Mechanism of the Optical Activation of α-Substituted Carbonyl Compounds *via* Optically Active Immonium Salts

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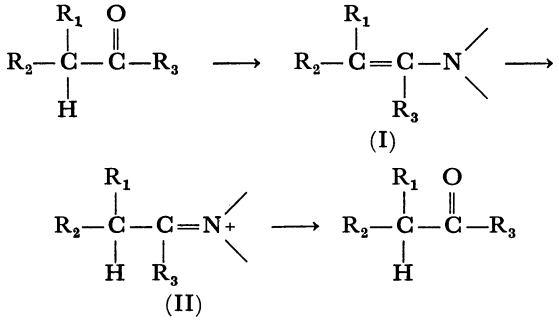
The degree of the optical activations of racemic α-substituted carbonyl compounds *via* the formation of optically active immonium salts and the subsequent hydrolysis were largely affected by acids used for the hydrolysis of the enamines. The ratio of the diastereomeric immonium salts depends on the temperature. There is a relationship between the configuration of the optically activated carbonyl compounds and those of amines used. These suggest that the optical activation is due to the asymmetric transformation.

Enamines are known to be very useful starting materials for various organic syntheses.[1] Asymmetric alkylation and halogenation were reported by Yamada *et al.*[2] Optical activation of racemic α-substituted carbonyl compounds *via* enamine has been studied in our laboratory. Formation of an enamine (I) causes deprotonation from the α-carbon of the racemic α-substituted carbonyl compounds, and formation of the immonium salt (II) causes protonation to the carbon, which is the first step of hydrolysis of the enamine.[3] In an asymmetrical circumstance, it is possible that an asymmetric protonation to the enamine takes place at the step of formation of the salt. On hydrolysis of the salt, the optically active carbonyl compound can be recovered.



In our previous paper, optical activation of racemic α-substituted carbonyl compounds were reported.[4,5] The hydrolysis of the immonium salts consisting of the optically active amine enamine of the racemic α-substituted carbonyl compounds and achiral acid gave the optically active compounds. This paper deals with the mechanism of this optical activation.

Experimental

Optical rotations were determined with a JASCO Digital Automatic Polarimeter Model DIP 181. Gas chromatographic analyses were carried out on a 2 m column of 20% Carbowax 20 M on Cromosorb W with a Hitachi Gas Chromatograph, Model K 53. Nuclear magnetic resonance spectra were obtained with a JNM-PS-100 Spectrometer with tetramethylsilane as an internal standard.

S(+)-2-Methylpiperidine. This was obtained by the procedure described by Kostyanovsky *et al.*[6]

R(−)-2-Methylpyrrolidine. This was prepared according to the method reported in our previous paper.[5]

S(−)-Benzyloxycarbonylcysteic Acid Ethyl Ester. This was prepared by treatment of L-cysteic acid with carbobenzoxy chloride. It was purified *via* its ethyl ester sodium salt. Using 29 g (0.155 mol) of L-cysteic acid, 32.2 g (58.9%) of *S*(−)-benzyloxycarbonylcysteic acid ethyl ester sodium salt, as white needle, was obtained: mp 164—172 °C; $[\alpha]_D^{23}$ −18.4° (*c* 0.74 H_2O); IR (Nujol) 3350 cm^{-1} (ν_{NH}), 1739 cm^{-1} (ν_{CO}), 1690 cm^{-1} (ν_{CO}), 1528 cm^{-1} (δ_{NH}), 1258 cm^{-1} (ν_{CN}); NMR ($CDCl_3$) 1.16 (CH_3, t, *J* 7.2 Hz), 2.96 (S-CH_2, d, *J* 6.0 Hz), 4.13 ($COOCH_2$, q, *J* 7.2 Hz), 4.40 (CH-N, q), 5.04 (NH, broad), 5.11 (O-CH_2, s), 7.43 (phenyl, 5H). *S*(−)-Benzyloxycarbonylcysteic acid ethyl ester was obtained by treatment of the salt with cation exchange resin (Dowex 50 W). NMR spectrum showed that the peak at 2.96 ppm was shifted to lower field, 3.60 ppm.

