Racemization of Mandelic Acid at the Surface of Talc Powder

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The addition of talc powder in an ethanolic solution of mandelic acid gave a large change of its optical rotation. It was confirmed by absorption spectrography, thin-layer chromatography, and gas chromatography that mandelic acid was racemized at the surface of the talc powder. The IR spectra showed that racemization took place when mandelate anions adsorved weakly at the surface of the talc. It was concluded that the H atom at the C atom in the second position of a mandelate anion was adsorbed at a basic site of the talc surface to deprotonate and also that the deprotonation was enhanced by the interaction between the carboxyl group and an acidic site.

Racemization of an optically active substance is of great interest with regard to the origin of life. Furthermore, racemization is of practical importance in pharmaceutical technology. In the case of such substances as amino acids, only one enantiomer is physiologically active. The inactive enantiomer can be converted into the active enantiomer by racemization.

Previously, the authors reported mechanochemical racemization of L-leucine in the presence of such an inorganic powder as talc.[1] This paper deals with the racemization of optically active mandelic acids in suspensions of talc.

Experimental

The materials used were *S*(+)-mandelic acid [*S*(+)-α-hydroxyphenylacetic acid] and *R*(−)-mandelic acid purchased from Aldrich Chemical Co. The samples of inorganic powder used were kaolin (acid washed, American standard) of Fisher Scientific Company, talc of Sanko Seiyaku Co., SiO_2 (precipitated) of Koso Chemicals Co., and γ-Al_2O_3 of Nishio Kogyo Co. The following samples were prepared:

$Talc_{AA}$: Talc was set aside in a vapor of acetic acid at a room temperature for more than 2 d, it was then washed with ethanol several times and dried at 60 °C.

$Talc_{TEA}$: Talc was set aside in a vapor of triethylamine at a room temperature for more than 2 d, it was then washed with ethanol several times and dried at 60 °C.

Inorganic Powder-M: After the suspension of the inorganic powder in an ethanol solution of mandelic acid had been set aside at 5 °C for more than 1 d, the supernatant was removed and the precipitation was dried at 60 °C. Ethanol, 2-propanol, 2-butanol, and formic acid were of guaranteed grade. Dioxane and cyclohexane, both of a guaranteed grade, were dried with molecular sieves 4A of Wako Pure Chemicals Industries, Ltd.

A certain amount of inorganic powder was added to the flask containing 30 ml of a mandelic acid solution, and the following processes were carried out at 5 °C or 20 °C; (i) the mixture was set aside after a vigorous shaking, (ii) it was stirred at 190 rpm., or (iii) it was stirred at 380 rpm. An aliquot of these suspensions was taken into a test tube at several intervals. (iv) Separately, 3—5 ml of an ethanol solution of mandelic acid were added to a test tube containing a certain amount of inorganic powder. The test tube was shaken vigorously, and then set aside at 5 °C for 1 h. The optical rotation of the supernatants obtained by centrifuging these suspensions were measured with a JASCO digital polarimeter (Model DIP-140). The absorption spectra of these supernatants were obtained using a Hitachi recording spectrophotometer (Model 340). The concentrated solutions of the supernatants were developed on thin layers of silica gel with a solvent system of 2-butanol-2-propanol-formic acid-water (15:15:4:10).[2] Gas chromatographic determination of the trimethylsilyl derivatives of mandelic acid in the supernatant was carried out at 170 °C with a Shimadzu gas chromatograph (Model 6A), using a column containing 10% SE 52 chromosorb W 60/80 mesh treated with AW-HMDS of Shimadzu Seisakusho.[3] IR spectra were measured with a JASCO diffraction granting infrared spectrophotometer (Model A-2). The Hammett's acidity function, H_0, and basicity function, H'_0, for inorganic powder were obtained by the indicator method.[4]

