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Intermolecular Hydrogen Bonding of Enantiomers of Pantolactone Studied by Infrared and ^{1}H-NMR Spectroscopy

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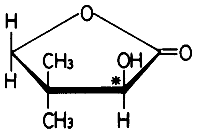
Intermolecular associations of the enantiomers of pantolactone in carbon tetrachloride solution have been studied by infrared and ^{1}H-NMR spectroscopic methods. The spectroscopic data have been analyzed by the least squares method to obtain the association constants and thermodynamic parameters. It was found that pantolactone takes a cyclic dimer structure by dint of hydrogen bonding. The association constant for homochiral dimerization was obtained to be 8.9 mol^{-1} dm^3 at 26°C and the enthalpy and entropy changes were −35 kJ mol^{-1} and −97 J K^{-1} mol^{-1}, respectively. The association constant for heterochiral dimerization is just twice as large as that for homochiral dimerization, that is, no selective association exists between enantiomers.

In a previous study a general method for analyzing spectrophotometric data of a multicomponent equilibrium system has been developed.[1] The method was applied to the analysis of intermolecular hydrogen bond system of pantolactone **1** in carbon tetrachloride solution. Some spectroscopic measurements of pantolactone have been made, infrared spectra by Kuhnert-Brandstätter and Friedl[2] and Raman and ^{1}H-NMR spectra by Johnson *et al*,[3] but no quantitative analysis on intermolecular hydrogen bonding has yet been worked out. In the present work the infrared and ^{1}H-NMR studies of pantolactone were undertaken for elucidating the association mode and obtaining the association constants and thermodynamic parameters of the intermolecular hydrogen bonding. Pantolactone is an optically active molecule and a stereoselective association between enantiomers is possible. In order to elucidate this problem the quantitative analysis of the concentration dependence of the OH proton chemical shift was made on the solutions of the pure enantiomer (L-pantolactone), racemic mixture (DL-pantolactone), and the mixture of the enantiomers (D- and L-pantolactones) at different ratios.



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Experimental

Materials and Methods. Enantiomers of pantolactone (dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone) were purchased from Tokyo Kasei Co. and purified by sublimation *in vacuo*. Spectroscopic grade carbon tetrachloride was dried over molecular sieves of 3A and was used as the solvent.

Infrared spectra were measured on a JASCO A-3 infrared spectrophotometer interfaced to a personal computer (NEC PC-9801). The concentration dependences of the absorption intensities in the O–H and C=O stretching regions were measured in the concentration range from 0.08 to 0.003 M (1 M=1 mol dm^{-3}) at 26 °C. The temperature dependence of the absorption intensities of the O–H stretching vibrations was measured at several temperatures from 20 to 58 °C. The Raman spectra of L-pantolactone in CCl$_4$ solution (0.08 M) were measured on a JEOL-400D Raman spectrometer.

^{1}H-NMR spectra were measured mainly on a JEOL FX-200 spectrometer operated at 200 MHz and in part on a JEOL GX-500 spectrometer at 500 MHz locked on deuterium of 5 vol% cyclohexane-d_{12} in CCl$_4$ solvent at 30 °C. Chemical shifts were measured relative to the ^{1}H resonance of internal tetramethylsilane. Solutions were prepared in the concentration range from 0.07 to 0.0005 M for pure L-enantiomer, and from 0.2 to 0.01 M for racemic mixture (DL-pantolactone). The measurements for the solutions of different mole ratio of D- and L-enantiomers were performed at the total concentration of 0.07 M.

Procedure for Analysis. The self association of pure enantiomer (D- or L-pantolactone) is expressed for *n* merization by

$$nX \rightleftharpoons X_n, \quad K_n = [X_n]/[X]^n, \tag{1}$$

where X stands for D or L, [X] and [X$_n$] are the concentrations of monomer and *n*-mer, respectively, and K_n is the association constant for *n* merization of pure enantiomer.

