FTIR Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Antagonist S-145 and Related Compounds. Part 2.[†]

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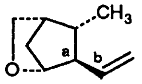
The FTIR spectra of thromboxane A_2 receptor antagonists, a S-145 analogue (**1**),[‡] ONO-3708 (**2**), a 13-APA analogue (**3**), SQ-29548 (**4**), and EP-045 (**5**), and related compounds have been measured in dilute CCl_4 and $CHCl_3$ solutions. The spectra were subjected to curve analysis in order to separate overlapping absorption bands. For (**1**)–(**5**), intramolecular hydrogen bonds involving twelve-, fourteen-, twelve-, thirteen-, and thirteen-membered rings are found between a carboxy group of the α-side chain and a functional group of the ω-side chain, respectively. In (**3**)–(**5**), these hydrogen bonds are also found to be of a zwitterion form. The formation ratio (ρ) of the intramolecular hydrogen bond in CCl_4 solution show high values of 85 for (**1**), 78 for (**2**), 75 for (**3**), 89 for (**4**), and 96% for (**5**). On the basis of these findings on the intramolecular hydrogen bonds, the conformations of (**1**)–(**5**) have been identified and are found to be similar.

Thromboxane A_2 (TXA_2)[1] is a very potent inducer of blood platelet aggregation and of contraction of arterial smooth muscle.[2] TXA_2 receptor antagonists are promising as new medicines or preventives for cardio- and cerebro-vascular diseases.[3] To carry out drug design and explain the onset mechanism of physiological activity, the active conformation of these antagonists in the TXA_2 receptor must be known. The conformer preference for the TXA_2 antagonist having α- and ω-side chains is generally governed by the environment of the active site of the TXA_2 receptor. However, this environment is not known, despite the fact that this receptor is found on circulating platelets and vasculature.

Recently, a non-polar hydrocarbon phase was reported to be suitable as the environment for the active site of the TXA_2 receptor;[4] the relative permittivity of non-polar hydrocarbons is *ca.* 2. In a previous paper,[5] we reported the conformations of the TXA_2 receptor agonist U-46619[6] and antagonists S-145[7] and BM-13177[8] in dilute CCl_4 and $CHCl_3$ solutions, assuming the existence of a hole in a protein as the binding site in the TXA_2 receptor because the continuous permittivity value of the protein is 3.5,[9] which is intermediate between the values of CCl_4 and $CHCl_3$ solvents. For these compounds, an analogous result has been obtained by conformational analyses using molecular mechanics and molecular orbital calculations.[10]

The typical TXA_2 receptor agonists and antagonists are shown in Figure 1, together with the related compounds. The conformations of the α- and ω-side chains in TXA_2, the TXA_2 receptor agonists U-44069,[6] 9,11-Azo-PGH_2,[11] and STA_2,[12] and the antagonist PTA_2[13] are presumed to be almost the same as those found for U-46619 in CCl_4 and $CHCl_3$ solutions[5] because the two side chains and their configurations in all these compounds are the same as those of U-46619. However, no information has so far been available on the exact conformation of the side chains for the TXA_2 antagonists (**1**),[14] ONO-3708 (**2**),[15] 13-APA,[16] the 13-APA analogue (**3**), SQ-29548 (**4**),[17] and EP-045 (**5**)[18] in those solutions. Of them, (**1**) with its potent inhibitory activity against platelet aggregation and with no partial agonistic activity was prepared in our laboratory.[14] Because the side chains and their configurations in (**1**) are the same as those of S-145, we became interested in comparing the conformations in both compounds in CCl_4 and $CHCl_3$ solutions from the standpoint of drug design. In order to determine the conformations of (**1**)–(**5**) in those solutions, we carried out FTIR spectra measurements for (**1**)–(**6**), (**8**), (**9**), model compounds (**10**)–(**14**) having one functional group, and 1:1 mixtures of (**10**) and (**7**) or (**11**)–(**14**) in dilute CCl_4 and $CHCl_3$ solutions and for (**3**)–(**5**) and a 1:1 mixture of (**10**) and (**13**) in a highly concentrated solution. 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**)–(**5**) and discuss the conformational resemblance between the compounds. To help determine the conformation about a C(12)–C(13) bond in U-46619, the geometry of model compound (**15**) was optimized by MINDO/3 and AM1 methods.



