FTIR Spectral Study of Double Cyclic Intermolecular Hydrogen Bonding in Glutaric Acids

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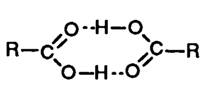
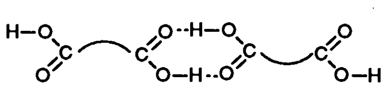
The concentration dependence of the FTIR spectra of glutaric acid **1**, 3-methylglutaric acid **2** and 3,3-dimethylglutaric acid **3** has been measured in CCl_4 solution. In these compounds, double cyclic intermolecular hydrogen-bonded dimers involving a 16-membered ring are formed between the molecules, in which the two carboxy groups are approximately in parallel alignment with each other. The percentage (*h*) of these dimers at 3×10^{-5} mol dm^{-3} in dilute CCl_4 solution has high values of 73% for **1**, 85% for **2** and 44% for **3**. The association constant is 7.7×10^4 dm^3 mol^{-1} for **2**. Conformational analysis of compound **1** has been carried out by the *ab initio* MO method at the 3-21G(*) level.

Many IR spectral studies[1,2] have been reported on cyclic intermolecular hydrogen bonds **Ia** in alkanecarboxylic acids in CCl_4 solution, but not in ω-alkanedicarboxylic acids. It has also been reported[3] that α-keto- and α-alkoxy-carboxylic acids in CCl_4 solution form intramolecular hydrogen bonds, but compounds where the substituent is further away do not. For the thromboxane A_2 receptor agonist, antagonist and antagonist S-145 chain-analogues [$PhSO_2NH(CH_2)_nCO_2H$ (n = 6–8, 10 and 11)], rings of more than nine members formed by intramolecular hydrogen bonds were found between the carboxy and amide functional groups.[2,4–6]

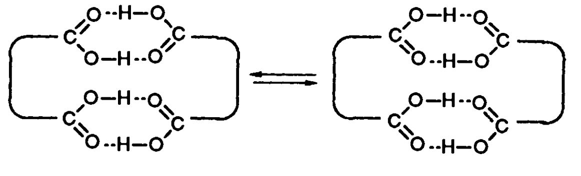
We have taken an interest in ω-alkanedicarboxylic acids $HO_2C(CH_2)_nCO_2H$ (n = 3–14), which can form intermolecular hydrogen bonds **Ib**, **IIa** and **IIb** and intramolecular hydrogen bonds **IIIa**–**IVc**, where τ is the torsion angle O=C–O–H of the carboxy groups and the suffixes 1 and 2 show the left and right carboxy groups, respectively. Therefore, we first obtained FTIR spectra for glutaric acid (n = 3) **1**, 3-methylglutaric acid [$HO_2CCH_2CH(CH_3)CH_2CO_2H$] **2** and 3,3-dimethylglutaric acid [$HO_2CCH_2C(CH_3)_2CH_2CO_2H$] **3** in dilute CCl_4 solution, in order to elucidate their hydrogen-bonded structure. The concentration dependence of the FTIR spectra of **1**–**3** was also measured. Full optimization curve analysis was applied to all spectra. The results observed for ω-alkanedicarboxylic acids (n = 4–14) will be reported in a separate paper.[7] To aid the determination of the hydrogen-bonded structure of **1**, its conformers were optimized by the *ab initio* MO method at the 3-21G(*) level.[8]



