Evidence of Existence of Two Stereospecific Control Mechanisms in Asymmetric Transformation of 2-Phenylpropanal *via* Enamines

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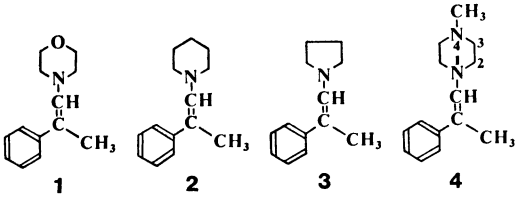
(Received August 16, 1977)

The temperature dependence of asymmetric transformation of 2-phenylpropanal *via* achiral enamine salt of *d*-10-camphorsulfonic acid was examined. The relation between the rotation of 2-phenylpropanal obtained and reaction temperature showed a notable change in specific rotation of the aldehyde obtained. Two courses are postulated for the optical activation.

Asymmetric transformation of racemic α-substituted carbonyl compounds was achieved by treatment of the enamines with chiral acids.[1] This is attributed to the difference in free energy between mutually interconvertible diastereoisomeric iminium salt (thermodynamical control).[2-4] However, Duhamel and Plaquevent recently reported some experimental facts explicable in terms of kinetic control, though the mechanism was not described in detail.[5]

The rotation of the α-substituted carbonyl compounds obtained depends remarkably on the reaction temperature as well as the solvent used.[1] Accordingly, the temperature effect on the asymmetric transformation was examined in detail using 2-phenylpropanal (hereafter called PPA) as a model α-substituted carbonyl compound. From the relation between reaction temperature and specific rotations of PPA, it was found that thermodynamical control or kinetic control alone is not sufficient to account for the results.

Achiral enamines **1**, **2**, **3**, and **4** are morphorine, piperidine, pyrrolidine, and *N*-methylpiperazine enamines, respectively, of racemic PPA.



1 **2** **3** **4**

Experimental

Optical rotations were determined with a JASCO Digital Automatic Polarimeter Model DIP 181. Gas chromatographic analyses were carried out using a 2 m column of 20% SE-30 on Chromosorb W with a Hitachi Gas Chromatograph Model K53. Nuclear magnetic resonance spectra were measured with a JNM-PS-100 Spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in δ values. Infrared spectra were obtained with a JASCO Model IR-G and mass spectra with a Hitachi GC-MS RM-50 (column: 10% SE-30 on Chromosorb W, 3 mm × 1 m).

Reagents and Solvent. *d*-10-Camphorsulfonic acid was prepared according to the directions of Reychler.[6] $[\alpha]_D^{23}$ +21.8° (*c* 8.81 H_2O), lit, $[\alpha]_D^{20}$ +22.6° (*c* 8.3, H_2O). Chloroform was purified by being shaken 7 times with water, dried over calcium chloride, and distilled.

Preparation of Enamines. Enamines were prepared by the usual azeotropic procedure using benzene as a solvent.