In the solution of mixture of D- and L-enantiomers the following equilibrium was assumed,

$$\begin{aligned} &2D \rightleftharpoons D_2, \quad 2L \rightleftharpoons L_2, \\ &\quad K_2 = K_{DD} = K_{LL} = [D_2]/[D]^2 = [L_2]/[L]^2, \\ &D + L \rightleftharpoons DL, \\ &\quad K_{DL} = [DL]/[D][L], \end{aligned} \tag{2}$$

where K_2(=K_{DD}=K_{LL}) and K_{DL} are the association constants for dimerization of pure enantiomer and for hetero-association of D- and L-enantiomers, respectively. [D] and [D$_2$] ([L] and [L$_2$]) are concentrations of monomer and dimer of the D- (L-) enantiomer and [DL] is the concentration of hetero-associate DL between D- and L-enantiomers.

The absorbances *A* for the solution containing *n* absorbing components are expressed by the sum of absorptions of *n* components,

$$A_\nu = l\sum_{i=1}^{n} E_{\nu i}C_i(K), \tag{3}$$

where A_ν is the absorbance at the wave number ν, *l* is the path length, $E_{\nu i}$ is the molar absorption coefficient at the wave number ν of the *i*-th absorbing component, and C_i is the concentration of the *i*-th component which is a function of the association constant *K*. The association constants and molar absorption coefficients were determined from the observed absorbance data by the method of least squares as described previously.[1]

The chemical shifts (Δ) of the OH proton of pantolactone in the chemical equilibrium system (2) are expressed by

$$\Delta_{\mathrm{D}} = \delta_{\mathrm{D}}P_{\mathrm{D}} + \delta_{\mathrm{DD}}P_{\mathrm{DD}} + \delta_{\mathrm{DL}}P_{\mathrm{DL}}(\mathrm{D}),$$
$$\Delta_{\mathrm{L}} = \delta_{\mathrm{L}}P_{\mathrm{L}} + \delta_{\mathrm{LL}}P_{\mathrm{LL}} + \delta_{\mathrm{DL}}P_{\mathrm{DL}}(\mathrm{L}), \qquad (4)$$

where Δ_{D} and Δ_{L} are observed chemical shifts for the D- and L-enantiomers, $\delta_{\mathrm{D}}(=\delta_{\mathrm{L}})$, $\delta_{\mathrm{DD}}(=\delta_{\mathrm{LL}})$ and δ_{DL} are the intrinsic chemical shifts for the D- (or L-) monomer, homo-dimer D_2 (or L_2) and hetero-associate DL, respectively. P_i is the fraction of the i species given by

$$P_{\mathrm{D}} = [\mathrm{D}]/([\mathrm{D}] + 2[\mathrm{D_2}] + [\mathrm{DL}]),$$
$$P_{\mathrm{DD}} = 2[\mathrm{D_2}]/([\mathrm{D}] + 2[\mathrm{D_2}] + [\mathrm{DL}]),$$
$$P_{\mathrm{DL}}(\mathrm{D}) = [\mathrm{DL}]/([\mathrm{D}] + 2[\mathrm{D_2}] + [\mathrm{DL}]), \qquad (5)$$

and P_{L}, P_{LL} and $P_{\mathrm{DL}}(\mathrm{L})$ are given similarly. The association constants K_2 and K_{DL} and limiting shifts δ_{D}, δ_{DD}, and δ_{DL} were determined by the least squares method[1] with reference to the observed chemical shifts.

