F.T.I.R. Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Antagonist S-145† and Related Compounds. Part I.

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F.t.i.r. spectra of the thromboxane A_2 receptor (TXA_2R) antagonists, S-145 (**1**) and BM-13177 (**4**) and TXA_2R agonist, U-46619 (**6**), have been measured in dilute CCl_4 and $CHCl_3$ solutions. These spectra were subjected to curve analysis to separate overlapping absorption bands. For compounds (**1**) and (**6**), the intramolecular hydrogen bonds involving twelve- and fifteen-membered rings were found between the functional groups of α- and ω-side chains, respectively. The formation ratio (ρ) of the intramolecular hydrogen bond in CCl_4 showed the high values of 89% for (**1**) and 81% for (**6**). For (**4**), the intramolecular hydrogen bond was found between the NH bond in the 2-sulphonamido group and π-electrons on the 1-phenyl group. In order to estimate ρ values of (**1**) and (**6**), the concentration dependence of the F.t.i.r. spectra of lauric acid (**7**) as the model compound of the α-side chain was also measured in CCl_4 and $CHCl_3$ solutions. The true molar absorption coefficients of OH and C=O stretching bands and an association constant for (**7**) were determined. On the basis of information on intramolecular hydrogen bonding, the conformations of (**1**), (**4**), and (**6**) were examined and found to resemble each other.

TXA_2, a chemically unstable substance, possesses potent vasoconstriction, platelet aggregation, and bronchoconstriction activities.[1] As compounds which block these activities are anticipated to be useful as a remedy or a preventive for myocardial and cerebral infarctions,[2] much work has been done on TXA_2R antagonists in recent years.[3] In our laboratory, S-145 (**1**) which possesses strong TXA_2R antagonist properties was discovered,[4] and we have taken an interest in its conformation in solutions from a standpoint of drug design.

For structure–activity relationship analysis, the conformations of α- and ω-side chains in prostaglandin-related compounds were investigated by *X*-ray diffraction, n.m.r. and c.d. spectroscopy, and molecular mechanics calculation methods.[5] The conformations have been reported to be approximately parallel arrangements of two side chains, but no information has been available on the exact conformations of the side chains in solution. The binding site of TXA_2 in the receptor remains to be clarified. Assuming that the site is in a hole in a biopolymer such as protein, we presumed that the dielectric value in the hole would be close to that of protein. The continuous dielectric value of protein is about 3.5,[6] which is intermediate between the 2.228 of CCl_4 at 25 °C and the 4.806 of $CHCl_3$ at 20 °C. Therefore, in order to determine the conformations of S-145 (**1**), BM-13177 (**4**), and U-46619 (**6**) in these solvents, we carried out F.t.i.r. spectral measurements for compounds (**1**)–(**6**), model compounds (**7**)–(**12**) containing one functional group, and 1:1 mixtures of (**7**) and (**10**), (**9**) and (**10**), (**8**) and (**11**), and (**7**) and (**12**) in dilute CCl_4 and $CHCl_3$ solutions. The concentration dependence of F.t.i.r. spectra of (**7**) was also measured in these solutions. Full optimization curve analysis was applied to all spectra. In this paper, we examine the conformations stabilized by the intramolecular hydrogen bonds observed in (**1**)–(**6**) and discuss the structural resemblance among their conformations. To aid in the determination of conformations of (**4**) and (**5**), the geometry of (**11**) was optimized by the MNDO method.

Experimental

Compounds (**1**)–(**6**) and (**10**) were prepared as reported elsewhere[4,7] and (**7**)–(**9**), (**11**), and (**12**) were obtained from commercial sources. F.t.i.r. spectra were recorded on a Nicolet 20 SXB FTIR spectrometer. The solvent CCl_4 was dried over molecular sieves 4 Å and purified by distillation. The solvents $CHCl_3$ and $CDCl_3$ were also purified by column chromatography (aluminium oxide 90). Compounds were dissolved in CCl_4 at concentrations (c) below 7×10^{-5} mol dm^{-3} [cell length (l) = 5.0 cm] and in $CHCl_3$ and $CDCl_3$ at c below 3.5×10^{-4} mol dm^{-3} (l = 1.0 cm), except for the concentration dependence measurement of (**7**). All operations for these solutions were performed in a dry box filled with N_2 gas. All measurements were carried out at 27 °C. The curve-fitting calculations for peak separation of the spectra observed were carried out using the Nicolet FOCAS program (full optimization curve analysis software). This calculation allows the parameters of band frequency (ν), band width at half-intensity ($\Delta\nu_{1/2}$), absorbance (D), and composition as the percent Gaussian *vs.* Lorentzian contribution to each individual curve. The ν_{OH}, ν_{NH}, and $\nu_{C=O}$ bands show OH, NH, and C=O stretching vibration bands, respectively, ε is the molar absorption coefficient ($\varepsilon = D/cl$) and A is the integrated intensity [$A = (1/nl)\int \ln (I_0\nu/I\nu)d\nu$, where n is the number of molecules in 1 cm^3]. Spectral parameters were obtained by the curve-fitting calculation. Since the overtone and combination bands are very weak, these bands have been neglected in the calculation.

Results and Discussion

The spectral parameters obtained for dilute CCl_4 and $CHCl_3$ solutions of (**1**)–(**6**) are listed in Table 1, together with the ratio (N) of the non-intramolecular hydrogen bonded molecules estimated. The F.t.i.r. spectra of (**1**) and (**6**) in CCl_4 and the results of the peak separations for their spectra are shown in Figures 1 and 2, respectively. In general, the formation of the intramolecular X–H - - - - O=Y bond causes a shift of the stretching vibration bands, ν_{XH} and $\nu_{Y=O}$, to lower wavenumber.