Results and Discussion

Racemization of Mandelic Acid at the Surface of Talc Powder. In Figs. 1 and 2, α is the optical rotation of the supernatant obtained by centrifuging an ethanolic suspension of mandelic acid and talc. The value of $|\alpha|$ decreased immediately after adding talc to the solution of the optically active mandelic acid at 5 °C, though the value remained constant after the lapse of more than 10 min. Figure 3 shows the effect of talc on the absorption spectra of an ethanol solution of mandelic acid. The absorbance around 250—260 nm increased on addition of talc. According to many studies concerning the degradation of mandelic acid on oxidation or γ-irradiation, the main products are benzaldehyde, benzoic acid, and phenylglyoxylic acid.[5] On fractionating these solutions by thin-layer chromatography, benzoic acid was confirmed to be formed, but no spot corresponding to any product other than benzoic acid was observed. The areas of ΔABD, S_{252}, and ΔBCE, S_{257}, were not changed by adding talc. The concentrations of mandelic acid in the solutions were determined using gas chromatography. The concentrations in the supernatants in Fig. 3 were identical with the concentration in the original solution. These results show that degradation and adsorption of mandelic acid at the surface of talc are negligible. It is also confirmed that optically active mandelic acids are racemized at the surface of talc, though the diastereomers of these active forms were not separated because of the difficulty in synthesis.

Effect of the Polarity of Solvents. In Table 1, α_0 is the optical rotation of the original mandelic acid solution, and $\Delta\alpha$ is equal to $\alpha_0-\alpha$. The value of $|\Delta\alpha|$ obtained by adding a mandelic acid solution to a suspension of talc, which had been stirred for more than 10 min, was smaller than the value obtained by adding talc to a mandelic acid solution. This fact shows that solvent molecules and mandelic acid molecules compete with each other for the surface of the talc. Bubbling nitrogen gas during stirring did not show any effect on $|\Delta\alpha|$; this fact shows that oxygen has little effect on racemization. The effect of the polarity of solvents on racemization was investigated, using the mixtures of various ratios of dioxane and cyclohexane at 20 °C. Here, $(\bar{S}/S_0)$ stands for $1/2\,\{(S_{252}/S_{252,0})+(S_{257}/S_{257,0})\}$, where $S_{252,0}$ and $S_{257,0}$ are S_{252} and S_{257} for original solutions, respectively. $(\bar{S}/S_0)$ was proportional to the concentration of mandelic acid determined by gas chromatography. As is shown in Table 1, $(\bar{S}/S_0)$ decreased on interaction with talc and this tendency became greater with decrease in the polarity of the solvent. Probably, the adsorption of mandelic acid on the surface of talc is greater in the solvent of lower polarity. The racemization percentage, R, is defined as $[\{(\bar{S}/S_0)-(\alpha/\alpha_0)\}/(\bar{S}/S_0)]\times 100$. As is shown in Table 1, racemization does not take place in the suspension containing 5 v/v% of dioxane, though R is 4—15% in the suspension containing more than 10 v/v% of

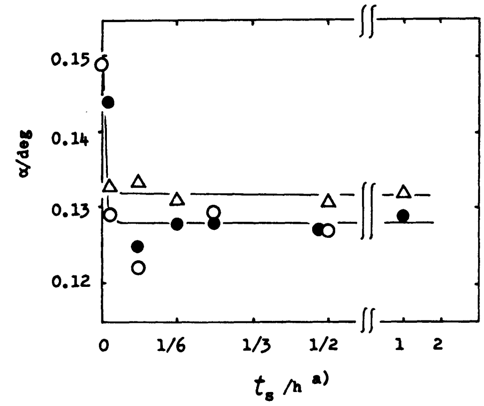


Fig. 1. Decrease in α of an ethanol solution of $S(+)$-mandelic acid at the surface of talc powder.
6.6×10^{-3} M of $S(+)$-mandelic acid solution: 30 ml, talc: 10 g, temperature: 5 °C.
Stirring velocity/rpm
△: 0, ●: 190, ○: 380
a) t_s is the stirring time.

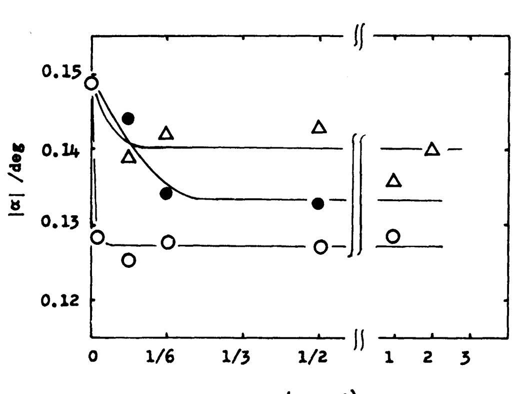


Fig. 2. Decrease in $|\alpha|$ of an ethanol solution of $R(-)$-mandelic acid at the surface of talc powder.
6.6×10^{-3} M of $R(-)$-mandelic acid solution: 30 ml, talc: 10 g, temperature: 5 °C.
Stirring velocity/rpm
△: 0, ●: 190, ○: 380
a) t_s is the stirring time.