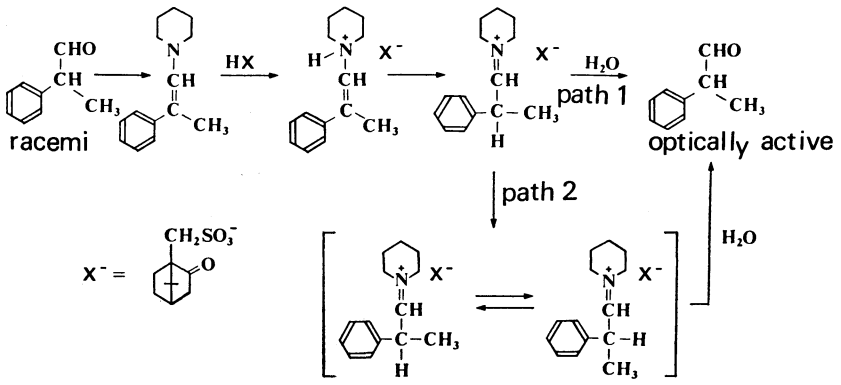
*1-(β-Methylstyryl)morphorine (**1**)*: Bp 108—111 °C (0.5 mmHg). Yield 90.8%. Mp 59.5—62 °C. MS *m/e* 203 (M^+), 144 (base), 130, 91. IR (film) 1685, 1640, 1600, 1499, 1450, 1378, 1298, 1260, 1120, 865, 760, 705, 650, 605, 545 cm^{-1}. NMR ($CDCl_3$) mixture of two geometrical isomers in the ratio 77 : 23 at room temperature. Major isomer 1.08 (d, J=1.1 Hz, CH=C-CH_3), 2.78 (m), 3.7 (m), 6.02 (q, J=1.1 Hz, CH=C-CH_3), 7.3 (m, phenyl). Minor isomer 1.96 (d, J=1.3 Hz, CH=C-CH_3), 2.64 (m), 3.55 (m), 5.76 (q, J=1.3 Hz, CH-C-CH_3), 7.3 (m, phenyl). Found: C, 76.53; H, 8.50; N, 6.88%. Calcd for $C_{13}H_{17}ON$: C, 76.81; H, 8.48; N, 6.89%.

*1-(β-Methylstyryl)piperidine (**2**)*: Reported previously.[1] Found: C, 83.46; H, 9.91; N, 6.83%. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96%.

*1-(β-Methylstyryl)pyrrolidine (**3**)*: Also reported.[1] Found: C, 83.11; H, 9.26; N, 7.37%. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48%.

*1-(β-Methylstyryl)-4-methylpiperazine (**4**)*: Bp 111—114 °C (2.5 mmHg). Yield 97.7%. MS *m/e* 216 (M^+, base), 144, 131, 115, 91. IR (film) 2950, 2800, 1640, ($\nu_{C=C}$), 1600, 1495, 1455, 1375, 1290, 1118, 1148, 1015, 760, 700 cm^{-1}. NMR ($CDCl_3$) mixture of two geometrical isomers in the ratio 7 : 4 at room temperature. Major isomer 2.09 (d, J= 1.0 Hz, CH=C-CH_3), 2.30 (s, N-CH_3), 2.5 (m), 6.12 (q, J=1.0 Hz, N-CH=C), 7.3 (m, phenyl). Minor isomer 1.97 (d, J=1.2 Hz, CH=C-CH_3), 2.22 (s, N-CH_3), 2.3 (m), 2.7 (m), 5.89 (q, J=1.2 Hz, N-CH=C), 7.5 (m, phenyl). Found: C, 77.68; H, 9.42; N, 12. 84%. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95%.

Asymmetric Transformation of Enamine. Under vigorous stirring with a homogenizer, enamine **1**, **2**, or **3** (0.01 mol) and *d*-10-camphorsulfonic acid monohydrate (0.01 mol) were added to 50 ml of chloroform. In order to control the temperature in the reaction flask, the temperature of the bath in which the flask was immersed was regulated with Dry Ice–ethanol or ice–water. Temperature in the flask was measured with a thermocouple. The reaction was continued for 30 min. The reaction mixture was washed with three 20 ml portions of water in order to remove *d*-10-camphorsulfonic acid completely. After the chloroform layer had been dried, the optical rotation was measured. The concentration of PPA in the chloroform solution was measured gas chromatographically. The yield of PPA was 90—100% in every case. Use of double the molar quantity of the acid to be hydrolyzed is necessary for enamine **4**. Two cases were examined: (a) 0.01 mol of **4** was treated with 0.02 mol of *d*-10-camphorsulfonic acid monohydrate, and (b) 0.01 mol of **4** was treated with a mixture of 0.01 mol of *d*-10-camphorsulfonic acid



Scheme 1.

