Optical Activation of 2-Phenylpropionaldehyde *via* Some 2-Substituted Pyrrolidine Enamines

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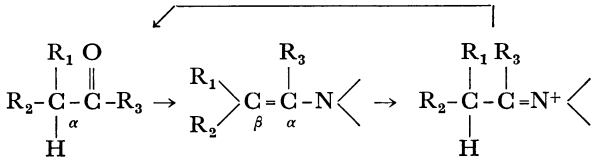
Optical activation of 2-phenylpropionaldehyde (PPA) *via* enamines using L-proline derivatives as amine components was studied. *S*(+)-PPA was obtained when *R*(−)-2-methylpyrrolidine and *S*(−)-2-ethoxycarbonylpyrrolidine were used, while *R*(−)-PPA was obtained when *S*(−)-prolinamide, *N*-(L-prolyl)pyrrolidine, *N*-(L-prolyl)piperidine, *S*(+)-2-(1-pyrrolidinylmethyl)pyrrolidine, and *S*(+)-2-(piperidinomethyl)pyrrolidine were used. This suggests that there are two mechanisms for optical activation.

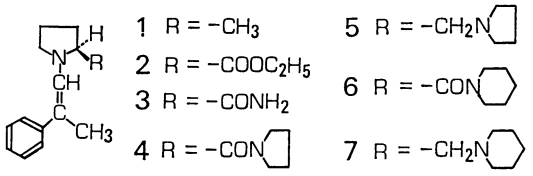
The syntheses of optically active carbonyl compounds have been studied by many workers.[1] The optical activation *via* enamines has been studied in our laboratories.[2-4] Formation of an enamine causes deprotonation from the α-carbon of a racemic α-substituted carbonyl compound, the transformation of the enamine into the iminium salt causing protonation at the carbon. In an asymmetrical circumstance, it is possible that stereospecific protonation to the enamine takes place in the formation of the salt.



Carbonyl compound Enamine Iminium salt

In the case of optical activation of 2-methylcyclohexanone *via* optically active 2-methylpiperidine enamine, the chirality of the ketone obtained is determined by the stability of the iminium salt. The stability was affected by an interaction between the substituent in amine component and the residue of the enamine.

We have extended the study to the optical activation of PPA *via* enamine using amines derived from L-proline without inversion at the asymmetric carbon, and found that the chirality of the PPA obtained *via* enamines, **3**—**7** is *R*, and that *via* enamines, **1** and **2**, is *S*. This suggests that two reactions may participate in the induction of optical activity.



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% Carbowax 20 M on Chromosorb W and 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 or sodium 2,2-dimethyl-2-silapentane-5-sulfonate 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).

Preparation of Amines. *S(−)-2-Ethoxycarbonylpyrrolidine*: Esterification of L-proline was carried out in the usual way.

S(−)-Prolinamide: A solution of *N*-benzyloxycarbonyl-L-proline (37.7 g, 0.15 mol) and triethylamine (15.3 g, 0.15 mol) in chloroform was cooled in an ice bath. Ethyl chloroformate (16.4 g, 0.15 mol) was added to the solution at 5—10 °C during a period of 10 min with stirring, the reaction being continued at 5—10 °C for 30 min. Aqueous ammonia (28 %, 40 ml) was then added dropwise to the reaction mixture with vigorous stirring under cooling. The pasty reaction mixture was stirred at 5—10 °C for 1 h. After removal of the aqueous layer, the chloroform layer was washed with an aqueous $NaHCO_3$ solution (5%) and water, and dried over Na_2SO_4. Chloroform was removed *in vacuo*, the residual oil (37.2 g) being crystallized from ethyl acetate. Recrystallization from ethyl acetate gave 29.4 g (78.4%) of *N*-benzyloxycarbonyl-L-prolinamide as mp 91—93.5 °C. IR (Nujol) 3180, 3370, 1670 cm^{-1}; NMR ($CDCl_3$) δ=7.36 (5H, s), 5.9—6.3 (2H, broad), 5.18 (2H, s) 4.2—4.44 (1H, broad), 3.4—3.7 (2H, broad), 1.7—2.4 (4H, m); $[\alpha]_D^{23}$ −34.0° (*c*=2.2, EtOH).