For compound (**1**), the intensities of the free ν_{OH} band at 3 533

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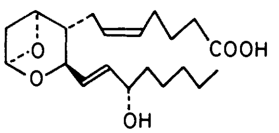
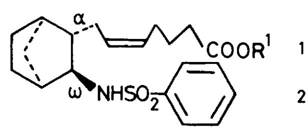
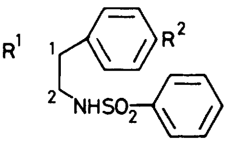
† (5*Z*)-7-{(1*R**,2*S**,3*S**,4*S**)-3-Phenylsulphonylaminobicyclo[2.2.1]-hept-2-yl}hept-5-enoic acid.



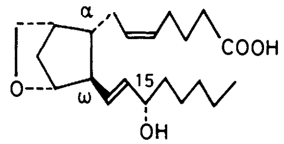
TXA$_2$



(1) R^1 = H
(2) R^1 = CH$_3$
(3) R^1 = Na



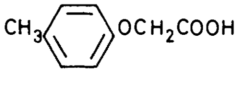
(4) R^2 = OCH$_2$COOH
(5) R^2 = H



(6)

$CH_3(CH_2)_{10}COOH$

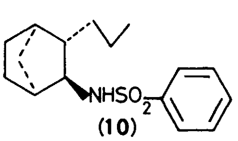
(7)



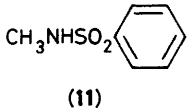
(8)

$CH_3(CH_2)_{16}COOCH_3$

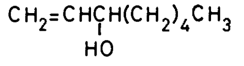
(9)



(10)



(11)



$$CH_2{=}CH\underset{HO}{C}H(CH_2)_4CH_3$$

(12)

Table 1. F.t.i.r. spectral data of compounds (**1**)–(**6**) in CCl_4 and $CHCl_3$.

			CCl_4 (l = 5.0 cm)						$CHCl_3$ (l = 1.0 cm)					
Compd.	Assignment[a]		ν/cm^{-1}	ε/mol^{-1} dm^3 cm^{-1}	Δν$_{1/2}$/ cm^{-1}	A/10^{-8} cm^2 s^{-1} molecule^{-1}[b]	N(%)[c]	c/10^{-5} mol dm^{-3}	ν/cm^{-1}	ε/mol^{-1} dm^3 cm^{-1}	Δν$_{1/2}$/ cm^{-1}	A/10^{-8} cm^2 s^{-1} molecule^{-1}	N(%)[c]	c/10^{-4} mol dm^{-3}
(**1**)	ν_{OH}	F	3 532.8[d]	19.1	24.8	6.1		3.0834	3 515.0	64.7	48.9	38.6		2.8053
		H	3 246.4	60.9	257.4	182.1 (203.9)			*e*					
	$\nu_{C=O}$	F	1 756.1	53.9	20.6	13.7	10.7[f]		1 745.4	270.7	32.1	108.5	67.7[f]	
		H	1 716.2	259.3	28.9	97.3			1 709.3	153.7	25.6	52.3		
		H	1 710.6	224.8	13.1	35.9								
	ν_{NH}	F	3 394.4[d]	10.3	22.8	3.2			3 383.2	60.0	31.9	29.3		
		H	3 242.8	184.4	71.6	184.0 (206.0)			~3 250	*e*				
(**2**)	$\nu_{C=O}$	F	1 741.2	360.2	16.2	75.3	65.5[g]	2.6409	1 730.1	386.2	25.3	124.7	95.0[g]	2.7431
		H	1 723.6	234.8	15.1	45.1			1 718.7	66.3	17.2	17.6		
	ν_{NH}	F	3 393.7	53.6	25.9	17.3			3 384.5	78.9	30.4	32.5		
		H	3 315.3	65.9	50.4	45.4			3 319.0	14.6	101.8	16.3		
(**3**)	ν_{NH}	F							3 382.1	9.2			9.3[h]	2.5958
		H		*i*					~3 070[j]	~60	~415			2.7435
(**4**)	ν_{OH}	F							3 510.8	57.0	53.6	37.5		3.1576
		H							3 473.4	67.1	63.7	54.7		
	$\nu_{C=O}$	F							1 779.8	238.9	26.9	86.2		
		F		*i*					1 766.8	103.2	56.3	70.9		
	ν_{NH}	F							3 392.3	16.1	23.2	4.1	16.6[k]	
		H							3 372.4	53.8	61.4	41.1		
(**5**)	ν_{NH}	F	3 400.2	36.8	24.9	11.2	34.3[k]	5.6325	3 391.0	15.2	23.1	4.3	15.6[k]	3.2448
		H	3 378.3	37.0	53.4	23.0			3 370.7	56.3	65.8	44.8		
(**6**)	ν_{OH}	F	3 530.3	32.3	26.4	11.2		3.9943	3 514.7	59.6	50.8	37.5		2.8530
		H	3 194.2	49.5	160.6	86.3 (107.1)			~3 130[j]	*e*				
	$\nu_{C=O}$	F	1 758.0	97.5	18.1	23.6	19.4[f]		1 747.4	215.1	27.7	74.5	53.8[f]	
		H	1 735.5	341.1	18.9	92.9			1 733.6	76.7	14.1	13.2		
		H	1 720.0	43.1	31.5	16.6			1 720.4	141.3	31.5	54.1		
	ν_{OH}	H[l]	3 602.3	21.2	29.3	7.3			3 598.6	34.6	42.5	11.56		
	(15-OH)	H	3 078.0	27.9	146.9	39.7 (49.3)			*e*					