Results and Discussion

Infrared Spectra. The concentration dependences of absorption bands of the O–H and C=O stretching vibrations of L-pantolactone in CCl_4 solutions at 26 °C are shown in Figs. 1 and 2, respectively. The broad band at 3460 cm^{-1} which is enhanced with concentration can readily be assigned to the intermolecularly hydrogen-bonded O–H stretching vibration, while the band at 3570 cm^{-1} enhanced with dilution can be assigned to the O–H stretching vibration of the monomer species. The observation of an isosbestic point at 3550 cm^{-1} suggests that the chemical equilibrium between two components would be predominant in this system. The temperature dependence of absorption intensities in the O–H stretching region was measured (data are not shown). No absorption band above 3600 cm^{-1} was recognized even at high temperature of 70 °C in the dilute solution. It is known that the hydrogen bond free O–H stretching band appears at the wave number above 3600 cm^{-1}.[4] Therefore it suggests that pantolactone exists exclusively in intra- and/or intermolecular hydrogen bonded forms. In the C=O stretching region the main peak at 1795 cm^{-1} is enhanced while the shoulders at 1780 and 1765 cm^{-1} diminish with dilution. Then the band at 1795 cm^{-1} is assigned to the C=O stretching vibration of the monomer species, while the shoulders at 1780 and 1765 cm^{-1} are assigned to the bands of intermolecularly hydrogen-bonded species.

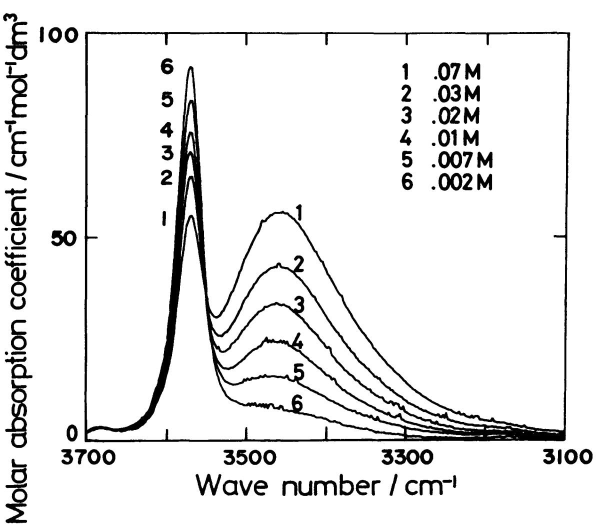


Fig. 1. Concentration dependence of the infrared spectra in the O–H stretching region of L-pantolactone in CCl_4 solutions at 26 °C.

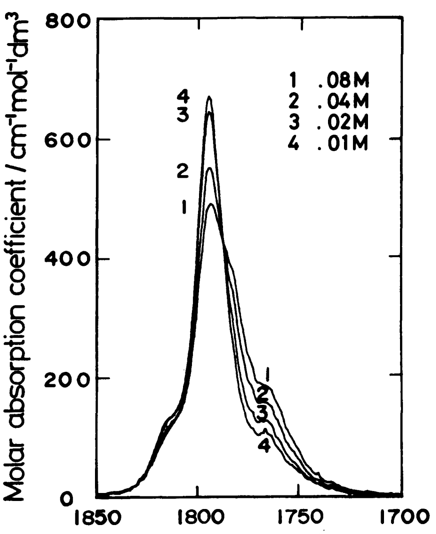


Fig. 2. Concentration dependence of the infrared spectra in the C=O stretching region of L-pantolactone in CCl_4 solutions at 26 °C.

^{1}H-NMR Spectra. In ^{1}H-NMR spectrum of L-pantolactone two methyl groups give rise to the separate signals at δ 1.0 and 1.2 and methylene protons give rise to the AB quartet at δ 3.9 because of the existence of an asymmetric carbon atom. These methyl and methylene chemical shifts are independent of the concentration. The resonance lines of hydroxyl and methine protons are spin–spin coupled with each other and exhibit concentration dependence. Their chemical shifts vary from δ 3.5 to 2.2 and from δ 4.03 to 3.92, respectively, and the spin–spin coupling constant $^3J_{\mathrm{HCOH}}$ changes from 3.7 to 2.3 Hz with the change in concentration from 0.07 to 0.0005 M.