Hydrogenolysis of *N*-benzyloxycarbonyl-L-prolinamide (29.4 g) in ethanol was carried out with 5% Pd-C (1.8 g) in an atmosphere of hydrogen, L-prolinamide (5.7 g, 42.2%) being obtained as very fine white needles. Mp 104.0 °C; IR (Nujol) 3390, 3200, 1645 cm^{-1}; NMR (D_2O) δ=3.8 (1H, t), 3.0 (2H, t), 1.6—2.4 (4H, m); MS 114 (M^+), 70 (base), 43, 44; $[\alpha]_D^{23}$ −106.9° (*c*=0.90, EtOH).

N-(L-Prolyl)pyrrolidine: This was prepared according to the method reported by Otani and Yamada.[5]

S(+)-2-(1-Pyrrolidinylmethyl)pyrrolidine: This was prepared according to the method reported by Sone *et al.*[6]

N-(L-Prolyl)piperidine: The method employed was virtually identical with that for *N*-(L-prolyl)pyrrolidine except that pyrrolidine was replaced by piperidine. *N*-benzyloxycarbonyl-L-proline (43.8 g) gave *N*-(benzyloxycarbonyl-L-prolyl)-piperidine (19.0 g) as white needles from ether-ethyl acetate (4 : 1). Yield 34.3%; mp 93.5—94.5 °C; IR (Nujol) 1635 cm^{-1}; NMR ($CDCl_3$) δ=7.20 (5H), 4.75 (1H, t), 3.2—3.8 (6H, broad), 1.2—2.4 (10H, broad); $[\alpha]_D^{23}$ −14.5° (*c*=1.0, benzene).

Hydrogenolysis of *N*-(benzyloxycarbonyl-L-prolyl)piperi-

dine (18.8 g) in ethanol was carried out with 5% Pd-C (1.0 g) in an atmosphere of hydrogen, *N*-(L-prolyl)piperidine (8.0 g, 74%) being obtained. Bp 128 °C (2 mmHg); IR 3450, 1635 cm^{-1}; NMR ($CDCl_3$) δ=3.9 (1H, t), 3.4—3.7 (4H, broad), 3.06 (1H, s), 2.7—3.3 (2H, m), 1.3—2.4 (10H, broad); $[\alpha]_D^{23}$ −65.1° (c=2.0, benzene).

S(+)-2-(Piperidinomethyl)pyrrolidine: The method used here was virtually identical with that described for *S*(+)-2-(1-pyrrolidinylmethyl)pyrrolidine except that pyrrolidine was replaced by piperidine. Bp 72.0 °C (1.5 mmHg); IR 3300 cm^{-1}; NMR ($CDCl_3$) δ=1.2—2.0 (10H, broad), 2.2—2.7 (7H, broad), 2.7—3.2 (2H, m), 3.4 (1H, s); $[\alpha]_D^{23}$ +1.58° (c=2.2, benzene).

R*(−)-2-Methylpiperidine*: *dl*-2-Methylpiperidine (99 g) was treated with *d*-10-camphorsulfonic acid (125 g) in benzene. Recrystallization of the resulting salt was repeated seven times. The free base was isolated from the salt by the general method. Yield 4.1 g; bp 116—120 °C; $[\alpha]_D^{23}$ −16.4° (c=1.1, hexane).

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

2: IR 1665 cm^{-1} ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers in a 22 : 5 ratio at room temperature; major isomer δ=2.09 (C=C–CH_3, s), 6.30 (N–CH=C, s), minor isomer δ=1.96 (C=C–CH_3, s), 6.00 (N–CH=C, s); $[\alpha]_D^{23}$ +0.34° (c=33, benzene).

3: This could not be distilled because of its high boiling point and viscosity. Analysis was carried out using GC-MS. *m/e* 186, 125 (base), 117, 105, 97, 77, 70; $[\alpha]_D^{23}$ +24° (calculated for 100% yield).

4: Bp 175 °C (1.5 mmHg); IR 1638 cm^{-1} ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers in a 25 : 7 ratio at room temperature; major isomer δ=2.15 (C=C–CH_3, s), 6.42 (N–CH=C, s), minor isomer δ=2.01 (C=C–CH_3, s), 6.13 (N–CH=C, s).