(**15**)

Experimental

Compounds (**1**)–(**9**) were either synthesized by us or supplied by Seno and Hagishita. Compounds (**10**)–(**14**) were commercially available. FTIR spectra were recorded on a Nicolet 20 SXB FTIR spectrometer at 27 °C. Purification of CCl_4, $CHCl_3$, and $CDCl_3$, operations for their solutions, and curve-fitting calculations for peak separation were as previously described.[5] Spectral parameters were obtained by curve-fitting calculation. Because the overtone and combination bands in the region of 3 500–3 200 cm^{-1} are very weak,[19] they were ignored in this calculation. In the Tables, ν, ε, $\Delta\nu_{1/2}$, and *A* are the band frequency, the molar absorption coefficient, the band width at half-intensity, and the integrated intensity, respectively. The ν_{OH}, ν_{NH}, $\nu_{NH_2^+}$, $\nu_{C=O}$, $\nu_{asCO_2^-}$, and $\nu_{sCO_2^-}$ bands show OH, NH, NH_2^+, C=O, antisymmetric CO_2^-, and symmetric CO_2^- stretching vibration bands, respectively, and a $\delta_{NH_2^+}$ band shows NH_2^+ in-plane bending band. ^1H NMR spectra were recorded with a Varian LX-200 FT spectrometer at 23 °C. The MINDO/3[20] and AM1[21] calculations were carried out on a VAX 6320 computer using the QCPE program No. 506 (AMPAC).

[†] Part 1 is ref. 5.

[‡] [ε]-[5*Z*)-7-{(1*R*,2*R*,3*S*,5*S*)-2-Benzenesulphonylamino-6,6-dimethylbicyclo[3.1.1]hept-3-yl}hept-5-enoic acid.