Enamines. The preparation of enamines of α-phenylpropionaldehyde and 2-methylcyclohexanone were reported in our previous paper.[4,5] Enamine from piperidine and 2-methylbutanal: bp 36—38 °C (0.7 Torr); IR (film) 1655, 1665 cm^{-1} ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers (8 : 3 at room temperature), major isomer, 1.00 (CH_3, t, *J* 7.7 Hz), 1.71 (CH_3, s), 1.98 (CH_2, q, *J* 7.7 Hz), 5.43 (C=CH, s), minor isomer, 1.63 (CH_3, s), 2.18 (CH_2, q, 7.9 Hz), 5.35 (C=CH, s). Enamine from 2-methylpiperidine 2-methylbutanal: Yield 89%; bp 45—46.5 °C (2.2 Torr); IR (film) 1670, 1650 cm^{-1} ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers (5 : 2 at room temperature), major isomer 1.73 (CH_3, s), 5.34 (C=CH, s), minor isomer 1.64 (CH_3, s), 5.23 (C=CH, s); $[\alpha]_D^{23}$ −6.79° (neat). Enamine from *S*(+)-2-methylpiperidine and 2-(2-cyanoethyl)cyclohexanone was not isolated.

Hydrolysis. Acid (0.01 mol) was added to a benzene solution (20 ml) of the enamine (0.01 mol) and the mixture was stirred. To the solution in an ice bath, water (20 ml) was added dropwise with vigorous stirring. The reaction was continued until the completion of the hydrolysis which was confirmed gas chromatographically. The benzene layer was separated, washed with water until the amine and the acid were removed completely, and dried over anhydrous Na_2SO_4. In the case of α-phenylpropionaldehyde, it was purified by column chromatography on silica gel (benzene : hexane 1 : 1). The purity was checked by TLC on silica gel (benzene : hexane 1 : 1, R_f 0.38). Optical rotations of carbonyl compounds were measured in benzene. The recoveries were obtained with a gas chromatograph.

Optical Rotation of the α-Phenylpropionaldehyde Recovered at Regular Time Interval. To a benzene solution (50 ml) of the optically active enamine from 2-methylpiperidine and α-phenylpropionaldehyde (2.15 g, 0.01 mol) was added 1 M hydrochloric acid (15 ml, 0.015 mol) under vigorous stirring. After ten minutes, benzene layer was separated, and additional aliquot (50 ml) of benzene was immediately applied to the aqueous layer, and reaction was continued.

Table 1. Optical activation of some carbonyl compounds *via* optically active enamines

Amine component	Carbonyl component	Acid component	Recovered carbonyl compound $[\alpha]_D^{23}$ in benzene		ee	Recovery (%)	Lit.
S(+)-2-Methyl-piperidine	α-phenylpropion aldehyde	HCl	−80.8° (*c* 25.0)			91	5
		H_2SO_4	−65.2° (*c* 0.99)			67	
		p-toluene-sulfonic acid	−60.4° (*c* 1.88)			81	
		CH_3COOH	−54.5° (*c* 1.21)			62	
	2-methyl-cyclohexanone	HCl	−2.87° (*c* 42.2)	*R*	20.2[9]	77	5
		CH_3COOH	−0.92° (*c* 30.0)	*R*	6.5	61	
	2-methylbutanal	HCl	−1.82° (*c* 18.9)	*R*	5.7[10]	73	
		CH_3COOH	−0.72° (*c* 25.9)	*R*	2.2	58	
	2-(2-cyanoethyl)-cyclohexanone	HCl	−0.858° (neat)	*R*		84	
		CH_3COOH	−0.099° (neat)	*R*		78	
R(−)-2-Methyl-pyrrolidine	α-phenylpropion-aldehyde	HCl	+51·6° (*c* 8.11)			79	5
	2-methyl-cyclohexanone	HCl	+0.881° (*c* 15.5)	*S*	6.2	60	5

The same treatment was repeated four times at ten minutes intervals. Finally, the aqueous layer was refluxed, and extracted with benzene. Every benzene extract was washed with water and dried, and the optical rotation and the concentration were measured.

Results and Discussion

Optical Activation of Racemic Carbonyl Compounds via *Optically Active Immonium Salts.* Hydrolysis of immonium salts consisting of optically active amine enamines of racemic α-substituted carbonyl compounds and achiral acids gave the corresponding optically active carbonyl compounds. The results are shown in Table 1.

Strong acids were well suited for the introduction of optical activity. This tendency was observed with both six and five membered ring amines. It is known that strong acid components are preferable for the stability of immonium salts.[7] The result suggests that the stability of an immonium salt is an important factor for the introduction of optical activity. This is also supported in the case of the immonium salts consisting of pyrrolidine or piperidine enamine and chiral acids.