In Fig. 3 is shown the mole ratio dependence of ^{1}H-NMR spectra for the solutions of the total concentration 0.07 M of the mixture of D- and L-enantiomers. The hydroxyl and methine proton signals are observed at δ 3.48 and 4.03 for the pure L-enantiomer solution of 0.07 M (Fig. 3(a)), but at δ 3.40 and 4.01 for the racemic solution (L:D=1:1) (Fig. 3(f)). At the mole ratios of $0<D/L<1$, the chemical shifts monotonously change between the extreme values (Fig. 4) and the peak areas are proportional to the mole ratio of enantiomers.[5–9]

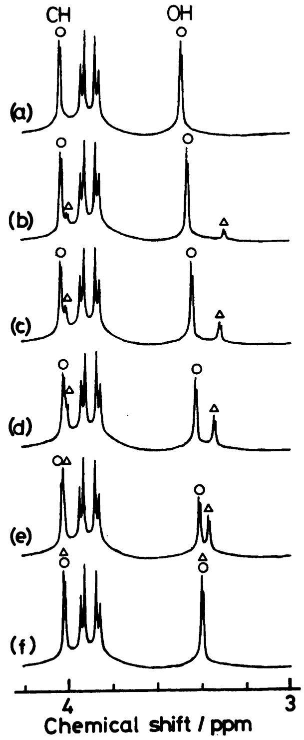


Fig. 3. 500 MHz proton magnetic resonance spectra of CCl_4 solutions of the total concentration 0.07 M of D- and L-pantolactone at 30 °C. The resonance lines of L- and D-enantiomers are denoted with the circles (O) and triangles (△), respectively. Enantiomeric compositions $D{:}L$ are: (a) 0:1; (b) 1:9; (c) 2:8; (d) 3:7; (e) 4:6; (f) 5:5.

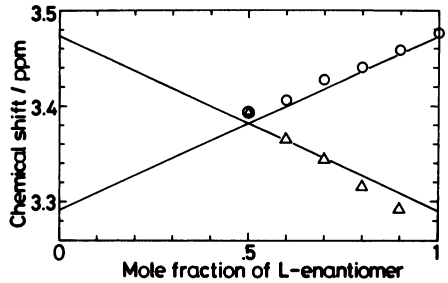


Fig. 4. The observed and calculated chemical shifts of the OH proton resonance against the mole fraction of L-enantiomer in the solutions of the total concentration 0.07 M of D- and L-pantolactone. The solid lines (—) are calculated, and the circles (O) and triangles (△) are observed for L- and D-enantiomers, respectively.

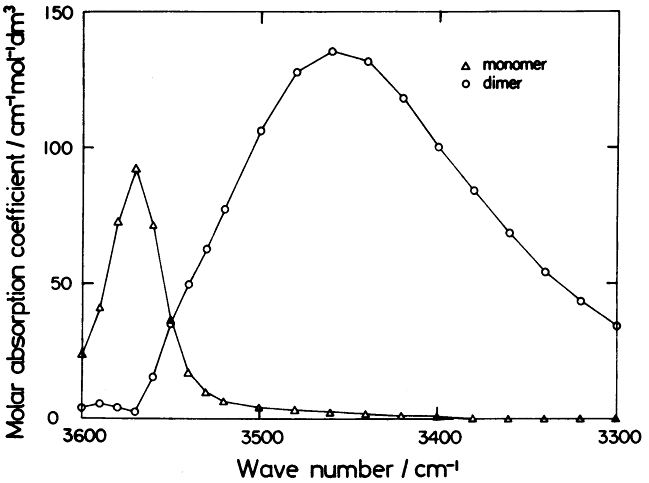


Fig. 5. Molar absorption coefficients for monomer (△) and dimer (O) species of L-pantolactone in the O-H stretching region at 26 °C.