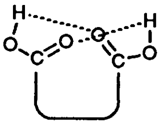
Ia



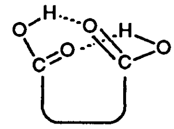
Ib



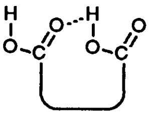
IIa **IIb**



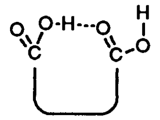
IIIa $\tau_1 = \tau_2 = 0°$



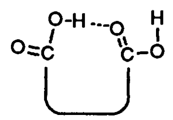
IIIb $\tau_1 = \tau_2 = 90°$



IVa $\tau_1 = \tau_2 = 0°$



IVb $\tau_1 = 90°, \tau_2 = 0°$



IVc $\tau_1 = 180°, \tau_2 = 0°$

Experimental

Compounds **1**–**3** were obtained from a commercial source and purified by recrystallization. FTIR spectra were recorded on a Nicolet 20 SXB FTIR spectrometer at 27 °C. Purification of CCl_4, operation for solution, and curve fitting calculation for peak separation were as previously described.[2] In Table 1, ν, ε, $\Delta\nu_{\frac{1}{2}}$ and A are the band frequency, the molar absorption coefficient, the band width at half-intensity and the integrated intensity of the C=O stretching vibration ($\nu_{C=O}$) bands, respectively, and N and h (= 100 − N) are the percentage of non-hydrogen-bonded and hydrogen-bonded molecules, respectively. It was assumed that the ε value of the free $\nu_{C=O}$ band in **1**–**3** is equal to that of lauric acid [$CH_3(CH_2)_{10}CO_2H$] because the pK_{a1} and pK_{a2} values of $HO_2C(CH_2)_nCO_2H$, for which $n > 2$ are almost constant.[9]

In CCl_4 solution, the A value (10^{-8} cm^2 s^{-1} molecule^{-1}) of the free $\nu_{C=O}$ band at 1758.7 cm^{-1} and the A value per $\nu_{C=O}$ band of dimer at 1710.5 cm^{-1} for lauric acid are 133 and 170, respectively.[2] Because compounds **1**–**3** have two carboxy groups, their total A values of the observed $\nu_{C=O}$ bands were presumed to be between 266 and 340. The total A values of these compounds at *ca.* 3×10^{-5} mol dm^{-3} in CCl_4 solution were in this region. However, when these solutions of **1** and **2** were diluted to a concentration (c) below 5×10^{-6} mol dm^{-3}, the total A values were reduced to a value below 200, in spite of the fact that they show the hydrogen-bonded $\nu_{C=O}$ bands. Therefore, we assumed that the total A value of these compounds at $c < 5 \times 10^{-6}$ mol dm^{-3} is 290 because the free molecules increase, and their c values were estimated using this A value. Although the estimated c value changes slightly with each measurement, the variation of the N value was within ±2%. The *ab initio* MO calculation[8a] was carried out on a VAX

Table 1 FTIR spectral data for compounds **1**–**3** in CCl_4 solution (5 cm cell)

Compound	Assignment[a]	ν/cm^{-1}	ε/dm^3 mol^{-1} cm^{-1}	$\Delta\nu_{\frac{1}{2}}$/cm^{-1}	$A/10^{-8}$ cm^2 s^{-1} molecule^{-1}	N[b](%)	h[c](%)	c[d]$/10^{-5}$ mol dm^{-3}
1	F	1759.5	270.1	18.4	65.8	26.9	73.1	2.8459
	H	1722.8	900.0	15.1	179.5			
	H	1708.4	234.9	16.7	50.9			
2	F	1759.4	140.5	21.3	39.9	14.0	86.0	2.9696
	H	1721.2	1182.2	14.4	232.4			
	H	1705.7	238.2	14.9	44.8			
3	F	1760.1	407.0	17.6	99.1	58.8[e]	41.2	2.7099
	F	1746.5	183.4	18.4	41.3			
	H	1722.1	472.8	15.7	97.8			
	H	1707.5[f]	204.7	19.6	51.9			