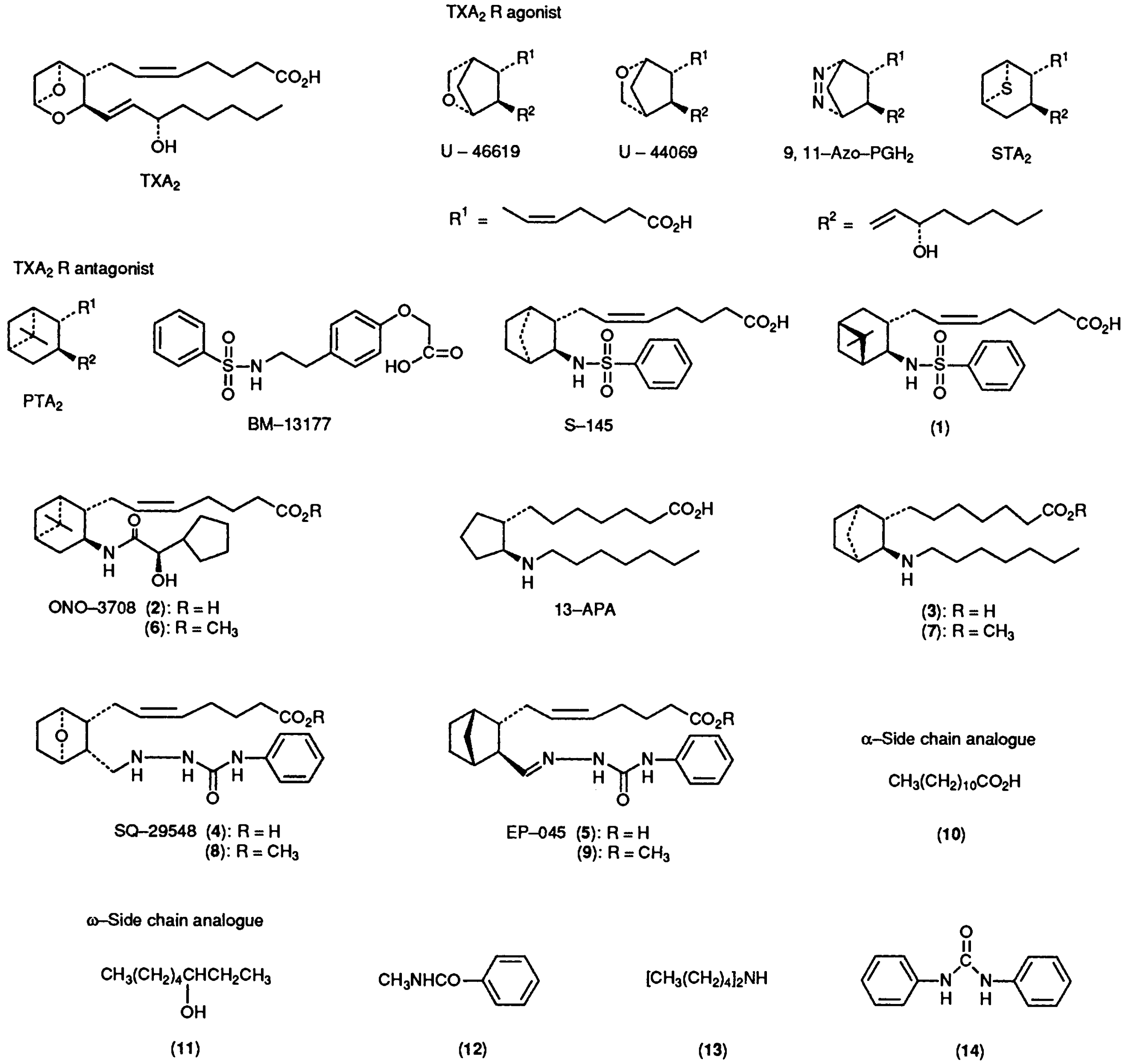


Figure 1. Typical TXA_2 receptor agonists and antagonists and related compounds.

Results and Discussion

The spectral parameters obtained for dilute CCl_4 and $CHCl_3$ solutions of (1)–(5) and the assignments of absorption bands are shown in Table 1, together with the estimated ratio (N) of the non-intramolecular hydrogen-bonded molecules. In oder to confirm these assignments for (2), (4), and (5), the FTIR spectra of their methyl esters (6), (8), and (9) were measured for these solutions and the spectral parameters and the assignments are also shown in Table 2, together with the N values. When the intramolecular hydrogen bonding is to be considered, the amount of intermolecular hydrogen-bonded molecules between the functional groups of the α- and/or ω-side chains in (1)–(9) needs to be known, although there is little possibility of intermolecular hydrogen bonds being due to the formation of intramolecular hydrogen bonds. Thus, we carried out the next examination, but compounds having a methyl ester group were excluded because of weak hydrogen bonding interaction ability.[22]

FTIR Spectra of Model Compounds **(10)**–**(14)** *and* 1:1 *Mixtures of their Compounds.*—The spectral parameters obtained for the model compounds and the mixtures are shown in Table 3; the parameters of the mixture corresponding to (1) are not tabulated, because it has been reported[5] that the mixture does not form the intermolecular hydrogen bond between (10) and ±2-*exo*-propylbicyclo[2.2.1]hept-3-*endo*-(phenylsulphonyl)-amine. The mixtures of (10) and (11) or (12), (10) and (13), and (10) and (14) correspond to the functional groups in (2), (3), and (4) or (5), respectively. The measurements were conducted in CCl_4 and $CHCl_3$ solutions at almost the same concentration as (1)–(5). The FTIR spectra of the mixtures of (10) and (8) or (9) were also measured in the same manner, although their parameters were omitted from Table 3.