[a] F and H show free and intramolecular hydrogen bonded bands, respectively. [b] *A* is the integrated intensity (see the text) and the values given in parentheses were estimated by extrapolation of 100% formation of the hydrogen bond. [c] Ratio of non-intramolecular hydrogen bonded molecules. [d] The ε and *A* values were estimated to the approximately 10.7% of the parameters in (**7**) (Table 3) or (**10**) (Table 2), because the molar absorption coefficient ratio of the band at 1 756.1 cm^{-1} to 100% free $\nu_{C=O}$ band of (**7**) is 10.7%. [e] The parameters were not obtained because the band was overlapped by solvent absorptions. [f] Molar absorption coefficient ratio of the band to 100% free $\nu_{C=O}$ band of (**7**) (Table 3). [g] Molar absorption coefficient ratio of the band to the $\nu_{C=O}$ band of (**9**) (Table 2). [h] Molar absorption coefficient ratio of the band to the ν_{NH} band of (**10**) (Table 2). [i] The parameters were not obtained because of low solubilities. [j] In $CDCl_3$. [k] Molar absorption coefficient ratio of the band to the ν_{NH} band of (**11**) (Table 2). [l] The exact parameters were not obtained because a weak band was overlapped by the water absorption in the solvent.

cm^{-1} and the free $\nu_{C=O}$ band at 1 756 cm^{-1} for the carboxy group and the free ν_{NH} band at 3 394 cm^{-1} for the sulphonamido group remarkably decreased and new bands appeared at lower wavenumbers, respectively. Analogous to (**1**), for (**6**), the intensities of the free ν_{OH} band at 3 530 cm^{-1} and the free $\nu_{C=O}$ band at 1 758 cm^{-1} for the carboxy group and the ν_{OH} band at

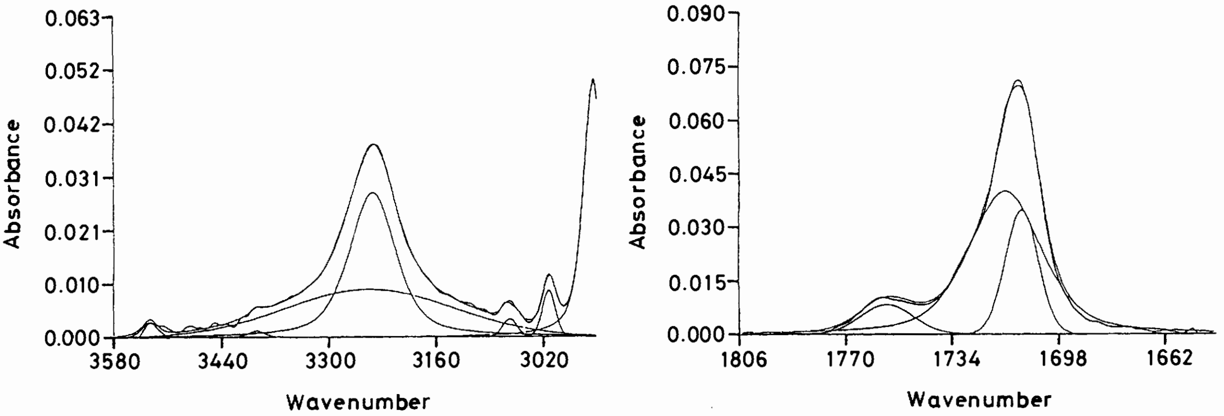


Figure 1. F.t.i.r spectra of (**1**) at a concentration of CCl_4 of 3.0834 × 10^{-5} mol dm^{-3} in a 5.0 cm cell and the results of peak separation of their spectra.

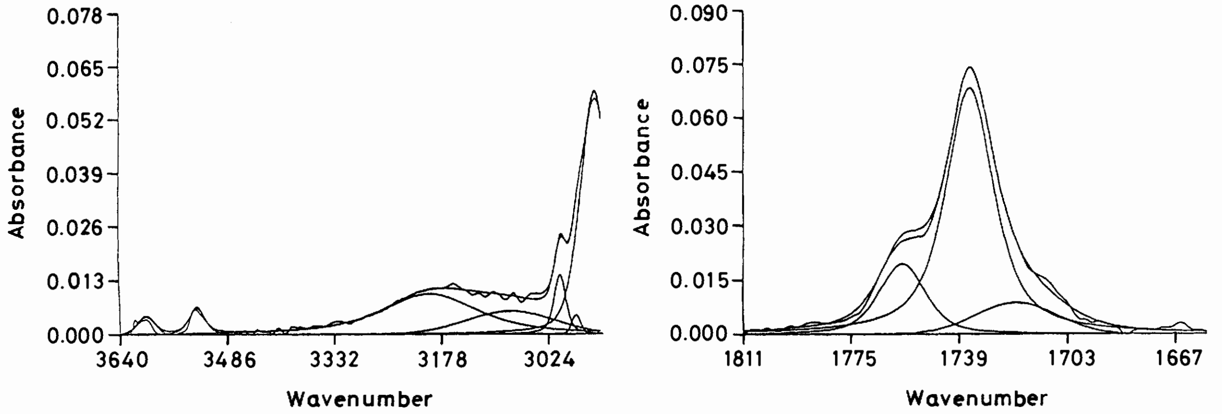
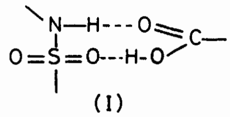
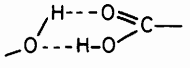


Figure 2. F.t.i.r. spectra of (**6**) at a concentration in CCl_4 of 3.9943 × 10^{-5} mol dm^{-3} in a 5.0 cm cell and the results of peak separation of their spectra.

3 602 cm^{-1} for a hydroxy group remarkably decreased and new bands appeared at lower wavenumber, respectively. These findings suggest that the intramolecular hydrogen bonds (**I**) involving the twelve-membered ring in (**1**) and the bonds (**II**) involving the fifteen-membered one in (**6**) are formed between



(I)



(II)

the α- and ω-side chains. Interestingly, many i.r. studies have been reported on the intramolecular hydrogen bonds formed in chain compounds with non-vicinal functional groups in CCl_4,[8] but not on their bonds for compounds with rings of more than nine members.