[a] F and H show free and intermolecular hydrogen-bonded $\nu_{C=O}$ bands, respectively. [b] Percentage (N) of non-hydrogen-bonded molecules, $N = [\varepsilon/(2 \times 501.9)] \times 100$, where 501.9 is the true ε value of free $\nu_{C=O}$ band of lauric acid and its value was doubled because compounds **1**–**3** have two carboxy groups.[2] [c] Percentage (h) of the double cyclic intermolecular hydrogen bonded molecules, where $h = 100 - N$. [d] Concentration. [e] Since compound **3** shows two free $\nu_{C=O}$ bands, it was assumed that the ε value for this compound is equal to the sum of the ε values for these bands. [f] The band may be overlapped by the dimer $\nu_{C=O}$ band of the **Ib** type. Assuming that the free molecules of $2N$% in **1**–**3** exist in equilibrium with dimers of the **Ib** type as well as in lauric acid, where the N value was doubled because compounds **1**–**3** have two carboxy groups, the percentages (σ) of their dimers were estimated using the equations,[4,6] $c_f = 2Nc/100$, $\log c_f = 0.245\sigma_0^{\frac{1}{2}} - 5.492$, and $\sigma = \sigma_0 N/100$, where c_f is the concentration of free molecules, c is the total concentration, and σ_0 is the percentage of the dimers at c_f. The estimated σ values showed the value of 2% for **1**, 0% for **2** and 10% for **3**, although the application of these equations may overestimate the σ values because the assumption neglects the equilibrium between the free molecules and the dimers of the **II** type. Regression analysis was done between the c and σ values using the spectral parameters of lauric acid reported by us.[2] The analysis gave the equation, $\log c = 0.287\sigma^{\frac{1}{2}} - 5.484$ ($n = 7$, $r = 0.99$). If the intermolecular hydrogen bonds **II** in **1**–**3** are not formed, the σ value is approximately estimated using the equation, $\log 2c = 0.287\sigma^{\frac{1}{2}} - 5.484$, where the c value is doubled because these compounds have two carboxy groups.

6320 computer using the *ab initio* MO package GAUSSIAN 86,[8b] where the *d*-polarization function is placed on the oxygen atom at the 3-21G(*) level.

Results and Discussion

No Intramolecular Hydrogen Bonding in **1**–**3**.—The spectral parameters of the $\nu_{C=O}$ bands in **1**–**3** and their assignments are listed in Table 1, together with the N and the h values. These FTIR spectra and the results of the peak separation of their spectra are shown in Fig. 1. For compounds **1** and **2**, the intensities of the free $\nu_{C=O}$ bands at 1759.5 and 1759.4 cm^{-1} for the carboxy groups decreased and new $\nu_{C=O}$ bands appeared at 1722.8 and 1708.4 cm^{-1} and at 1721.2 and 1705.7 cm^{-1}, respectively. Also the intensities of the $\nu_{C=O}$ bands at 1760.1 and 1746.5 cm^{-1} in **3** decreased and new $\nu_{C=O}$ bands appeared at 1722.1 and 1707.5 cm^{-1}; the former bands were assigned to the free $\nu_{C=O}$ bands because they agreed with the free $\nu_{C=O}$ bands at 1760.1 and 1746.3 cm^{-1}, which were observed for *tert*-butylacetic acid [$(CH_3)_3CH_2CO_2H$] **4** in CCl_4 solution. Correspondingly, the intensities of the free OH stretching vibration (free ν_{OH}) bands at 3533.0 cm^{-1} in **1**, 3531.1 cm^{-1} in **2** and 3529.0 cm^{-1} in **3** decreased and the broad bands appeared at *ca.* 3000 cm^{-1}, respectively. The free ν_{OH} band of **3** also agrees with the free ν_{OH} band at 3529.6 cm^{-1} in **4**. These results indicate that compounds **1**–**3** form the intermolecular hydrogen bonds **Ib**–**IIb** and/or the intramolecular hydrogen bonds **IIIa**–**IVc**. In addition, the structural information from the free ν_{OH} and the free $\nu_{C=O}$ bands can be expected because these bands are altered by the compounds.