In comparison with the corresponding spectral parameters in the model compounds, (8) and (9), no changes were found for the mixtures except for the mixture of (10) and (13) in $CHCl_3$ solution; the parameters for the mixtures agreed well with the sum of those of the corresponding two compounds. These results indicate that the mixtures, except for the mixture of (10) and (13) in $CHCl_3$ solution, do not form the intermolecular

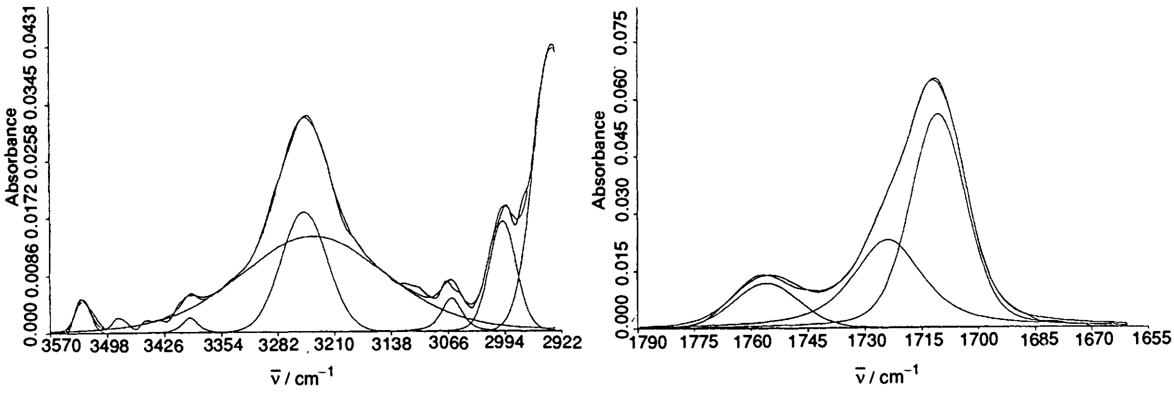


Figure 2. FTIR spectra of (1) at 3.1907 × 10^{-5} mol dm^{-3} in CCl_4 solution in a 5.0 cm cell and the results of peak separation of their spectra.

hydrogen bond between two kinds of compounds in this case. This also indicates that the changes of FTIR spectra shown in Tables 1 and 2, except for (3) in $CHCl_3$ solution, are attributable to the formation of intramolecular hydrogen bonding.

For the mixture of (**10**) and (**13**) in $CHCl_3$ solution, 22% of the $\nu_{C=O}$ bands, which are due to a carboxy group in (**10**), disappeared, and the $\nu_{asCO_2^-}$ band was observed at 1 688 cm^{-1}, indicative of intermolecular hydrogen bonding of the zwitterion form as mentioned below. For (**3**) in $CHCl_3$ solution, the formation ratio of the intramolecular hydrogen bonding of the zwitterion form showed the high value of 82%. This indicates that the greater part of the changes of FTIR spectra in (**3**) in $CHCl_3$ solution are attributable to the formation of intramolecular hydrogen bonding, since there is little possibility of intermolecular hydrogen bonding due to the formation of intramolecular hydrogen bonding.

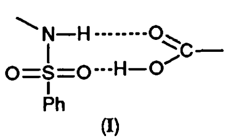
Because (**10**) forms a dimer of 14% in CCl_4 and 9% in $CHCl_3$ solutions at the concentrations measured, dimerization may occur in their solutions of (**1**)–(**5**). In order to estimate the reliable ρ ($= 100 - N - \sigma$) value, the amount of dimer of these compounds needed to be known. Regression analysis was done between the concentration ($c_f = cN/100$) of molecules having a free carboxy group and the ratio (σ%) of dimer using the spectral parameters of (**10**) reported by us,[5] where c is the total concentration. The analysis gave good relationships which can be expressed as equation (1) for CCl_4 and (2) for $CHCl_3$ solutions, where n is the number of data points and r is the correlation coefficient.