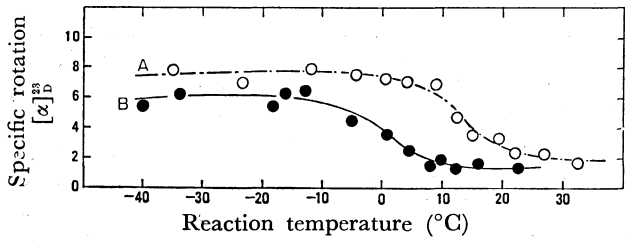


Fig. 1. Relationship between reaction temperature and rotation of 2-phenylpropanal.
Curve A; 1-(β-Methylstyryl)piperidine (**2**).
Curve B; 1-(β-Methylstyryl)pyrrolidine (**3**).

monohydrate and 0.01 mol of *p*-toluenesulfonic acid monohydrate. The subsequent procedure is identical with that described in the hydrolyses of **1**, **2**, and **3**.

Results and Discussion

1-(β-methylstyryl)piperidine and 1-(β-methylstyryl)-pyrrolidine salts of *d*-10-camphorsulfonic acid were hydrolyzed at various temperatures. The relation between the rotation of PPA obtained from the hydrolyzates and the hydrolysis temperature is shown in Fig. 1.

Two flat levels and a transient stage between them are seen in each case, suggesting that optical activation is induced by two courses. In the transient stage, the two reaction courses would participate in the induction of optical activity. There are two types of enamine salt, enaminium and iminium.[7,8] Protonation to an enamine first occurs rapidly on a nitrogen atom, transfer of the proton to the β-carbon atom taking place. The following two reaction courses are presumed: a) asymmetric rearrangement of the proton from the nitrogen atom in the enaminium salt to the β-carbon atom in the iminium salt under the asymmetric circumstance caused by chiral acid anion, and b) a thermodynamic equilibrium between the resulting two enantiomeric iminium salts since the proton attached to the β-carbon atom is fairly labile.[9] On account of the instability of enaminium structure, the optical activity induced by the former course might be retained at a low temperature. At a high temperature, the asymmetrically attached proton to the β-carbon atom in the iminium salt becomes easily exchangeable, and a thermodynamic equilibrium would be attained between the two diastereomeric iminium salts. The optical activities of the

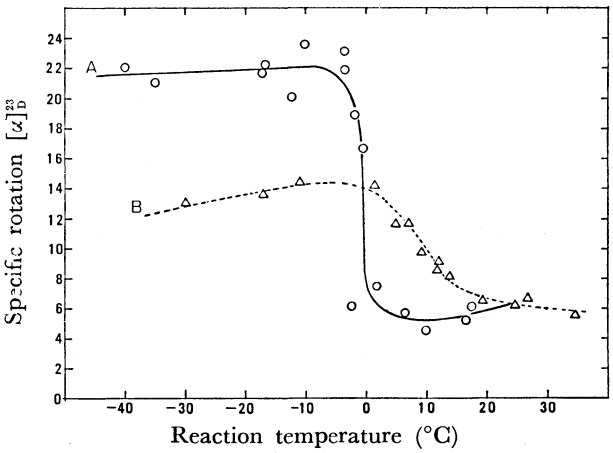


Fig. 2. Relationship between reaction temperature and rotation of 2-phenylpropanal obtained from the hydrolyzate of 1-(β-methylstyryl)morphorine salt of *d*-10-camphorsulfonic acid.
Curve A; Solvent $CHCl_3$.
Curve B; Solvent $CHCl_3$: CH_3OH(9 : 1).

PPA obtained would reflect the equilibrium. Path 1 (Scheme 1) represents the former mechanism controlled kinetically and path 2 the latter mechanism controlled thermodynamically. The higher flat level (Fig. 1) corresponds to the former, and the lower flat level corresponds to the latter.