If compounds **1**–**3** form the intramolecular hydrogen bonds between the carboxy groups, these compounds are presumed to exist in the conformations **IIIa**, **IIIb**, **IVa**, **IVb** or **IVc**. Usually the free $\nu_{C=O}$ band of aliphatic carboxylic acids in CCl_4 solution appears at *ca.* 1760 cm^{-1} and its carboxy group exists in the conformation **Va**.[3] When R of **Va** was substituted by OMe and OPh groups an equilibrium existed between the conformers **Va** and **Vb** and the free $\nu_{C=O}$ band of the latter conformer shifted to higher wavenumber ($\Delta\nu$ *ca.* 30 cm^{-1}) than that of the former.[3] Furthermore, although the frequency of the free $\nu_{C=O}$ band of **Vc** is not available, it is presumed to be higher than that of **Vb** or **V′b** because the C=O bond lengths calculated for formic acid by the *ab initio* MO method became shorter in the order of the conformers of the **Va**, **V′b** and **Vc** types.[10] For all compounds, the $\nu_{C=O}$ band was not observed at wavenumber higher than 1760 cm^{-1}. The results indicate that these compounds do not form the intramolecular hydrogen bonds **IVb** and **IVc** with the carboxy group which corresponds to the **Vc** and the **V′b** types, respectively. In addition, the intramolecular hydrogen bond may not be formed between the OH and C=O moieties in the carboxy group of the **Va** type because the conformational behaviour of the C=O bond length calculated for methyl formate is similar to that of formic acid.[10]

In order to investigate the existence of the intramolecular hydrogen bonds **IIIa**, **IIIb** and **IVa**, these geometries of **1** were optimized using the 3-21G(*) basis set. This was not done for **IVb** and **IVc** because they were not observed. The results obtained are given in Table 2 and the geometries of the linear conformer **VIa** and the U-shaped ones **VIIa**, **VIIb** and **VIII** are shown in Fig. 2. These calculations showed that the conformer **VIIa** which corresponds to the **IIIa** type is more stable than the linear one **VIa** and the conformer **VIII** which corresponds to the **IVa** type is slightly less stable. However, the O • • • H distances of these conformers are much larger than the sum (2.6 Å) of the van der Waals radii of these atoms. On the other hand, **VIIb** which corresponds to the **IIIb** type became extremely unstable, in spite of the fact that its O • • • H distance is shorter than 2.6 Å. These results suggest that compounds **1**–**3** do not form the intramolecular hydrogen bonds **IIIa**, **IIIb** and **IVa**. Thus, these compounds **1**–**3** do not form any intramolecular hydrogen bonds.

The carboxy groups of the conformers **VIa**, **VI′a**, **VIIa** and **VIII** exist in planar conformation as in **Va**. The conformer **VIa** is slightly more stable than the conformer **VI′a**, in which the carboxy groups lie in the same plane, while the conformer **VIb**, in which the τ values were changed from 0 to 90°, becomes extremely unstable. These results also suggest that intramolecular hydrogen bonds of the type **IIIb** and the **IVb** are not formed.

Double Cyclic Intermolecular Hydrogen Bonding in **1**–**3**.—Fig. 3 shows plots of c against the h values for **1**–**3**. These h values