$$\log c_f = 0.245\sigma^{1/2} - 5.492\ (n = 6, r = 0.998) \quad (1)$$

$$\log c_f = 0.250\sigma^{1/2} - 4.258\ (n = 7, r = 0.996) \quad (2)$$

Assuming that the free molecules of N% in (**1**)–(**5**) exist in equilibrium with the dimer, the σ values of their compounds were approximately estimated using equations (1) and (2). However, the application of these equations to (**1**)–(**5**) may overestimate the σ values because the assumption neglects the equilibrium between the free molecules and the intramolecular hydrogen-bonded molecules in their compounds. Nevertheless, the estimated σ values in CCl_4 solution showed very low values of 0.4% for (**1**), 1.7% for (**2**), 2.0% for (**3**), 0.1% for (**4**), and 0% for (**5**) and in $CHCl_3$ solution, of 2.0% for (**1**), 5.4% for (**2**), 0% for (**3**), 2.1% for (**4**), and 3.6% for (**5**). These results indicate that, as a first approximation, the existence of dimer in these compounds can be neglected in the curve analysis for the solutions examined. However, the measured value for (**3**) in CCl_4 solution was adopted as the σ value because only (**3**) gives a dimer $\nu_{C=O}$ band with a peak at 1 709 cm^{-1}.

Intramolecular Hydrogen Bonds in (**1**).—When the hydrogen bond is formed between the XH and Y=Z groups, the XH and Y=Z stretching vibration bands, ν_{XH} and $\nu_{Y=Z}$ bands, shift to lower wavenumbers and the intensity of the ν_{XH} band in general remarkably increases.[23] For (**1**) in CCl_4 solution as shown in Figure 2, the intensities of the free ν_{OH} band at 3 529 cm^{-1} and the free $\nu_{C=O}$ band at 1 756 cm^{-1} for the carboxy group and of the free ν_{NH} band at 3 394 cm^{-1} for a sulphonamido group remarkably decreased, and new bands appeared at 3 237, 1 724 and 1 711, and 3 249 cm^{-1}, respectively. In addition, compared with the ν_{asSO_2} band at 1 353 cm^{-1} and the ν_{sSO_2} band at *ca.* 1 163 cm^{-1} observed for the sulphonamido group of (±)2-*exo*-propylbicyclo[2.2.1]hept-3-*endo*-(phenylsulphonyl)amine, the shifts to lower wavenumbers ($\Delta\nu_{asSO_2} = 32$ and $\Delta\nu_{sSO_2} =$ *ca.* 13 cm^{-1}) of corresponding bands for (**1**) were observed in CCl_4 solutions. From these findings, it is clear that (**1**) in CCl_4 solution exists in the conformation with the twelve-membered ring due to the intramolecular hydrogen bonds of (**I**) between the carboxy and the sulphonamido groups such as observed with S-145.[5]



(**I**)

The spectral behaviour of (**1**) in $CHCl_3$ solution resembled that in CCl_4 solution. This indicates that in $CHCl_3$ solution, (**1**) forms the intramolecular hydrogen bonds (**I**) as well as in CCl_4 solution. The ρ values of (**1**) are estimated to be 85% in CCl_4 and 54% in $CHCl_3$ solutions. As shown in Figure 2, (**1**) in CCl_4 solution gives two intramolecular hydrogen-bonded $\nu_{C=O}$ bands, suggesting that an equilibrium exists between two conformers of the twelve-membered ring. These findings are similar to those found[5] for S-145 and indicate that the conformation of (**1**) is identical to that of S-145 in CCl_4 and $CHCl_3$ solutions. This suggests that the conformation is affected little by the steric hindrance of the bicyclic ring as presumed for familiar types of U-46619 in the Introduction. Furthermore, we have reported[24] that three stereoisomers of S-145, which possess TXA_2 receptor antagonist properties, have a conformation similar to that of S-145 because they display similar spectral behaviours. This also suggests that the conformation of the ring formed by (**I**) is not appreciably influenced by the configurations of the α- and ω-side chains in this case.

Intramolecular Hydrogen Bonds in (**2**) *and* (**6**).—For (**2**) in the CCl_4 solution as shown in Figure 3, the intensities of the free ν_{OH} bands at 3 532 cm^{-1} for the carboxy group and at

Table 1. FTIR spectral data of compounds (1)–(5) in CCl_4 and $CHCl_3$ solutions.