Table 2 shows that the degree of the optical activation and direction of the optical rotation were affected by both the structure and the strength of acidity of chiral acids. *S*(+)-Cysteic acid has an amino group, a carboxyl group and a sulfonyl group. *S*(−)-*N*-Benzyloxycarbonylcysteic acid ethyl ester has neither a free amino group nor a free carboxyl group, but a sulfonyl group. *S*(−)-*N*-Benzyloxycarbonylalanine has a carboxyl group. The direction of the optical rotation of the recovered carbonyl compounds in the case of *S*(−)-*N*-benzyloxycarbonylcysteic acid ethyl ester was opposite to that in the case of *S*(+)-cysteic acid or *S*(−)-*N*-benzyloxycarbonylalanine. This means that *S*(+)-cysteic acid has the inner salt structure, ^-O_3S–CH_2–$\underset{\displaystyle NH_3^+}{\underset{|}{CH}}$–COOH, and its carboxyl group is used to form immonium salts. The degrees of the optical rotation in Table 2 suggest that sulfonic acid

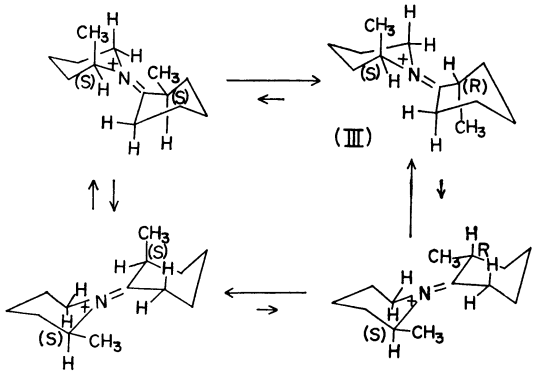


Fig. 1.

was superior to carboxylic acid, and *S*(+)-cysteic acid react with enamines as an carboxylic acid. One of the reasons of the low optical rotation of recovered α-phenylpropionaldehyde in the case of L-tartaric acid, D-camphoric acid and D-quinic acid[4] may be the weak acidity of these acids.

Table 1 also shows that carbonyl compounds with *R*-configuration was obtained by the use of *S*-amines as the amine components. In the case of 2-methylcyclohexanone, the result was interpreted by the stability of the immonium salt. As there are large interactions between the equatorial methyl group and the hydrogen on the α-methylene of the ring, the structure (III), in which two methyl groups occupies the axial positions, was most stable. When *S*-amine is used as the amine component, introduced asymmetric carbon into the enamine is an *R*-configuration. In the case of the asymmetric alkylation to cyclohexanone enamine, the same results were observed.[2]

Optical Rotation of the α-Phenylpropionaldehyde Recovered at Regular Time Intervals. Considering the mechanisms of the optical activation, there are (1) asymmetric synthesis, (2) asymmetric transformation, and (3) asymmetric destruction. It is known that the proton at the β-carbon of the enamine grouping is easily exchanged.[8] In our previous paper,[5] HCl salt of the enamine was hydrolyzed with rich D_2O

TABLE 2. OPTICAL ACTIVATION OF SOME CARBONYL COMPOUNDS FROM THE IMMONIUM SALTS CONSISTING OF CHIRAL ACIDS AS THE ACID COMPONENT

Amine component	Carbonyl component	Acid component	Recovered carbonyl compound			Lit.
			$[\alpha]_D^{23}$ in benzene		Recovery (%)	
Piperidine	α-Phenylpropion-aldehyde	D-10-Camphorsulfonic acid	+16.2° (c=3.67)		89.6	4
		S(+)-Cysteic acid	−1.06° (c=4.25)		82.0	
		S(−)-*N*-Benzyloxycarbonyl-cysteic acid ethylester	+2.80° (c=4.50)		80.9	
		α-Bromo-*d*-camphor-π-sulfonic acid	+3.67° (c=4.31)		78.1	
		S(−)-*N*-Benzyloxycarbonyl-alanine	−0.58° (c=10.8)		65.7	
	2-Methylcyclo-hexanone	D-10-Camphorsulfonic acid	+0.63° (c=2.30)	*S*	73.1	4
		S(+)-Cysteic acid	−0.03° (c=33.3)	*R*	86.2	
		S-(−)-*N*-Benzyloxycarbonyl-cysteic acid ethylester	+0.11° (c=18.2)	*S*	69.8	
	2-Methylbutanal	D-10-Camphorsulfonic acid	+0.000° (c=4.41)		68.0	
		S(+)-Cysteic acid	+0.000° (c=5.22)		72.0	
Pyrrolidine	α-Phenylpropion-aldehyde	D-10-Camphorsulfonic acid	+13.8° (c=7.10)		84.1	
		S(+)-Cysteic acid	−0.58° (c=6.03)		83.9	
		S(−)-*N*-Benzyloxycarbonyl-cysteic acid ethylester	+1.43° (c=7.57)		78.9	
		α-Bromo-*d*-camphor-π-sulfonic acid	+3.96° (c=3.37)		71.3	
		S(−)-*N*-Benzyloxycarbonyl-alanine	−0.19° (c=9.90)		67.9	
	2-Methylcyclo-hexanone	D-10-Camphorsulfonic acid	+0.39° (c=10.8)	*S*	88.8	4