The F.t.i.r. spectra of compounds (**4**) and (**5**) in $CHCl_3$ and the results of the peak separation of their spectra are shown in Figure 3; compound (**4**) has poor solubility in CCl_4. The intensities of the free ν_{NH} bands at 3 392 cm^{-1} for the sulphonamido group in (**4**) and at 3 391 cm^{-1} in (**5**) decreased and new bands appeared at 3 372 and 3 371 cm^{-1}, respectively. The behaviour of the ν_{NH} bands in (**4**) is the same as those in (**5**) in spite of the fact that the former has an OCH_2CO_2H group. This suggests that the NH bonds of (**4**) and (**5**) are intramolecularly hydrogen-bonded to π-electrons in the 1-phenyl group as well as in *N*-methylphenylacetamide.[9] These suggestions were substantiated by the results of the following experiments.

(*a*) *F.T.I.R. Spectra of Model Compounds* (**7**)–(**12**) *and* 1:1 *Mixtures of Their Compounds*.—The spectral parameters obtained for the model compounds and the mixtures are listed in Table 2. The mixtures (**7**) and (**10**), (**9**) and (**10**), (**8**) and (**11**), and (**7**) and (**12**) correspond to the functional groups in (**1**), (**2**), (**4**), and (**6**), respectively. All measurements were conducted in CCl_4 and $CHCl_3$ solutions at almost the same concentration as (**1**), (**2**), (**4**), and (**6**). Compared with the corresponding spectral parameters in the model compounds, no changes were found for the mixtures; the parameters for the mixtures agreed well with the sum of those of the corresponding two model compounds. These results indicate that the mixture does not form an intermolecular hydrogen bond between two kinds of compounds in this case. The changes of F.t.i.r. spectra in (**1**), (**2**), and (**4**)–(**6**) are thus attributable to the formation of intramolecular hydrogen bonds between the functional groups. Since the intramolecular hydrogen bond of the OH - - - - π-electrons has been reported for α-unsaturated alcohol systems such as (**6**) and (**12**),[10] it is not discussed.

Because (**7**) forms a dimer, due to the presence of the carboxy group, of 17% in CCl_4 and 8% in $CHCl_3$ at the concentrations measured, there is the possibility of dimerization occurring in solutions of (**1**) and (**6**). In order to estimate the reliable $\rho(= 100 - N)$ value, the amount of dimer of these compounds needs to be known, although there is little possibility of dimerization due to the formation of intramolecular hydrogen bonds. In addition, the true molar absorption coefficient for the free $\nu_{C=O}$ band of the carboxy group in the model compound (**7**) is required to estimate the *N* value. Thus we carried out the next examination.

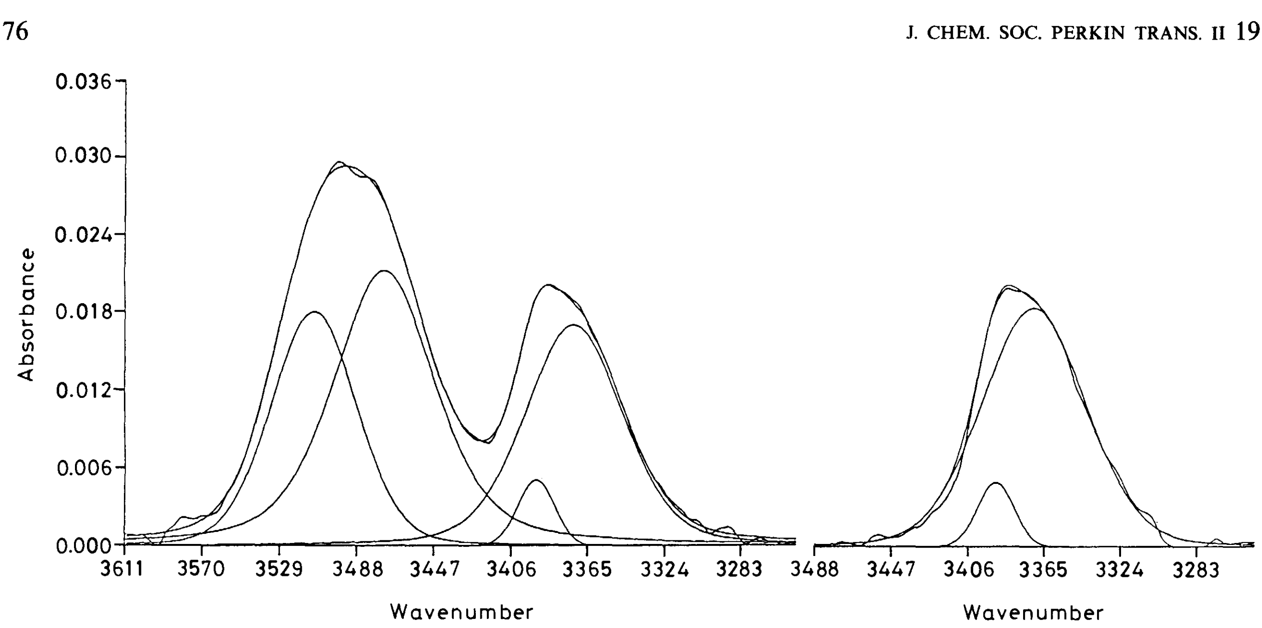


Figure 3. F.t.i.r. spectra of (4) (left) and (5) (right) in $CHCl_3$ and the results of peak separations of their spectra. Spectra were obtained using a 1.0 cm cell; (4) 3.1576×10^{-4} mol dm^{-3} and (5) 3.2448×10^{-4} mol dm^{-3}.