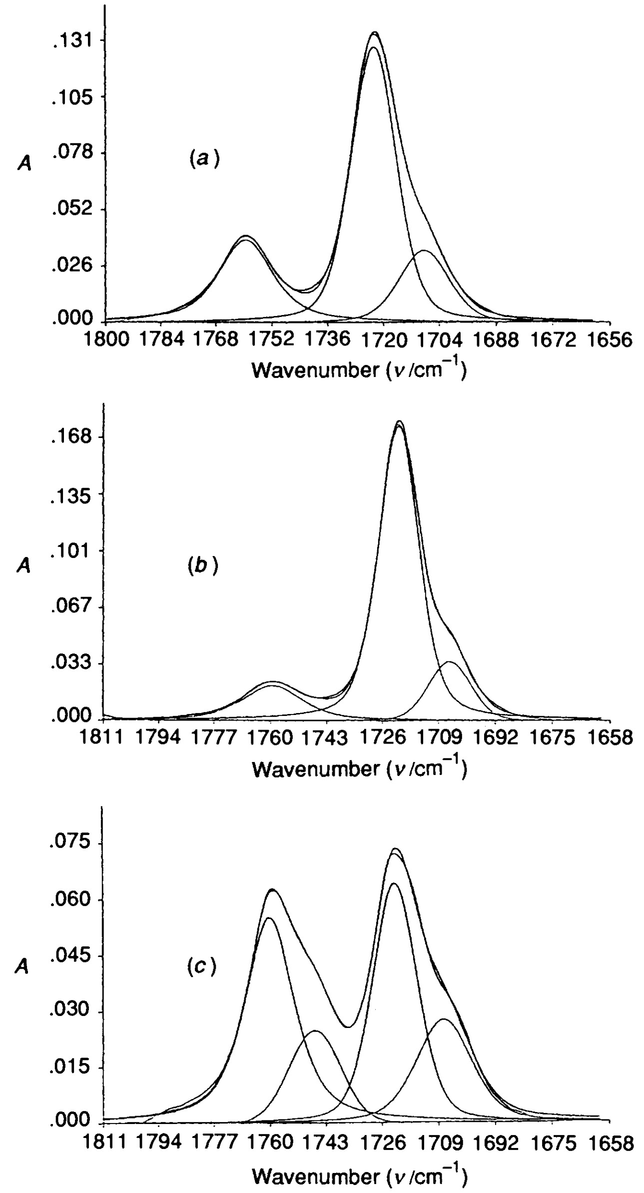
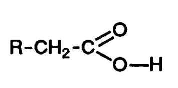
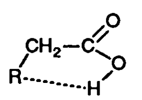


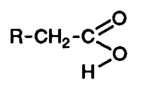
Fig. 1 FTIR spectra of **1**–**3** in CCl_4 solution and the results of peak separation of their spectra. Spectra were obtained using a 5.0 cm cell; (*a*): **1**, 2.8459 × 10^{-5} mol dm^{-3}, (*b*): **2**, 2.9696 × 10^{-5} mol dm^{-3} and (*c*): **3**, 2.7099 × 10^{-5} mol dm^{-3}.



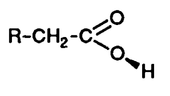
Va τ = 0°



Vb τ = 180°



V'b τ = 180°



Vc τ = 90°

decrease with decreasing *c* value, which demonstrates that compounds **1**–**3** form the intermolecular hydrogen bonds **Ib** and/or **II**. If the intermolecular hydrogen bonds **II** in **1**–**3** are not formed, the percentage of dimers **Ib** of the **Ia** type are estimated to be 19% at 3 × 10^{-5} mol dm^{-3} (see Table 1, footnote *f*). Fig. 3 shows a high *h* value of 73% for **1**, 85% for **2** and 44% for **3** at 3 × 10^{-5} mol dm^{-3}. This suggests that these compounds form the intermolecular hydrogen bonds **IIa** and/or **IIb**.

Since the carboxy groups in the conformers **VIIa** and **VIII** of **1** are approximately parallel to each other, although these