5: Bp 154 °C (3 mmHg); IR 1630 cm^{-1} ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers in a 4 : 1 ratio at room temperature; major isomer δ=2.13 (C=C–CH_3, s), 6.55 (N–CH=C, s), minor isomer δ=2.05 (C=C–CH_3, s), 6.21 (N–CH=C, s); $[\alpha]_D^{23}$ +326.4° (c=1.0, benzene).

6: Bp 189 °C (2 mmHg); IR 1640 cm^{-1} ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers in a 16 : 7 ratio at room temperature; major isomer δ=2.12 (C=C–CH_3, s), 6.34 (N–CH=C, s), minor isomer δ=2.00 (C=C–CH_3, s), 6.05 (N–CH=C, s); $[\alpha]_D^{23}$ −2.3° (c=9.0, benzene)

7: Bp 139 °C (1.5 mmHg); IR 1630 cm^{-1} ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers in a 39 : 7 ratio at room temperature; major isomer δ=2.12 (C=C–CH_3, s), 6.54 (N–CH=C, s), minor isomer δ=2.03 (C=C–CH_3, s), 6.18 (N–CH=C, s); $[\alpha]_D^{23}$ +265.2° (c=1.7, benzene).

8: Physical data except for specific rotation were reported.[3] $[\alpha]_D^{23}$ −400° (neat).

Hydrolysis of Enamines. *Procedure A*: An equivalent aqueous HCl was added to a benzene solution of enamine in an ice bath with vigorous stirring for 30 min. The aqueous layer was removed and the benzene layer was washed with water several times, dried over Na_2SO_4 and the optical rotation was measured. The concentration of the solution was determined gas-chromatographically.

Procedure B: Dry HCl gas was bubbled into the anhydrous benzene solution of enamines to give the salts. The solution was heated up to 50 °C immediately and the temperature was maintained at 50—60 °C for 30 min. Water was added to the solution with vigorous stirring at 0 °C. Subsequent procedure was identical to that described above.

Oxidation of PPA. *R*(+)-2-Methylpiperidine enamine[3] of PPA (14.6 g) was hydrolyzed by procedure A, optically active PPA (7.06 g, 77.6%) being obtained. $[\alpha]_D^{23}$ +8.58° (c=8.8, benzene). The aldehyde was suspended in water (10 ml), and aqueous $KMnO_4$ (4.5 g in 100 ml) was added dropwise to the suspension.

The precipitated MnO_2 was filtered off, and the aqueous solution was made basic with NaOH pellets. After being washed with ether to remove PPA, the aqueous layer was acidified with HCl, and extracted with $CHCl_3$. The chloroform layer was dried over Na_2SO_4, and concentrated.

The residual oil was distilled to yield 4.1 g (52%). $[\alpha]_D^{23}$ +1.97° (c=6.3, benzene). This was identified as 2-phenylpropionic acid by IR and NMR.

Results and Discussion

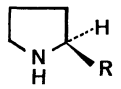
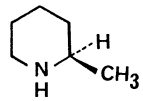
Determination of the Absolute Configuration of PPA. In order to elucidate the optical activation mechanism, it is necessary to know the relationship between the direction of optical rotation and the absolute configuration of PPA. The problem was solved by oxidation of (+)-PPA into (+)-2-phenylpropionic acid which is known to have *S*-configuration.

Optical Activation of PPA via *Chiral Enamines.* Enamines were hydrolyzed according to procedure A. The results of the optical activation of PPA *via* enamines of L-proline derivatives and of *R*(−)-2-methylpiperidine are given in Table 1. The direction of optical rotation of PPA obtained is seen to be dependent on the amine components of enamines. Enamines, **1**, **2**, and **8**,[3] gave *S*(+)-PPA. On the other hand, enamines **3**—**7** gave *R*(−)-PPA. The substituents of the amine components in **4**—**7** are bulkier than those of **1**, **2**, and **8**. However, the bulkiness does not seem to determine the chirality of PPA obtained, since the bulkiness of the substituent of the amine component in enamine **3** which gave the same *R*(−)-PPA as **4**—**7** is not so large as that of **2**. The electronic effect of CH_2–N< and CO–N< in the substituents of amine components probably controls the mechanism of the optical activation as well as their steric effect.