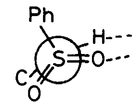
(*b*) *Concentration Dependence of F.T.I.R. Spectra of* (**7**) *in* CCl_4 *and* $CHCl_3$.—The spectral parameters obtained over a wide range of concentrations in CCl_4 and $CHCl_3$ are listed in Table 3. When an equilibrium, $2(7) \rightleftharpoons (7)\text{----}(7)$, exists in CCl_4 and $CHCl_3$, the association constant (K) is given by $K = d/(c - 2d)^2$, where c is the total concentration of (**7**) and d is the concentration of dimer [(**7**) - - - - (**7**)]. Here, the d value is given by $d = B/\varepsilon_0$, B is the absorbance per 1 cm cell of the dimer $\nu_{C=O}$ band and ε_0 is the true molar absorption coefficient of its band. Elimination of d between these expressions gives $B^{1/2} = K^{1/2}\varepsilon_0^{1/2}c - 2K^{1/2}\varepsilon_0^{1/2}(1/\varepsilon_0)B$. The K and ε_0 values were obtained by regression analysis using the data shown in Table 3. These values are shown in Table 4, together with the correlation coefficients (r). The K values of saturated open-chain carboxylic acids have been reported to be in the range 1 000–4 000 dm^3 mol^{-1} in CCl_4 and 100–420 dm^3 mol^{-1} in $CHCl_3$.[11] The K values (3 140 in CCl_4 and 230 dm^3 mol^{-1} in $CHCl_3$) obtained for (**7**) lie approximately in the centre of these ranges.

The ratios of dimer (σ) of (**7**) at the concentrations examined are also listed in Table 3. The ratios of monomer (M) are estimated by $M = 100 - \sigma$. The plots of the M values against the apparent ε and A values observed for the free ν_{OH} and the free $\nu_{C=O}$ bands of the monomer all give good linear relationships with $r > 0.99$. The true ε and A values of these bands were estimated by extrapolation to 100% monomer using these relationships. The true A value of the dimer $\nu_{C=O}$ band was estimated in the same manner ($r > 0.99$). These values are given as a standard value in Table 3. A large difference was recognized between the ε_0 values of free and dimer $\nu_{C=O}$ bands in (**7**). This indicates that the ε_0 values of these bands must be determined in a quantitative analysis. Since the D values used here were taken on an F.t.i.r. spectrometer of high detection sensitivity, they should be reliable.

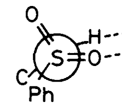
Assuming that the ε_0 values of free $\nu_{C=O}$ bands in (**1**) and (**6**) are equal to that of (**7**), we estimated the N values of their compounds from the ε values as shown in Table 1. Based on the assumption that N% of (**1**) and (**6**) in solution exists, in equilibrium with the dimer, the σ values were estimated from the relationship of the concentration of monomer ($c \times M/100$) *versus* the σ value in (**7**). These σ values were found to be below 3% in CCl_4 and 5% in $CHCl_3$. This finding indicates that, as a first approximation, the existence of dimer in (**1**) and (**6**) can be neglected in the curve analysis for the CCl_4 and $CHCl_3$ solutions examined.

(*c*) *Intramolecular Hydrogen Bonds in* (**1**)–(**6**).—The intramolecularly hydrogen-bonded structures of (**1**)–(**6**) in dilute CCl_4 and $CHCl_3$ solutions are shown in Figure 4, together with the ρ values. In (**1**), the spectral behaviour in $CHCl_3$ resembled that in CCl_4 as described above. Although one intramolecular hydrogen-bond band for (**1**) in $CHCl_3$ was observed at *ca.* 3 250 cm^{-1} because of its solvent absorption, two bands were observed at 3 246 ($\Delta\nu_{1/2}$ 257) and 3 243 cm^{-1} ($\Delta\nu_{1/2}$ 72 cm^{-1}) in CCl_4. Since the $\Delta\nu_{1/2}$ value of the hydrogen-bonded ν_{OH} band in general is larger than that of the hydrogen-bonded ν_{NH} band,[12] the former band was assigned to the ν_{OH} band and the latter one to the ν_{NH} band. In addition, compared with the antisymmetric $\nu_{SO_2^{as}}$ band at 1 353 cm^{-1} and the symmetric $\nu_{SO_2^{s}}$ band at *ca.* 1 163 cm^{-1} observed for the sulphonamido group of (**10**), the shifts to lower wavenumber ($\Delta\nu_{SO_2^{as}}$ 29 and $\Delta\nu_{SO_2^{s}}$ *ca.* 16 cm^{-1}) of these bands were observed for (**1**). From these findings, it is clear that (**1**) in CCl_4 mainly exists in the conformation with the twelve-membered ring formed by the intramolecular hydrogen bonds of (**I**) between the carboxy and sulphonamido groups and its conformation in $CHCl_3$ occurs in about one-third of the total molecules.

As shown in Figure 1, (**1**) exhibits two intramolecular hydrogen-bond $\nu_{C=O}$ bands at 1 716 and 1 711 cm^{-1}, indicating that the equilibrium exists between two conformers in the twelve-membered ring. The equilibrium (**III**) $\rightleftharpoons$ (**IV**) in the sulphonamido group of (**1**) may be possible, but the two intramolecular hydrogen-bond $\nu_{C=O}$ bands were similarly obtained for (5*Z*)-7-{(1*R**,2*R**,3*R**,4*S**)-3-phenylsulphonylaminobicyclo[2.2.1]hept-2-yl}hept-5-enoic acid[13] which has a geometry incapable of forming the conformer (**IV**) due to steric hindrance. This suggests that two of these bonded $\nu_{C=O}$ bands are attributable to the conformational change in the α-side chain.



(III)



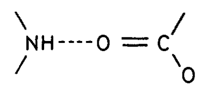
(IV)

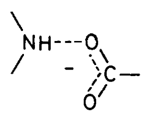
For (**2**) in CCl_4 and $CHCl_3$, new ν_{NH} and $\nu_{C=O}$ bands were observed at lower wavenumber, indicating the intramolecular hydrogen bond (**V**). The ρ value of (**2**) is smaller than that of (**1**) because there is only one hydrogen bond in (**2**).

Table 2. F.t.i.r. spectral data of compounds (**7**)–(**12**) and 1:1 mixtures of (**7**) and (**10**), (**9**) and (**10**), (**8**) and (**11**), and (**7**) and (**12**) in CCl_4 and $CHCl_3$.