In the case of asymmetric transformation of racemic PPA *via* chiral enamines using *S*(−)-prolinamide or *N*-(L-prolyl)piperidine as an amine component, hydrolysis at low temperature gave *R*(−)-PPA and that at a high temperature *S*(+)-PPA. This phenomenon was also interpreted in the same way discussed above.[10]

Figure 2 shows the correlation between reaction temperature and the optical rotation of PPA obtained from 1-(β-methylstyryl)morphorine enamine salt of *d*-10-camphorsulfonic acid. A sharp decrease in specific rotation in the temperature range −5—0 °C (Fig. 2-A) is noted, the transient stage (Fig. 1) being almost absent. This phenomenon may be due to the fact that the existence of oxygen atom in morphorine moiety stabilizes the enaminium structure by intramolecular hydrogen bonding with the hydrogen atom attached to the nitrogen atom. It is known that severance of the hydrogen bond takes place in narrow temperature range.

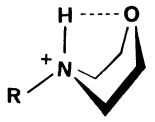


Fig. 3.

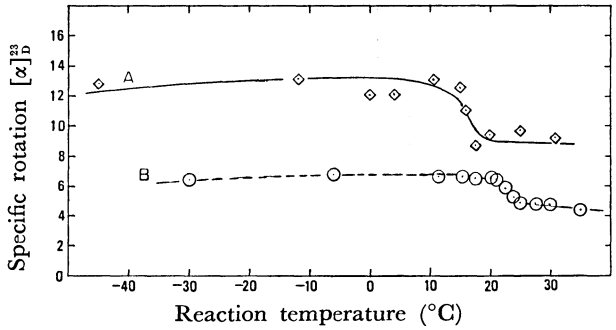


Fig. 4. Relationship between reaction temperature and rotation of 2-phenylpropanal obtained from the hydrolyzate of 1-(β-methylstyryl)-4-methylpiperazine salt.
Curve A; *d*-10-Camphorsulfonic acid : enamine (2 : 1).
Curve B; *d*-10-Camphorsulfonic acid : *p*-toluensulfonic acid : enamine (1 : 1 : 1).

Marman and Doty[11] examined the thermal transition profiles of the double helical complex of deoxyribonucleic acids into random coiles in neutral solutions and showed that the cleavage occurs in a narrow temperature range. Similar phenomena were reported by other workers.[12–15] Thus, the kinetical control disappears rapidly with severance of the hydrogen bond.

The ratio of the geometrical isomers at room temperature and the optical yield are given in Table 1. Low optical yields in the range of kinetical control (lower temperature range) are attributable to the mixture of two geometrical isomers. If the two isomers are separated from each other, higher optical yields are expected as shown by Duhamel and Plaquevent.[5] The stability of the enaminium salt of **1** at lower temperature may be responsible for the high optical yield. The stable enaminium structure controls the course of the transfer of the hydrogen atom from the nitrogen atom to the β-carbon atom.

When methanol (5 ml) was added to the solvent ($CHCl_3$, 45 ml) before hydrolysis to weaken hydrogen bonding, the curve became similar to that in the case of **2** and **3** as shown by curve B in Fig. 2. The addition gave rise to the lowering of optical yield especially in the lower temperature range. This confirms the stabilization of the enaminium structure by hydrogen bond in the case of **1**.

The relation between the rotation of PPA obtained with 1-(β-methylstyryl)-4-methylpiperazine and reaction temperature is shown in Fig. 4. The enamine could not be hydrolyzed easily by equimolar addition of acid such as *d*-10-camphorsulfonic acid monohydrate of *p*-toluenesulfonic acid monohydrate. The acid is apparently first consumed for protonation to the nitrogen atom at the 4-position, and use of double the molar quantity of acid is necessary.