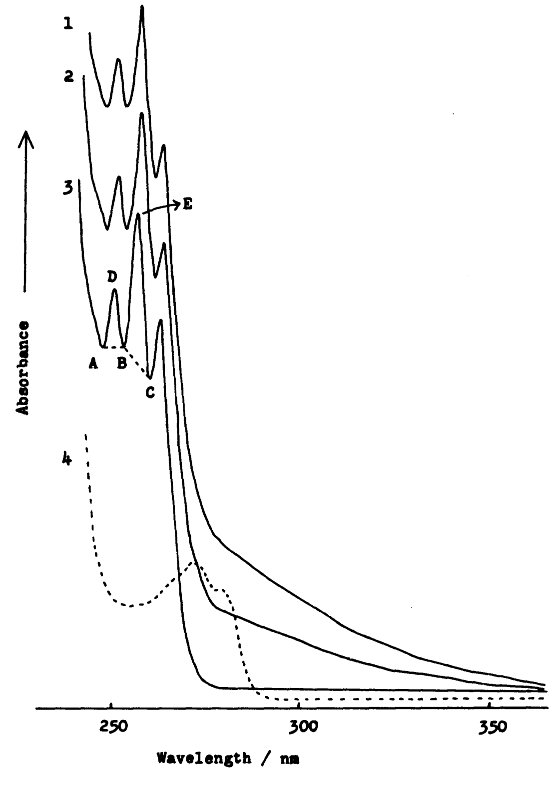


Fig. 3. Effect of talc on absorption spectra of an ethanol solution of mandelic acid.
1: The supernatant of the suspension of "3" and talc stirred for 30 min. 2: The supernatant of the suspension of "3" and talc stirred for 3 min. 3: An ethanol solution of 6.6×10^{-3} M of $S(+)$-madelic acid. 4: An ethanol solution of 4.6×10^{-4} M of benzoic acid. Experimental conditions for "1" and "2"; "3" 30 ml, talc 10 g, temperature 5 °C, stirring velocity 190 rpm.

dioxane. This suggests that racemization is an ionic reaction.

Complex Formation. It is clear from Figs. 4 and 5 that Eq. 1 is applicable;

$$\Delta\alpha = K'W_T{}^nC^m, \qquad 0<m, n<1, \tag{1}$$

where K' is a constant, W_T the amount of talc added to the suspension, and C the concentration of mandelic acid in the original solution. It is assumed that a complex M–T is formed between mandelic acid, M, and talc, T, as is shown in Eq. 2, and that Eq. 3 is applied;

$$\mathrm{M+T} \rightleftarrows \mathrm{M\text{–}T}, \; K = [\mathrm{M\text{–}T}]/[\mathrm{M}][\mathrm{T}], \tag{2}$$

$$\Delta\alpha \propto [\mathrm{M\text{–}T}] \propto [\mathrm{M}][\mathrm{T}], \tag{3}$$

where [M] and [M–T] are the concentrations of M and M–T, respectively, [T] is the amount of T, and K a constant. In this case, Eqs. 4 and 5 are applied;

$$C = [\mathrm{M}] + [\mathrm{M\text{–}T}], \tag{4}$$

$$W_T = [\mathrm{T}] + [\mathrm{M\text{–}T}]. \tag{5}$$

Equation 6 is obtained from the above equations;

$$\Delta\alpha = K''\{C/(1+K[\mathrm{M}])\}\{W_T/(1+K[\mathrm{T}])\}, \tag{6}$$

where K'' is a constant. Equation 1 is similar to Eq. 6. This suggests that complex formation between mandelic acid and talc participates in racemization. As is shown in Table 1, the value of R in ethanol at 20 °C was lower than the value at 5 °C. Probably, dissociation of the complex is more remarkable at 20 °C than at 5 °C.