			CCl_4 (l = 5.0 cm)						$CHCl_3$ (l = 1.0 cm)					
	Compd.	Assignment[a]	ν/cm⁻¹	ε/mol⁻¹ dm³ cm⁻¹	$\Delta\nu_{1/2}$/cm⁻¹	$A/10^{-8}$ cm² s⁻¹ molecule⁻¹	Ratio(%)[b]	$c/10^{-5}$ mol dm⁻³	ν/cm⁻¹	ε/mol⁻¹ dm³ cm⁻¹	$\Delta\nu_{1/2}$/cm⁻¹	$A/10^{-8}$ cm² s⁻¹ molecule⁻¹	Ratio(%)[b]	$c/10^{-4}$ mol dm⁻³
	(**7**)	ν_{OH} F	3 532.9	147.8	23.5	45.0		4.6325	3 513.7	101.1	46.5	56.7		2.8104
		D	~3 000	*c*					*c*					
		$\nu_{C=O}$ F	1 758.6	416.9	20.0	114.3			1 745.2	364.6	32.4	149.8		
		D	1 710.8	141.7	14.1	27.4	17.2 (16.1)[d]		1 707.6	52.7	16.6	10.7	7.7 (5.7)[d]	
	(**8**)	ν_{OH} F	3 526.7	92.7	31.8	35.5		6.8601	3 511.6	51.8	53.6	33.9		2.8945
		H	3 482.9	62.1	32.0	25.5			3 465.9	75.5	65.7	65.5		
		D	~3 050	*c*										
		$\nu_{C=O}$ F	1 791.5	361.0	20.3	93.2			1 780.9	199.0	27.7	67.4		
		F	1 763.1	153.7	13.9	26.2			1 769.9	132.0	56.8	90.8		
		D	1 739.5	71.0	32.1	27.6								
	(**9**)	$\nu_{C=O}$ F	1 741.6	550.0	15.8	115.0		4.8440	1 729.3	406.7	26.9	141.3		2.7436
	(**10**)	ν_{NH} F	3 394.4	96.1	22.8	30.2		4.8053	3 385.1	98.7	29.3	37.7		2.4844
	(**11**)	ν_{NH} F	3 398.1	107.3	23.5	35.4		6.1910	3 388.1	97.2	35.0	44.2		2.7626
	(**12**)	ν_{OH} H	3 619.1	65.3	20.6	17.1		4.5314	3 607.0	67.4	30.1	24.0		2.5894
e	(**7**)	ν_{OH} F	3 532.5	147.9	22.3	43.4		4.8022	3 514.5	105.0	43.7	57.7		2.4760
		D	~3 000	*c*					*c*					
		$\nu_{C=O}$ F	1 758.6	411.4	19.6	111.9			1 745.5	376.4	32.0	150.4		
		D	1 710.8	148.9	13.8	28.7			1 707.7	51.7	14.1	8.9		
	(**10**)	ν_{NH} F	3 394.6	97.0	20.3	29.8	100.9 (98.6)[f]	4.7644	3 385.7	100.6	27.3	35.9	101.9 (95.1)[f]	2.4947
e	(**9**)	$\nu_{C=O}$ F	1 741.5	555.9	15.9	117.5	101.1 (102.1)[f]	4.8574	1 729.4	415.2	26.6	140.3	102.1 (99.3)[f]	2.5091
	(**10**)	ν_{NH} F	3 394.0	92.7	24.1	30.9	96.4 (102.2)[f]	4.8189	3 384.7	101.7	29.4	37.8	103.0 (100.2)[f]	2.4912
e	(**8**)	ν_{OH} F	3 526.7	90.4	30.9	33.7		6.6909	3 507.7	55.9	54.8	37.3		3.1833
		H	3 483.0	63.7	32.1	28.5			3 463.3	69.0	59.8	55.5		
		D	~3 050	*c*										
		$\nu_{C=O}$ F	1 791.4	351.4	20.4	90.0			1 780.7	209.8	27.8	71.2		
		F	1 763.0	149.3	13.3	24.3			1 769.5	132.7	57.6	92.4		
		D	1 740.4	65.5	34.2	26.9								
	(**11**)	ν_{NH} F	3 397.9	105.2	23.9	35.6	98.0 (100.6)[f]	6.1793	3 388.2	94.1	35.2	44.3	96.8 (100.2)[f]	3.0254
e	(**7**)	ν_{OH} F	3 532.5	148.4	23.5	44.0		4.3925	3 514.6	102.8	43.9	58.7		2.5456
		D	~3 000	*c*					*c*					
		$\nu_{C=O}$ F	1 758.5	417.8	19.7	110.3			1 745.5	369.7	32.0	149.9		
		D	1 710.8	143.0	13.7	27.1			1 706.6	44.8	17.0	9.2		
	(**12**)	ν_{OH} H	3 619.5	64.4	21.6	17.4	98.6 (101.8)[f]	4.5314	3 607.4	62.4	33.9	23.7	92.6 (98.8)[f]	2.5894

[a] F, H, and D′ show free, intramolecular-hydrogen-bonded, and dimer bands, respectively. [b] Molar absorption coefficient ratio (integrated intensity ratio in parenthesis). [c] The parameters were not obtained because the band was overlapped by solvent absorption and/or ν_{CH} bands of solute. [d] Ratio of the parameter of the band to the true parameter of the dimer $\nu_{C=O}$ band (Table 3). [e] Mixture. [f] Ratio of the band of the mixture to the band of the model compound.


(V)


(VI)

For (**3**), the spectra were measured in $CHCl_3$ and $CDCl_3$ solutions because this compound has very low solubility in CCl_4. The free ν_{NH} band of the sulphonamido group in (**3**) remarkably decreased and a broad band appeared at *ca.* 3 070 cm⁻¹, indicating the existence of an intramolecular hydrogen bond (**VI**). The ρ value of (**3**) is much larger than those of (**1**) and (**2**). This implies the higher proton acceptability of the carboxy anion.