Table 1. The ratio of the geometrical isomers and the optical yield

Enamine	Ratio of geometrical isomers	Optical yield (ee)[a] %	
		Lower temp range[b]	Higher temp range[c]
1	77 : 23	9.2	2.5
2	87 : 13	3.4	0.8
3	84 : 16	2.5	0.8

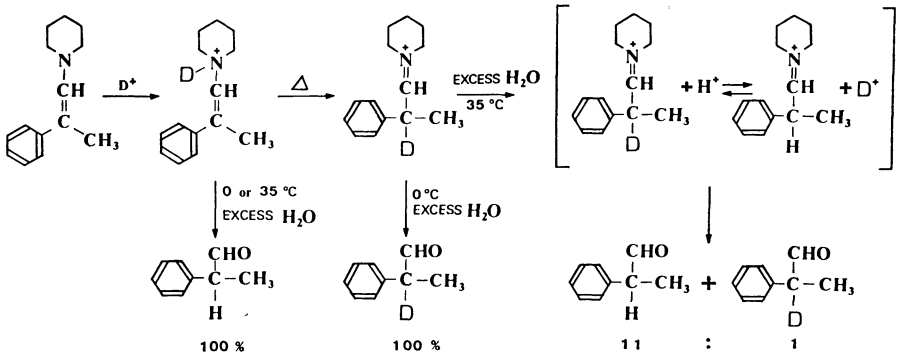
a) Optical yields are calculated based on $[\alpha]_D^{25}$ +238°.[5] b) The temperature range in which the asymmetric transformation is controlled kinetically. c) The temperature range in which the asymmetric transformation is controlled thermodynamically.

Curve A in Fig. 4 shows a case of the hydrolysis of enamine salt of *d*-10-camphorsulfonic acid monohydrate (molar ratio of the enamine and the acid; 1 : 2). It has two flat levels with a transient stage between them, as in the case of the curves in Figs. 1 and 2. The temperature range corresponding to the transient stage is 10—20 °C, narrower as compared to that of **2** and **3**. This tendency is similar to that of **1**, suggesting that the nitrogen atom at 4-position and hydrogen atom attached to the nitrogen atom at 1-position have a mutual interaction similar to the hydrogen bonding observed in the morphorine enamine salt, although the nitrogen atom at 4-position cannot operate as effectively as the oxygen atom in the morphorine enamine salt because of quaternarization.

Curve B shows a case of hydrolysis of the enamine salt of *d*-10-camphorsulfonic acid monohydrate and *p*-toluenesulfonic acid monohydrate (molar ratio of the enamine, *d*-10-camphorsulfonic acid monohydrate, and *p*-toluenesulfonic acid monohydrate; 1:1:1). The optical yield is reduced to one half its former results (Curve A, Fig. 4). An explanation of this result would be as follows: *d*-10-camphorsulfonate anion and *p*-toluenesulfonate anion form ion pairs with the two protonated nitrogen atoms in **4**, and only one acid anion of the two, probably the one that associated with the nitrogen atom at 1-position, can participate in the asymmetric transformation of PPA.

In order to get evidence for the two courses, isotopic labeling studies were carried out. As soon as dry DCl gas was added to enamine **2** in $CDCl_3$, the salt was hydrolyzed with H_2O (Scheme 2). Hydrolysis at 0 and 35 °C gave non-deuterated PPA (yield 100 %). This shows that the deuterium atom attached to the nitrogen atom exchange undergoes easily with hydrogen atoms in excess H_2O, the proton rearrangement from nitrogen atom to the β-carbon atom then occurring. Ease of this deuterium-proton exchange was already reported.[16] The above enaminium salt was completely rearranged to the corresponding iminium salt[16] and the resulting iminium salt was hydrolyzed with H_2O at 0 and 35 °C.

Hydrolysis at 0 °C gave Cα-deuterated PPA, indicating that the proton at β-carbon atom in the iminium salt is not exchangeable with hydrogen atom or deuterium atom at low temperature. In other words, optical yield is determined in the course of the rearrange-



Scheme 2.

ment from enaminium salt to iminium salt.

On the other hand, hydrolysis at 35 °C gave a mixture of the deuterated and non-deuterated PPA (1:11), indicating that the asymmetrically attached deuterium atom to the β-carbon atom in the iminium salt becomes easily exchangeable at 35 °C and the optical activation is controlled thermodynamically at the step of the iminium salt. The results of isotopic labeling studies also strongly support the existence of the two asymmetric transformation courses.

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