Table 1. Racemization of S(+)-Mandelic Acid on Talc in Various Solvents
mandelic acid concentration; 6.6×10^{-3} M
experimental conditions; (iii)

T[a) / °C	Solvent	t_s[b) / min	$(\bar{S}/S_0)$	α/α_0	R[c) / %
	Dioxane–Cyclohexane				
20	1 : 0[d)	1	0.980	0.863	11.9
		3—15[e)	0.925	0.887	4.1
	1 : 9	1	0.890	0.760	14.6
		15	0.713	0.655	8.1
	1 : 19	1	0.673	0.665	1.2
		7	0.434	0.446	—
		15	0.338	0.363	—
	Ethanol	1	0.984	0.895	9.1
		3—15[e)	0.972	0.926	4.7
5	Ethanol	1	1.00	0.865	13.5
		30	1.00	0.853	14.7

a) T is the temperature. b) t_s is the stirring time. c) $R=[\{(\bar{S}/S_0)-\alpha/\alpha_0\}/\bar{S}/S_0)]\times100$, R represents racemization percentage. d) These ratios are represented by volume. e) The data are the mean values for the stirring time between 3 min and 15 min, for $(\bar{S}/S_0)$ and α/α_0 remained nearly constant in these cases after a lapse of 3 min.

Active Sites at the Surface of Talc. Fukui et al. reported that both acidic and basic sites participated in dehydration of 2-propanol at the surface of talc.[6) Table 2 shows the values of Hammett's acidity function, H_0, and basicity function, H_0', for various talcs obtained by the indicator method.[4) Acidic sites with H_0 smaller than the pK_a value of mandelic acid (3.7 at 25 °C) are absent at the surface of talc$_{\mathrm{TEA}}$. Basic sites are expected to be absent at the surface of talc$_{\mathrm{AA}}$. On adding these talcs to an ethanolic solution of

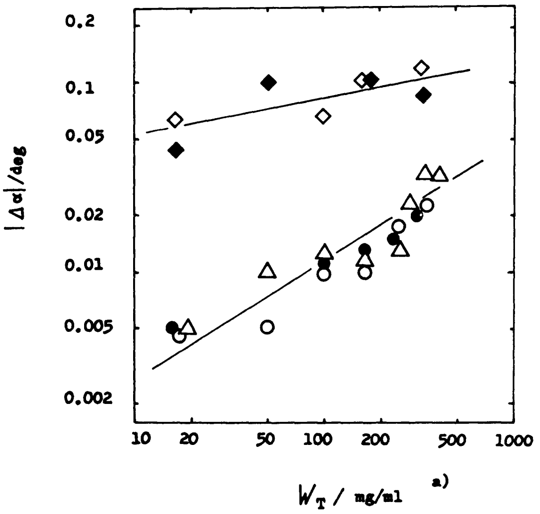


Fig. 4. Variation in α with the amount of talc

mandelic acid		concentration of mandelic acid / M	experimental conditions
◇	S	6.6×10^{-2}	(iv)
◆	R	6.6×10^{-2}	(iv)
△	S	6.6×10^{-3}	(iv)
○	S	6.6×10^{-3}	(iii)
●	R	6.6×10^{-3}	(iii)

Solvent: ethanol, Temperature: 5 °C
a) W_T is the amount of talc.

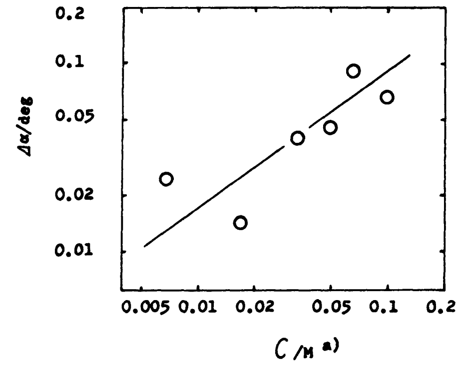


Fig. 5. Variation in α with the concentration of mandelic acid experimental conditions; (iv), solvent: ethanol, the amount of talc: 1 g/3 ml, temperature: 5 °C a) C is the concentration of S(+)-mandelic acid.