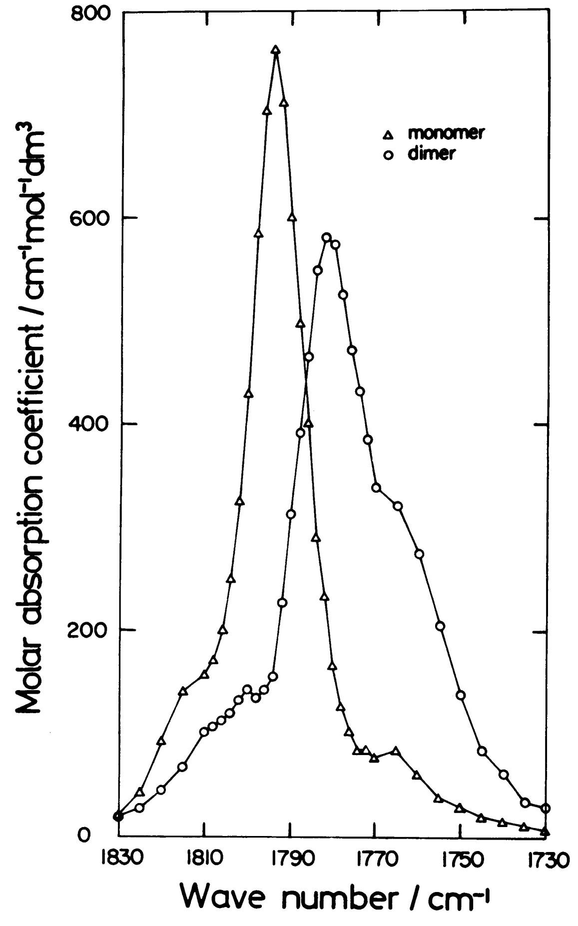
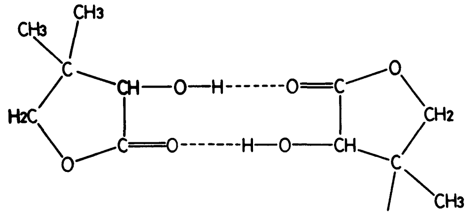


Fig. 6. Molar absorption coefficients for monomer (△) and dimer (O) species of L-pantolactone in the C=O stretching region at 26 °C.

Homochiral Association. The concentration dependences of infrared absorption intensities in the O-H and C=O stretching regions of L-pantolactone were analyzed on the basis of the monomer-dimer equilibrium model by the method of the least squares.1) The association constants for homochiral association were obtained as K_{LL}=8.9±0.6 and 9.8±0.8 M^{-1} at 26 °C from the spectral analyses in the O-H and C=O stretching regions, respectively. The calculated molar absorption coefficients of monomer and dimer species are shown in Figs. 5 and 6, in which those of dimer species are given in values per monomer unit. The observed spectra could be reproduced by using the coefficients with root-mean-squares deviations of 0.66 and 4.2 molar absorption units in the O-H and C=O stretching regions, respectively. The monomer-trimer model was also applied to the analysis but the agreement between the observed and calculated spectra was poor as compared with the monomer-dimer model. The least squares treatment on the monomer-dimer-trimer model could not give convergence. Therefore the dimerization would be predominant in the concentration range employed.

In the C=O stretching region the band at 1780 cm^{-1} can be observed, at most, as a shoulder even in the saturated solution as shown in Fig. 2. However, the quantitative analysis employed in this study clearly indicates that dimer species has a main peak at 1780 cm^{-1} and a shoulder at 1765 cm^{-1} as seen in Fig. 6. All the bands in the C=O stretching region were polarized in Raman scattering. Accordingly, the band at 1780 cm^{-1} could be assigned to the C=O stretching vibration of the dimer species and the shoulder at 1765 cm^{-1} might be an overtone or a combination band enhanced by a Fermi (anharmonic) resonance. The low frequency shift from 1795 to 1780 cm^{-1} of the C=O stretching suggests that the C=O groups are the proton acceptor sites of the intermolecular hydrogen bond.[10,11] In the calculated molar absorption spectra in Fig. 5, the dimer species exhibits only a broad band centered at 3460 cm^{-1} due to the intermolecular hydrogen bond but does not show any O–H stretching band free from hydrogen bonding. Therefore all the OH groups in the dimer species are responsible for intermolecular hydrogen bonding. It is consequently concluded that pantolactone takes a cyclic dimer structure as shown in **2**.