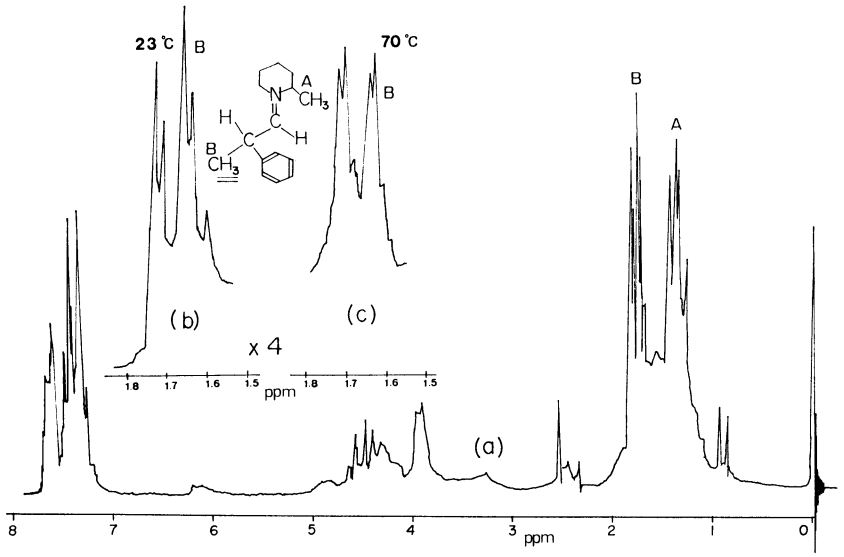


Fig. 2. (a) 100 MHz spectrum of the immonium salt, probe temperature 23 °C (in $CDCl_3$).
(b) Enlargement of the signal (B) due to the methyl group attached to the β-carbon, probe temperature 23 °C. (×4)
(c) The same part of the spectrum, probe temperature 70 °C. (×4)

and deuterated α-phenylpropionaldehyde was recovered. The isotope labeling experiment suggests that this optical activation is not due to the asymmetric synthesis. To see whether this activation is due to asymmetric destruction or not, variations in optical activity of the recovered α-phenylpropionaldehyde during the enamine hydrolysis were followed at ten minute intervals. After the reaction for 40 min, to ascertain the completion of hydrolysis, concentrated hydrochloric acid was added to the residual water phase and the solution was refluxed. Gas chromatographically, no α-phenylpropionaldehyde could be detected in the benzene extract of the solution. Total recovery of the aldehyde was 87.3%. It seems that some of the aldehyde was lost when the benzene extract was washed with water. As shown in Table 3, the directions of the optical rotation of all fractions were the same. This result clearly shows that the optical activation was not due to asymmetric destruction.

Studies of the NMR Spectra. Dry HCl gas was

TABLE 3.

Reaction time (min)	$[\alpha]_D^{23}$	Recovery (%)
10	+10.7°	64.2
20	+10.5°	19.4
30	+14.5°	3.7
40	(+)	trace
Recovered from aqueous layer		0
Total recovery		87.3

bubbled slowly into a $CDCl_3$ solution of optically active 2-methylpiperidine enamine of α-phenylpropionaldehyde and a slightly yellow solution of the corresponding immonium salt was obtained. NMR spectrum of the solution shows that the immonium salt was a mixture of two diastereomeric isomers (Fig. 2(a).). An increase in temperature as high as 70 °C gradually changed the region of the methyl groups (B) at the asymmetric carbon atoms in NMR spectra from (b) to (c). The major methyl proton signal at 23 °C (1.69 ppm, J 7.5 Hz) was changed to the minor one at 70 °C (1.68 ppm, J 7.3 Hz). On the contrary, the minor methyl proton signal at 23 °C (1.66 ppm, J 7.5 Hz) was changed to the major one at 70 °C (1.65 ppm, J 7.3 Hz). This result suggests that the ratio of the two diastereomers was controlled thermodynamically. Thus the mechanism of the optical activation is considered to be an asymmetric, reversible protonation to the enamine and successive hydrolysis of the immonium salt. The spectra of the D_2SO_4 salt and CD_3COOD salt were also obtained. The former has many unassignable peaks. The latter shows that the formation of immonium salt was incomplete by the addition of an equimolar CD_3COOD to the enamine. These spectra may suggest that H_2SO_4 and CH_3COOH are not so good as HCl for the optical activation.

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