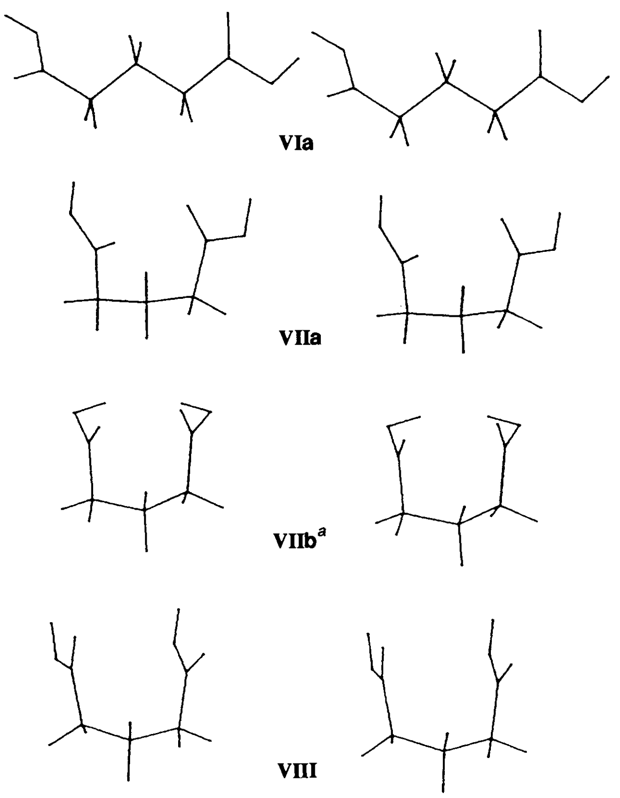


Fig. 2 Stereoviews of the conformations **VIa**, **VIIa**, **VIIb** and **VIII** of **1** optimized by *ab initio* MO calculation at the 3-21G(*) level. [a] The τ_1 and the τ_2 values were fixed at 90° (see Table 2).

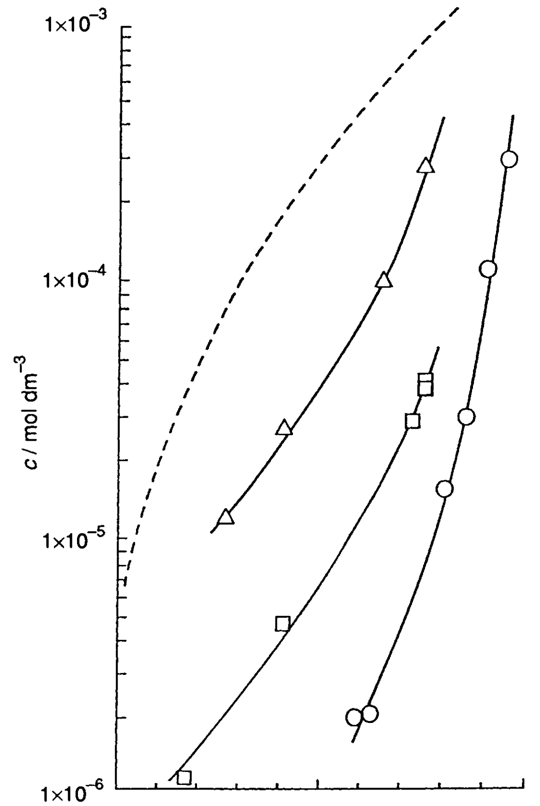


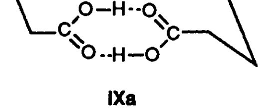
Fig. 3 Plots of *c* and *h* for **1** (□), **2** (○) and **3** (△) in CCl_4. Dotted line shows the plots of *c* and σ, which is the percentage of the dimer of the **Ia** type, in lauric acid.[2]

Table 2 Structures and energies of **1** optimized by *ab initio* MO calculation at the 3-21G(*) level