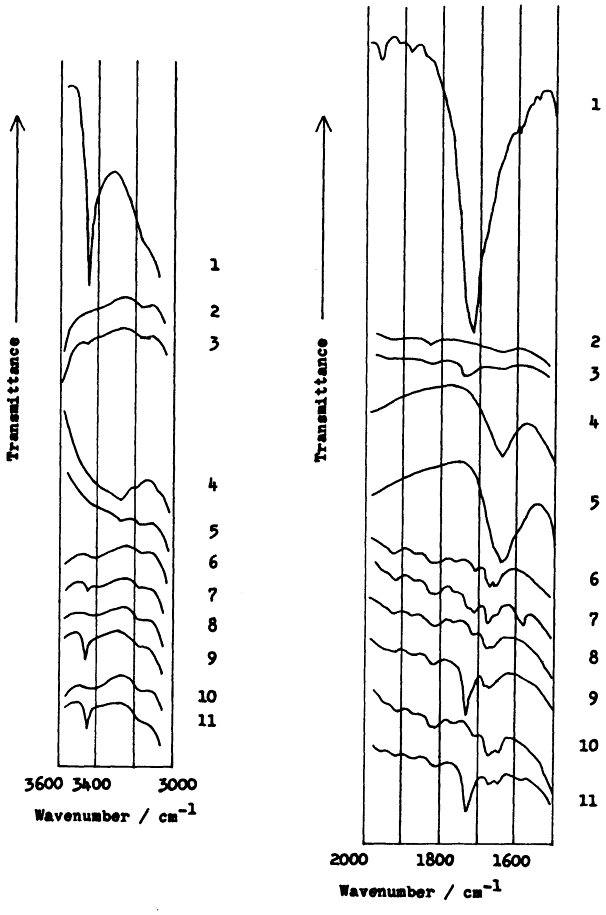


Fig. 6. IR spectra of mandelic acid and various inorganic powders by nujol method.
1: *R*(−)-mandelic acid, 2: kaolin, 3: kaolin-M, 4: γ-Al_2O_3, 5: γ-Al_2O_3-M, 6: talc, 7: talc-M, 8: $talc_{AA}$, 9: $talc_{AA}$-M, 10: $talc_{TEA}$, 11: $talc_{TEA}$-M.
Samples of No. 3, 5, 7, 9, and 11 were prepared using *R*(−)-mandelic acid.

mandelic acid at 5 °C, $|\alpha|$ and ($\overline{S}/S_0$) decreased; this is considered to be due to the adsorption of mandelic acid at the surface of these talcs, as the shape of the absorption spectra was changed only slightly. Comparison between α/α_0 and ($\overline{S}/S_0$) revealed that mandelic acid was not racemized at the surface of these talcs, as is shown in Table 2. It is judged from these results that both acidic and basic sites take part in racemization.

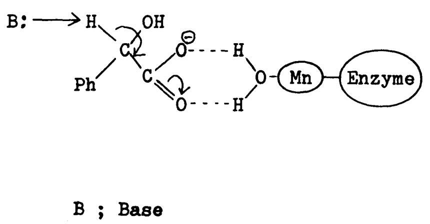
Addition of Various Inorganic Powders. On adding kaolin and γ-Al_2O_3 to an ethanolic solution of mandelic acid at 5 °C, $|\alpha|$ and ($\overline{S}/S_0$) decreased; this is considered to be due to the adsorption of mandelic acid on these powders. Addition of SiO_2 had little influence on α. Comparison between α/α_0 and ($\overline{S}/S_0$) revealed that racemization is slight at the surface of these powder. (Table 2) It is also clear from Table 2 that acidic sites, whose H_0 value is nearly equal to or smaller than the pK_a value of mandelic acid, exist at the surface of kaolin, talc and SiO_2. It is reported by many workers that basic sites exist at the surface of these powders.[6,7] It is also clarified in Table 2 that basic sites exist at the surface of γ-Al_2O_3.

Figure 6 shows the IR spectra of the various powders. In the spectra of kaolin–M, the band of the hydroxyl group at 3420 cm^{-1} was weak and the band of C=O was observed at 1730 cm^{-1}, though the band for mandelic acid was found at 1720 cm^{-1}. In the spectra of γ-Al_2O_3–M, no band was observed at 3420 cm^{-1} and a new band was found around 3200 cm^{-1}. No band was observed around 1720 cm^{-1} and the absorbance around 1600 cm^{-1} seemed to increase. In the spectra of $talc_{AA}$–M and $talc_{TEA}$–M, the band of C=O was at 1730 cm^{-1} and, in addition a new band was found at 1580 cm^{-1} in the spectra of talc–M, though the band of the hydroxyl group was at 3420 cm^{-1} in these spectra. In the spectra of SiO_2–M, the bands of mandelic acid in these regions were not

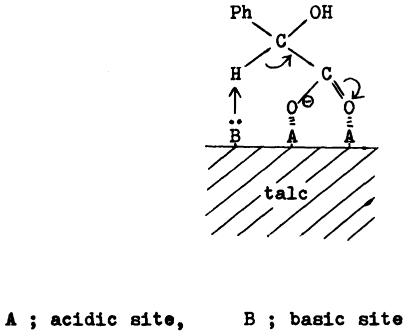
Table 2. Interaction of Mandelic Acid with Various Kinds of Inorganic Powders