The suggestion mentioned above and the results described in paragraph (*a*) indicated that (**4**) and (**5**) in $CHCl_3$ mainly exist in the *gauche*-conformer containing the hydrogen bond of the NH - - - - π-electrons as shown in Figure 4. Since the conformational equilibrium has been studied for the OCH_2CO_2H group,[14] it is not discussed. The change of the free ν_{NH} band of (**5**) in CCl_4 strongly resembles that in $CHCl_3$. This also indicated that, in CCl_4, (**5**) mainly has the conformation described above. In spite of the fact that (**5**) has the weakest hydrogen bond, the ρ value in $CHCl_3$ is larger than that in CCl_4 and different from those in (**1**), (**2**), and (**6**)

In (**6**), the spectral behaviour in $CHCl_3$ is similar to that in CCl_4 as mentioned above. In CCl_4 (**6**) gives two intramolecular hydrogen-bond ν_{OH} bands with peaks at 3 194 (10^8A 107) and 3 078 cm⁻¹ (10^8A 49 cm² s⁻¹ molecule⁻¹), but only at *ca.* 3 130 cm⁻¹ in $CHCl_3$ because of its solvent absorption. Because the latter *A* value is smaller than that of the free ν_{OH} band in the carboxy group of (**7**) in spite of the hydrogen bonded ν_{OH} band, the former band at 3 194 cm⁻¹ was assigned to the ν_{OH} band of the carboxy group and the latter band at 3 078 cm⁻¹ to the ν_{OH} band of the hydroxy group. From these results, it is obvious that (**6**) in CCl_4 mainly exists in the conformation with the fifteen-

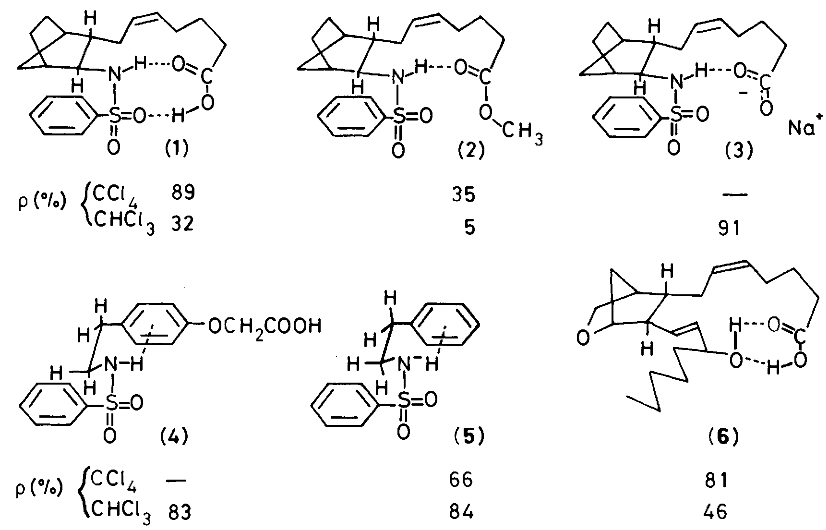


Figure 4. Conformations and the formation ratios (ρ) of the intramolecularly hydrogen-bonded molecules in (1)–(6) in CCl_4 and $CHCl_3$.

Table 3. Concentration dependence of intensities[a] of ν_{OH} and $\nu_{C=O}$ bands of lauric acid (7) in CCl_4 and $CHCl_3$.

			Monomer ν_{OH} band				Monomer $\nu_{C=O}$ band				Dimer $\nu_{C=O}$ band				
Solvent	c/mol dm^{-3}	l/cm	ν_{OH}/cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	ε	$10^8 A$	$\nu_{C=O}$/ cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	ε	$10^8 A$	$\nu_{C=O}$/ cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	ε^b	$10^8 A^b$	$\sigma(\%)^c$
CCl_4	1.0053×10^{-3}	1.0	3 532.8	23.9	59.9	18.7	1 758.6	20.0	167.7	43.9	1 710.6	14.1	552.8	112.9	67.2
	5.0763×10^{-4}	2.0	3 532.9	23.5	78.9	24.7	1 758.6	20.0	217.1	57.1	1 710.6	14.0	471.9	96.0	57.4
	1.0203×10^{-4}	5.0	3 532.6	23.5	130.7	40.4	1 758.5	19.8	356.9	95.7	1 710.7	13.9	246.8	47.5	30.0
	4.6325×10^{-5}	5.0	3 532.9	23.5	147.8	45.5	1 758.6	20.0	416.9	114.3	1 710.8	14.1	141.7	27.4	17.2
	2.0407×10^{-5}	5.0	3 532.7	24.7	160.7	50.5	1 758.6	19.1	453.1	115.6	1 710.2	10.3	82.5	10.8	10.0
	1.0203×10^{-5}	5.0	3 532.7	25.5	169.0	56.3	1 758.8	19.6	477.3	125.9	1 710.1	9.9	35.5	4.6	4.3
	5.1017×10^{-6}	5.0	3 533.1	29.0	174.1	59.6	1 759.1	22.0	480.2	144.9	d				~0
	Standard value		3 532.8[e]	24.8[e]	178.4	57.0	1 758.7[a]	20.1[a]	501.9	132.6	1 710.5[e]	12.7[e]	822.6[c]	170.1	
$CHCl_3$	9.9528×10^{-2}	0.010 60	3 513.3	55.1	15.8	10.2	1 746.5	26.9	57.5	18.9	1 707.9	18.8	587.8	161.8	85.9
	5.4568×10^{-2}	0.025 04	3 514.0	46.2	20.9	11.6	1 746.3	28.7	77.1	27.0	1 707.9	18.7	563.3	155.0	82.3
	9.9863×10^{-3}	0.099 28	3 514.9	43.3	53.5	30.7	1 746.1	30.7	167.8	64.3	1 707.9	18.6	411.6	112.5	60.2
	4.0101×10^{-3}	0.5	3 514.4	46.1	66.0	37.4	1 745.7	31.6	231.8	92.6	1 707.8	18.5	291.0	76.4	42.5
	1.5009×10^{-3}	1.0	3 514.5	45.9	83.8	46.5	1 745.6	32.0	299.5	121.9	1 707.5	18.0	178.1	42.2	26.0
	6.5488×10^{-4}	1.0	3 514.4	44.5	98.0	50.9	1 745.5	32.1	344.0	139.3	1 707.2	17.5	102.1	22.9	14.9
	2.8104×10^{-4}	1.0	3 513.7	46.5	101.1	56.7	1 745.2	32.4	364.6	149.8	1 707.6	16.6	52.7	10.7	7.7
	1.0931×10^{-4}	1.0	3 514.4	43.6	104.8	53.8	1 745.4	30.0	373.6	157.7	d				~0
	Standard value		3 514.2[e]	46.4[e]	112.7	61.4	1 745.7[e]	30.5[e]	399.9	164.1	1 707.7[e]	18.1[e]	684.0[c]	188.9	