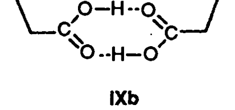
	Linear conformer			U-shaped conformer		
Parameter	**VIa**	**VI′a**	**VIb**[a]	**VIIa**	**VIIb**[a]	**VIII**
Total energy[b]	−490.892 73	−490.891 52	−490.853 42	−490.893 94	−490.865 31	−490.890 57
ΔE_t[c]/kcal mol^{-1}	0.0	0.76	24.67	−0.76	17.21	1.36
τ_1[d]/°	−0.8	0.0	90.0	4.9	90.0	2.2
τ_2[e]/°	0.0	0.0	90.0	2.1	90.0	−4.9
τ_3[f]/°	−53.9 (179.7)	0.0 (180.0)	+49.8 (−177.6)			
$R_{C=O}$ (R_{OH})[g]/Å	1.191 (0.968)	1.192 (0.968)	1.185 (0.966)	1.195 (0.968)	1.195 (0.972)	1.192 (0.968)
$R_{C=O}$ (R_{OH})[h]/Å	1.191 (0.968)	1.191 (0.968)	1.186 (0.966)	1.193 (0.968)	1.195 (0.972)	1.189 (0.969)
$R_{O\cdots O}$ $(R_{O\cdots H})$/Å				3.166 (3.229)[i]	2.851 (2.065)[i]	3.037 (3.113)[l]
$R_{O\cdots O}$ $(R_{O\cdots H})$/Å				3.561 (3.868)[j]	3.027 (2.346)[j]	4.742 (4.947)[l]

[a] Optimized geometry while the τ_1 and the τ_2 values are fixed at 90°. [b] Hartree. [c] Total energy difference (ΔE_t) is with respect to the conformer **VIa**. [d] Torsion angle O=C–O–H of the left carboxy group.[k] [e] Torsion angle O=C–O–H of the right carboxy group.[k] [f] Torsion angle C–C–C–O(H); the value in parentheses shows the torsion angle of the right carboxy group.[k] [g] Bond lengths of the left carboxy group.[k] [h] Bond lengths of the right carboxy group.[k] [i] Back non-bonded distance between oxygen and oxygen or hydrogen atoms.[k] [j] Front non-bonded distance between oxygen and oxygen or hydrogen atoms.[k] [k] See Fig. 2. [l] Cross non-bonded distance between oxygen and oxygen or hydrogen atoms.[k]

groups do not completely overlap, it is possible to form the intermolecular hydrogen bonds **IIa** and **IIb**. However, it was surmised that the intermolecular hydrogen-bonded structure of **1** is the **IIa** type so that the conformer **VIIa** is the most stable. As shown in Fig. 2, the conformation **VIIa** has *exo* and *endo* hydrogen atoms at the 3-position. Therefore, it was presumed that, in **2**, the stability of the conformer of the **VIIa** type increases because the compound can assume the *exo*-methyl conformation, but in **3**, its stability decreases due to the steric interaction between the *endo*-3-methyl and the carboxy groups. This agreed with the observed order of the *h* values *i.e.* **3** < **1** < **2**. As the FTIR spectra of compound **2** could be measured over the large range of 3 × 10^{-4}–1.9 × 10^{-6} mol dm^{-3}, its association constant (*K*) was estimated from the concentration dependence of the $\nu_{C=O}$ band at *ca.* 1721 cm^{-1} as previously described.[2] The obtained *K* value of 7.7 × 10^4 dm^3 mol^{-1} (data points = 6, correlation coefficient = 0.997) is much larger than the *K* value of lauric acid, 3.1 × 10^3 dm^3 mol^{-1}.[2] As shown in Fig. 3, the tendency of the characteristic curves for **1–3** differs from that of lauric acid. From these results, it is clear that compounds **1–3** in CCl_4 solution form the double cyclic intermolecular hydrogen bonds **IIa**.



IXa



IXb

In addition, compounds **1–3** exhibit two intermolecular hydrogen-bonded $\nu_{C=O}$ bands. The ratios of the intensities of these bands are nearly constant at the concentrations examined. These findings suggest that these compounds contain two conformers of a chair **IXa** and a boat form **IXb** with a 16-membered ring formed by intermolecular hydrogen bonds **IIa**.

In conclusion, we found that compounds **1–3** form double cyclic intermolecular hydrogen bonds involving a 16-membered ring, but not intramolecular hydrogen bonds. This information should be helpful for understanding the hydrogen bonds of dicarboxylic acids and studying molecular recognition and the interaction between drug and receptor.

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