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The dimer model is further supported by the analysis of the concentration dependence of the OH proton chemical shift in ^{1}H-NMR. The calculations of the least squares fitting[1] were carried out on the basis of several association models. The monomer-dimer model gives a better fit between the observed and calculated data as shown in Fig. 7.

The concentration dependence of the absorption intensities in the O–H stretching region was examined at various temperatures. The results were summarized in Table 1. The dimer model was not inferior to the other models as well. From the van't Hoff plot the enthalpy and entropy changes for dimerization were obtained as $\Delta H = -35 \pm 2$ kJ mol^{-1} (-18 ± 2 kJ mol^{-1} per hydrogen bond) and $\Delta S = -97 \pm 4$ J K^{-1} mol^{-1}, respectively. The thermodynamic parameters obtained in the present study may be compared with those for the cyclic dimerization of carboxylic acids in CCl_4 solutions which have been reported as $\Delta H = -12$ to -23 kJ mol^{-1} and $\Delta S = -30$ to -66 J K^{-1} mol^{-1} per hydrogen bond.[12] No absorption band of hydrogen-bond free O–H stretching above 3600 cm^{-1} could be observed even at 70 °C in the dilute solution (0.003 M). Therefore the monomer species would be stabilized at least by 6 kJ mol^{-1} by dint of an intramolecular hydrogen bond.

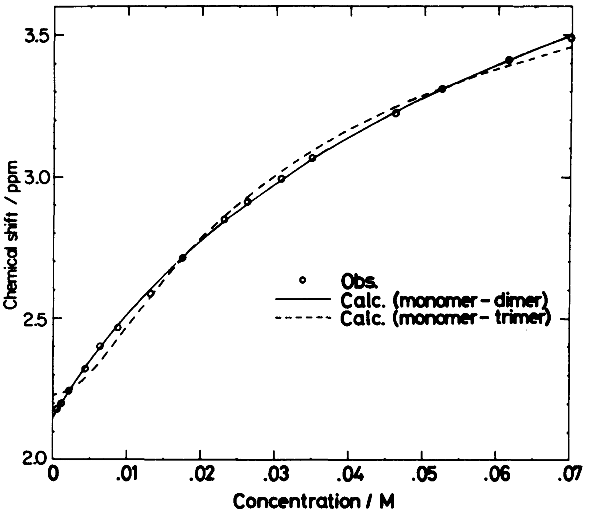

Fig. 7. Concentration dependence of the observed (○) and calculated OH proton chemical shifts of L-pantolactone in CCl_4 solutions at 30 °C. The solid (—) and broken (---) lines are calculated curves on the basis of the monomer–dimer and monomer–trimer models, respectively.

Table 1. Association constants of L-pantolactone at various temperatures

Temperature T/°C	Association constants K_2/M^{-1} O–H stretching	Association constants K_2/M^{-1} C=O stretching
20	11.6±0.7	
26	8.9±0.6	9.8±0.8
30	7.6±0.5	
40	5.3±0.5	
49	3.3±0.4	
58	2.3±0.3	

Heterochiral Association. Figure 8 shows the concentration dependences of the OH proton chemical shifts for the solutions of L-pantolactone (pure enantiomer) and DL-pantolactone (L:D=1:1). One can clearly recognize the differences between the chemical shifts for the pure enantiomer and racemic solutions in the high concentrations. It suggests that the association constant and/or limiting chemical shift for the heterochiral dimer would be different from those for the homochiral dimer.