Inorganic powders	H_0	H_0'	W_I[a)] / g	V_m[b)] / ml	Type of mandelic acid	($\overline{S}/S_0$)	Racemization[c)]
Kaolin	$0.8<H_0<3.3$	$H_0'<7.2$	1.5	5	*S*	0.773	−
					R	0.780	−
Talc	$0.8<H_0\leq3.3$	$H_0'<7.2$	1.0	3	*S*	1.00	+
					R	1.00	+
SiO_2	$0.8<H_0\leq3.3$	$H_0'<7.2$	1.5	5	*S*	1.00	−
					R	1.00	1/5
γ-Al_2O_3	$6.8<H_0$	$7.2<H_0'$	0.05	3	*S*	0.611	−
					R	0.597	4/7
$Talc_{AA}$	$0.8<H_0\leq3.3$	$H_0'<7.2$	1.0	3	*S*	0.900	−
$Talc_{TEA}$	$3.3<H_0<6.8$	$H_0<7.2$	1.0	3	*S*	0.892	−

a) W_I is the amount of inorganic powder. b) V_m is the volume of an ethanol solution of 6.6×10^{-3} M of mandelic acid. c) +: Racemization of mandelic acid was observed. −: Racemization was not observed. *x*/*y*: Racemization was observed *x* times, when the experiment was repeated *y* times.



Scheme 1.



Scheme 2.

distinguished clearly from broad and strong bands of the adsorbed water, though a small shoulder was observed around 1720 cm^{-1}.

Singurel[8] investigated the IR spectra of mandelic acid in carbon tetrachloride or in KBr pellets. He pointed out that the C=O vibrations at 1718 cm^{-1} and 1762 cm^{-1} belonged to the dimer and monomer, respectively. In the spectra of KBr pellets, a wide and intense absorption range between 2400 cm^{-1} and 3200 cm^{-1} was assigned to carboxylic OH groups of dimer molecules connected by hydrogen bonds and a band around 3400 cm^{-1} to the hydroxyl group. When a proton acceptor complexed with the COOH group of mandelic acid, the C=O band was observed between the monomer and dimer bands. Khadikar et al.[9] investigated the IR spectra of bivalent metal complexes of mandelic acid. The hydroxyl group frequency was observed around 3260 cm^{-1}, and the stretching frequency of the COO$^-$ group occured around 1600 cm^{-1}. They concluded that chelation took place involving coordination of hydroxyl and carboxyl groups of mandelic acid.

The above facts suggest that the hydroxyl group of mandelic acid interacts readily with the surface of γ-Al_2O_3. It interacts only weakly with the surface of kaolin, and does not interact at all with the surface of the various talcs. The COOH group interacts with a proton acceptor at the surface of kaolin and the various talcs. The COO$^-$ group of mandelate anions also interacts with the surface of talc. The COO$^-$ group coordinates with the surface of γ-Al_2O_3. These results show that racemization takes place in the mandelate anion, whose hydroxyl groups are free; it weakly interacts with the surface of the inorganic powders.

Mechanism of Racemization. Maggio et al.[10] studied the mechanism of the action of mandelate racemase, using the EPR and NMR techniquss. They showed that this enzyme bonded with Mn^{2+} to which a water molecule liganded, and concluded that deprotonation from the C atom at the second position of a mandelate anion was enhanced by hydrogen bonding of COO$^-$ with the ligand water, as is shown in Scheme 1. It is concluded from the above results that the H atom at the C atom in the second position of a mandelate anion interacts with the basic site at the surface of talc and that deprotonation is enhanced by interaction between the carboxyl group and the acidic site, as is shown in Scheme 2.

Difference between Racemization of *S*-Isomer and that of *R*-Isomer. The decrease in α for the solution of the *S*-isomer by adding talc powder was little influenced by the stirring velocity. On the contrary, the value of $|\Delta\alpha|$ decreased with the decrease in stirring velocity in the case of *R*-isomer, though the value at the stirring velocity at 380 rpm was identical with the value for *S*-isomer. (Figs. 1 and 2) The value of $|\alpha|$ for the solution containing 6.6×10^{-3} M of *R*-isomer did not decrease on adding talc by the process of (iv), though the value for the solution containing 6.6×10^{-2} M of *R*-isomer decreased. (Fig. 4) These results suggest that talc has a chiral surface.

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