	+21.0 +31.0
Z-DL-Phe[c]	Z-L-Phe· (-)-Ephedrine (76)	-29.0(-31.9)[4] -31.0	Z-D-Phe· (+)-Ephedrine (86)	+31.0(+33.9) +34.0
Z-DL-Phe[c]	Z-D-Phe· (+)-Ephedrine (74)	+30.1 +30.2	Z-L-Phe· (-)-Ephedrine (84)	-29.1 -31.2

[a] Induced by seeding the desired salt precipitate. [b] After acid decomposition, Z-amino acid recovered was hydrolyzed with 6N HCl and the optical rotation of the hydrolysate was measured at 25°C (C 1, 5N HCl); ephedrine was recovered as HCl salt and recrystallized from ethanol-acetone; its optical rotation was measured at 25°C (C 1, H_2O). [c] The solvent used was ether.

Resolution of optical isomers by selective crystallization of one antipode from a solution of racemic form was reported in 1867[6]. This was accomplished by providing seed crystals of one isomer in a supersaturated solution of the racemate and the precipitates formed were filtered quickly. The practical resolution by this principle was not used until early 1950. DL-amino acids such as Glu, Thr, His and Asn were successfully resolved by this method[7]. From the phase diagram containing optical isomers, this case occurs only with conglomerates and takes place in the region in which supersaturation by the two enantiomers may occur. Therefore, the number of useful resolution are limited.

The successful use of racemic compound as resolving agent as we showed for the optical resolution induced by seeding was not reported before, although it was similar to the so-called enantiomeric crystallization[6]. Since the enantiomeric compounds are usually impossible to separate from differences in solubility, it is doubtful from this experiment that the first and the second precipitated salts as mentioned are truely enantiomeric although each component of the two salts is enantiomeric.

Perhaps some of the compounds which can be resolved by reciprocal process will behave samely as the salt precipitation of our experiment. This is a simultaneous resolution of two pairs of racemic compounds resulting in four optically pure substances.

References and Notes

1. S. H. Wilen, A. Collet and J. Jacques, Tetrahedron, 33, 2725 (1977)
2. S. H. Wilen, Topics in Stereochemistry (E. L. Elied and N. L. Allinger eds.) Vol. 6, p. 107. Wiley-Interscience, New York (1971)
3. L. R. Overby and A. W. Ingersoll, J. Amer. Chem. Soc., 82, 2069 (1960)
4. K. Oki, K. Suzuki, S. Tuchida, T. Saito and H. Kotake, Bull. Chem. Soc. Jpn., 43, 2554 (1970)
5. C. H. Wong and K. T. Wang, J. Chinese Chem. Soc., 25, (1978) In press.
6. D. Gernez, Ann. Chem., 143, 376 (1867)
7. R. M. Secor, Chem. Rev., 63, 297 (1963)
8. Z is abbreviation for N-benzyloxycarbonyl, ppt for precipitation. Optical rotation was measured with Jasco Dip 180 automatic digital polarimeter.

(Received in Japan 15 June 1978; received in UK for publication 8 August 1978)