In the pure enantiomer solution (*e.g.* L-pantolactone) of the stoichiometrical concentration, $C = [\mathrm{L}] + 2[\mathrm{L_2}]$, the concentration of dimer is given from Eq. 2 by

$$[\text{dimer}] = [\mathrm{L_2}] = K_{\mathrm{LL}}[\mathrm{L}]^2 = K_2[\text{monomer}]^2. \tag{6}$$

In the racemic solution (DL-pantolactone) the total concentration of D- and L-pantolactone, C', is given by

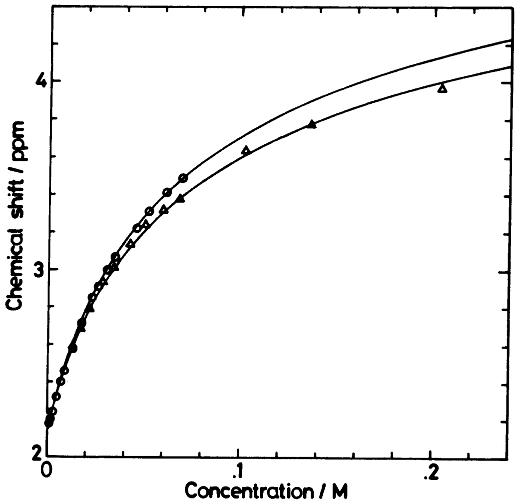

Fig. 8. Concentration dependence of the observed and calculated (solid line) OH proton chemical shifts of pantolactone in CCl_4 solutions at 30 °C. The observed shifts are denoted with ○ and △ for L- and DL-pantolactone, respectively.

$$C' = [D] + [L] + 2[D_2] + 2[L_2] + 2[DL]$$
$$= 2[L] + 4[L_2] + 2[DL], \qquad (7)$$

and the concentration of dimer species in the racemic solution is given as

$$\begin{aligned}[\text{dimer}] &= [D_2] + [L_2] + [DL] \\ &= K_2([D]^2 + [L]^2) + K_{DL}[D][L] \\ &= \frac{1}{4}(2K_2 + K_{DL})([D] + [L])^2 \\ &\quad + \frac{1}{4}(2K_2 - K_{DL})([D] - [L])^2 \\ &= \frac{1}{4}(2K_2 + K_{DL})[\text{monomer}]^2, \qquad (8)\end{aligned}$$

where the relations in the racemic solution, $[D]=[L]$ and $[\text{monomer}]=[D]+[L]$, were employed. From the comparison of Eqs. 6 and 8 , if the relation of $K_{DL}= 2K_2$ $(=2K_{LL})$ holds, the degree of dimer formation in the racemic solution may be regarded to be the same as that in the solution of the pure enantiomer.

In order to elucidate the difference between the homo- and hetero-chiral associations in pantolactone the simultaneous analysis of the concentration dependence of the OH proton chemical shifts was undertaken for the solutions of pure enantiomer (L-pantolactone), racemic mixture (DL-pantolactone), and different mole ratios of D- and L-enantiomers with the total concentration of 0.07 M. The results were summarized in Table 2. The calculated chemical shifts are in good agreement with the observed data as shown in Figs. 4 and 8. It turns out that the association constant for heterochiral dimerization, K_{DL}, is just twice as large as that for homochiral dimerization, K_2 $(=K_{LL})$, that is, no selective association exists between enantiomers. It is consequently concluded that the difference between the chemical shifts of the solutions of pure enantiomer and racemic mixture can be ascribed to the dissimilarity between the limiting chemical shifts of homo- and hetero-chiral dimers.

TABLE 2. ASSOCIATION CONSTANTS AND LIMITING CHEMICAL SHIFTS AT 30 °C

K_{LL}	$6.9\pm0.4\,M^{-1}$
K_{DL}	$13.8\pm0.4\,M^{-1}$
δ_L	2.132 ± 0.008
δ_{LL}	5.74 ± 0.08
δ_{DL}	5.25 ± 0.05

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