It was difficult to isolate the enamines **2**, **3**, and **6**, because their boiling points and viscosities are high and they are unstable at a high temperature. The result of the optical activation *via* **4** suggests that a certain racemization of the enamines takes place during the course of distillation. The extent of racemization was not estimated, so the data in Table 1 cannot be compared except for the directions of the optical rotation.

Mechanism of Optical Activation. Since all the amine components except for *R*(−)-2-methylpiperidine were derived from L-proline, enamines **1**—**7** and their salts seem to have the same stereochemical configuration as regards their asymmetric carbon adjacent to nitrogen atom. With respect to the stereochemistry, **8** and its salts are also identical with **1** and its salts. However, the direction of the optical rotation of PPA obtained from **1**, **2**, and **8** differs from that from **3**—**7**. This suggests that there are two optical activation mechanisms. In a previous paper,[4] the optical activation mechanism of 2-methylcyclohexanone *via* its optically active 2-methylpiperidine enamine was accounted for by the thermodynamical stability of the correspond-

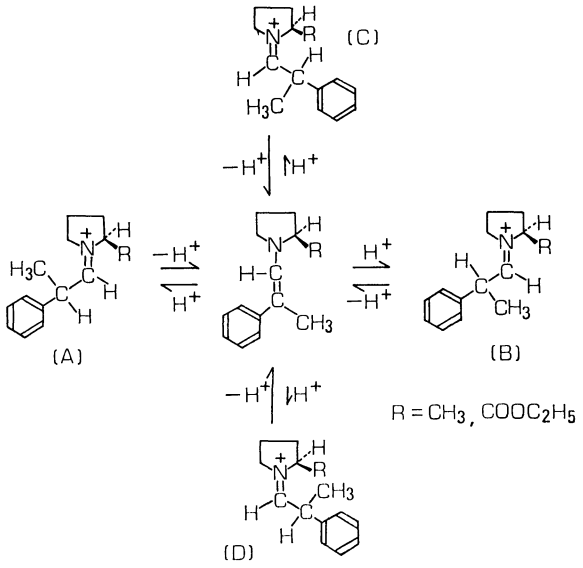
Table 1. Optical activation of PPA *via* enamines

Amine component		Enamine	Obtained ($[\alpha]_D^{23}$)	PPA[a]	Lit
	R=-CH_3	**1**	+51.6 (c=8.1)	*S*	3
	-$COOC_2H_5$	**2**	+0.34(c=33.2)[b]	*S*	
	-$CONH_2$	**3**	−3.10(c=9.1)[b]	*R*	
	-CON⟨ ⟩	**4**	−4.39(c=0.9) −18.6 (c=5.1)[b]	*R*	
	-CH_2N⟨ ⟩	**5**	−12.9 (c=3.0)	*R*	
	-CON⟨ ⟩	**6**	−2.30(c=9.0)[b]	*R*	
	-CH_2N⟨ ⟩	**7**	−9.72(c=2.2)	*R*	
		**8**	+80.8 (c=25.0)	*R*	3

a) Enamines hydrolyzed according to procedure A. b) No enamine isolated.

ing iminium salt. The mechanism seems to apply to the optical activation of PPA *via* enamines, **1**, **2**, and **8**. As shown in Scheme 1, the iminium salts would exist as an equilibrium mixture of diastereomeric isomers. The enamine can be considered to be an intermediate of these isomers in the solution. Displacement of the balance in the interconversion reaction in favor of one diastereomeric isomer results in the optically active aldehyde. The thermodynamical stability of the iminium salt determines the direction of the optical rotation of the aldehyde. The existence of the isomers (C) and (D) in the solution seems to be inappreciable in consideration of the steric interaction between substituent *R* and the substituents attached to β-carbon atom using Stuart and Dreiding models.[3] The structure shown in Fig. 1 is considered to be the most stable iminium salt. In this case, *S*(+)-PPA can be obtained from the hydrolyzate of this salt.

On the other hand, the reaction which gave *R*(−)-



Scheme 1.