[a] ε and A are expressed in mol^{-1} dm^3 cm^{-1} unit and cm^2 s^{-1} molecule^{-1} unit, respectively. [b] ε and A values per carboxy group. [c] Ratio of dimers ($\sigma = \varepsilon/822.6 \times 100$ in CCl_4 and $\sigma = \varepsilon/684.0 \times 100$ in $CHCl_3$), where 822.6 and 684.0 are the ε_0 values per $\nu_{C=O}$ band of dimer in CCl_4 and $CHCl_3$, respectively, (see Table 4), and ε is the apparent ε value of the dimer $\nu_{C=O}$ band at the concentration examined. [d] The i.r. parameters were not obtained because of a very weak band. [e] Mean value.

Table 4. Association constants and the true ε values of the dimer $\nu_{C=O}$ band for lauric acid (7) in CCl_4 and $CHCl_3$ at 27 °C.

Solvent	K/mol^{-1} dm^3	ε_0/mol^{-1} dm^3 cm^{-1}	n^a	r^b
CCl_4	3 136	1 645.2 (822.6)[c]	6	1.000
$CHCl_3$	231	1 367.9 (684.0)[c]	7	0.999

[a] Number of data points. [b] Correlation coefficient. [c] The value in parenthesis is the true ε value per $\nu_{C=O}$ band of dimer.

membered ring formed by intramolecular hydrogen bonds (**II**) between the carboxy and hydroxy groups, and its conformation in $CHCl_3$ accounts for about half of the total molecules. As shown in Figure 2, (**6**) in CCl_4 gives two hydrogen-bonded $\nu_{C=O}$ bands with peaks at 1 736 and 1 720 cm^{-1}, suggesting that an equilibrium exists between two conformers of the fifteen-membered ring.

(*d*) *Electronic Structures of Hydrogen Bond Systems in* (**1**) *and* (**6**).—In general, the formation of the hydrogen bond by the hydroxy group causes a shift of the ν_{OH} band to a lower wavenumber accompanied by a large increase of the A value.[15] However, when much delocalization of the OH bond electrons through the hydrogen bond system occurs in the compounds with a cyclic hydrogen bond, the A value does not rapidly increase with an increase in the shift.[16] Compounds (**1**) and (**6**) form the cyclic hydrogen bonds (**I**) and (**II**), respectively. In spite of the fact that the ν_{OH} band of the carboxy group of (**6**) shows a larger shift than that of (**1**), the A value of its band is about one-half of the value of (**1**). This indicates that the delocalization of the OH bond electrons through the sulphonamido group in (**1**) hardly occurs. This agrees with the fact that the resonance between the S=O bonds of the sulphonyl group and the lone pair or π-electrons is very small.[17] Interestingly, the cyclic hydrogen bond form (**II**) has not been found experimentally. If a contact is made between the hydroxy and carboxy groups in the interior of

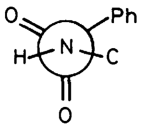
Table 5. Energy difference (ΔE) between the conformers, dipole moment (μ), and torsion angle C–N–S–C(τ) for *N*-methylbenzenesulphonamide (**11**) by MNDO calculation.

Form	ΔE/J mol^{-1}	μ/D	τ/°
(VII)	0	5.7	−90
(VIII)	5.1	6.2	180
(IX)	8.4	6.9	61

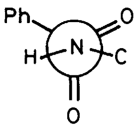
biopolymers such as enzymes and receptors, the formation of (**II**) may be possible.

(*e*) *Geometrical Resemblances of* (**1**), (**4**), *and* (**6**).—If the conformation illustrated in Figure 4 is adopted for (**1**) and (**6**) as an approximation, although it is suggested that an equilibrium in their compounds exists between the two ring-conformers, the geometrical arrangements of the functional groups in (**1**) strongly resemble the corresponding ones of (**6**).

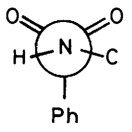
In (**4**), the conformers (**VII**)–(**IX**) for the sulphonamido group are possible by rotation along an N–S bond because the S=O bond is not linked by the intramolecular hydrogen bond. Thus, the geometries of these conformers (**11**) were optimized by the MNDO method.[18] As shown in Table 5, the conformer (**VII**) is the most stable among them and the increase in the conformational energy difference (ΔE) is consistent with the increase in the dipole moment. This result suggests that the ΔE value is primarily governed by electrostatic interaction. In addition, the S=O bond seems to be nearly parallel to the NH bond in (**VII**) because the calculated torsion angle of C–N–S–C of its form is −90°. On the basis of these results, we proposed the conformations shown in Figure 4 for (**4**) and (**5**). The conformation of the sulphonamido group in (**4**) is similar to that of (**1**). Namely, we found a geometrical resemblance between TXA$_2$R antagonists (**1**) and (**4**) and agonist (**6**) in nonpolar solvents.



(VII)



(VIII)



(IX)

In conclusion, the F.t.i.r. method used should be helpful for elucidating the conformation of prostaglandin-related compounds in solvents and the information obtained should be useful for understanding the intramolecular hydrogen bond and for investigating the structure–activity relationships.

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