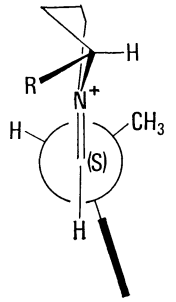


Fig. 1. The most stable structure of the iminium salt.

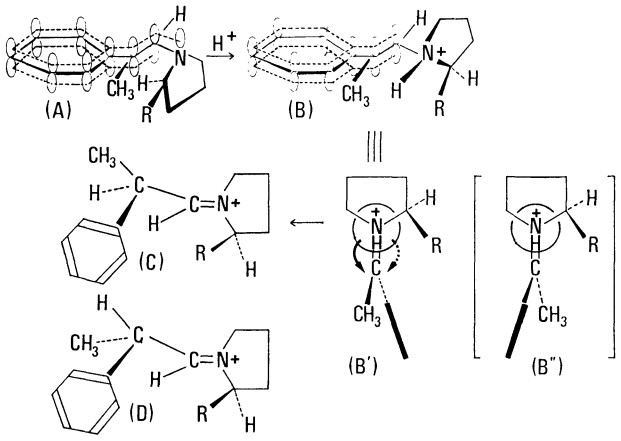


Fig. 2.

PPA is likely to proceed by a different mechanism from that mentioned above. This can be accounted for kinetically in the step of rearrangement from enammonium salt to iminium salt. It is known that protonation of enamines takes place on nitrogen and is followed by transfer of the proton to the β-carbon atom.[7] The electrostereochemical structures of the enamine and its salts are shown in Fig. 2. The enamine is characterized by the overlap of the nitrogen lone pair with the electrons of the double bond and the benzene ring

(Fig. 2(A)). The conversion from enamine into the corresponding enammonium salt implies the disappearance of the lone pair. Consequently, the amine moiety twists out of the coplanality of the olefinic group and the benzene ring (Fig. 2(B)). The geometrical isomer, structure (B″), would not exist because of the steric interaction between pyrrolidine ring moiety and C_β–CH_3. Thus, the predominant conformation of the enammonium salt would be structure (B′) in Fig. 2.

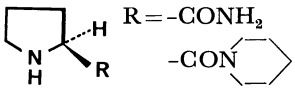
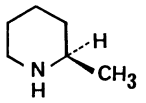
Rearrangement of the enammonium salt to the iminium salt implies the migration of the proton on the nitrogen atom to the β-carbon atom. The migration should take place following the path shown by the arrow(←) in Fig. 2-(B′) because the substituent **R** interferes in the migration in the opposite direction (←···). If hydrolysis of this iminium salt is rapid enough to neglect the contribution of the thermodynamical interconversion between C and D, it would predominantly give *R*(−)-PPA.

In the case of the methyl or ethoxycarbonyl group as a substituent of amine component, the thermodynamical equilibrium between the iminium salts is key step of the optical activation which gives *S*(+)-PPA.

On the other hand, when amine components have groups CH_2–N< or CO–N< as 2-substituents, the rearrangement from enammonium salt to iminium salt seems to be the key step of activation. The substituents probably stabilize the enammonium structure by the hydrogen bond between nitrogen or oxygen lone pair of these substituents and the *N*-coordinated hydrogen atom.

The isolation of the enammonium salt and its easy rearrangement to the corresponding iminium salt by heating were reported.[8] Enamines **3** and **6** which gave *R*(−)-PPA by the hydrolysis procedure A, were hydrolyzed according to procedure B. Application of heat before the addition of water promotes the rearrangement, and the thermodynamical equilibrium of the resulting iminium salts is reached. The results are shown in Table 2. *S*(+)-PPA was obtained according to procedure B, which supports the optical activation mechanism mentioned above.

TABLE 2. OPTICAL ACTIVATION OF PPA *via* ENAMINES (Hydrolysis by procedure B)

Amine component	Enamine	Obtained PPA($[\alpha]_D^{23}$)
 R=-$CONH_2$	**3**	+26.24 (c=0.2)
-CON<	**6**	+34.07 (c=3.1)
	**8**	+71.5 (c=20.8)

There are two optical activation mechanisms of PPA *via* enamines which can be applied to the optical activation of other α-substituted carbonyl compounds. It is necessary to control these two mechanisms in order to obtain the higher or desirable optically active compounds.

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