Compound	Assignment[a]		CCl_4 (cell length = 5.0 cm)						$CHCl_3$ (cell length = 1.0 cm)					
			ν/cm^{-1}	$\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$	$\Delta\nu_{1/2}/cm^{-1}$	$A/10^{-8}\ cm^2\ s^{-1}\ molecule^{-1}$	N^b (%)	$c/10^{-5}\ mol\ dm^{-3}$	ν/cm^{-1}	$\varepsilon/\ dm^3\ mol^{-1}\ cm^{-1}$	$\Delta\nu_{1/2}/cm^{-1}$	$A/10^{-8}\ cm^2\ s^{-1}\ molecule^{-1}$	N^b (%)	$c/10^{-4}\ mol\ dm^{-3}$
(1)	$\nu_{OH}(\alpha)$	F	3 528.9	29.8	22.9	3.4		3.1907	3 513.5	53.3	44.8	29.4		2.7123
		H	3 237	90	217	232			*c*					
	$\nu_{C=O}(\alpha)$	F	1 756.0	73.5	20.2	18.1	14.6		1 748.1	183.1	33.1	83.1	45.8	
		H	1 724.0	144.4	21.7	42.5			1 731.4	87.6	37.4	40.0		
		H	1 710.7	350.6	17.2	77.5			1 706.5	144.9	24.9	46.9		
	$\nu_{NH}(\omega)$	F	3 394.4[d]	12.7	22.8	4.0			3 388.4	43.5	34.3	19.3		
		H	3 249	113	69	95			~3 260	*c*				
(2)	$\nu_{OH}(\alpha)$	F	3 532.1	36.3	25.8	14.0		3.0392	3 514.3	57.2	48.9	38.1		2.8016
		H	3 154	59	233	168			*c*					
	$\nu_{C=O}(\alpha)$	F	1 756.8	110.4	20.3	27.5	22.0		1 743.3	298.4	32.3	122.6	74.6	
		H	1 732.7	217.8	22.9	74.3			1 715.2	118.4	30.7	50.2		
		H	1 721.7	155.8	25.4	50.7								
	$\nu_{OH}(\omega)$	F	3 627.2	24.1	22.8	7.3			3 620.1	38.3	30.6	12.7		
		H	3 403	35	178	72			3 392.4	30.3	136.0	49.2		
	$\nu_{NH}(\omega)$	F	3 424.7	54.0	16.8	13.5			3 411	61	31	23		
		F	3 409.7	30.1	21.5	8.0								
		H	3 362.5	18.5	36.5	9.4								
	$\nu_{C=O}(\omega)$	F	1 673.6	275.1	13.8	46.4			1 668.7	240.3	19.1	65.2		
		F							1 655.7	231.8	22.0	67.8		
		H	1 663	168	49	*c*			1 636.1	125.0	29.6	44.4		
(3)	$\nu_{OH}(\alpha)$	F	3 531.0	45.5	24.2	13.9		3.1818	3 515.2	16.7	45.1	9.1		2.9655
	$\nu_{C=O}(\alpha)$	F	1 758.5	112.9	18.8	20.3	22.5		1 743.8	70.7	35.1	33.8	17.7	
		D	1 709.3	20.1	12.9	3.2	(2.4)[e]							
	$\nu_{asCO_2^-}(\alpha)$	H	1 706.8	85.1	46.8	46.7			1 690.0	89.0	51.7	~59		
	$\nu_{NH_2^+}(\omega)$	H	~2 700	*f*					~2 700	*f*				
	$\delta_{NH_2^+}(\omega)$	H	*c*						1 636	58	~83	*c*		

Table 1 (*continued*)

			CCl_4 (cell length = 5.0 cm)						$CHCl_3$ (cell length = 1.0 cm)					
Compound	Assignment[a]		ν/cm^{-1}	ε/dm^3 mol^{-1} cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	A/10^{-8} cm^2 s^{-1} molecule^{-1}	N[b] (%)	c/10^{-5} mol dm^{-3}	ν/cm^{-1}	ε/dm^3 mol^{-1} cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	A/10^{-8} cm^2 s^{-1} molecule^{-1}	N[b] (%)	c/10^{-4} mol dm^{-3}
(4)	$\nu_{OH}(\alpha)$	F	3 531.2	25.7	25.6	8.2		3.3395	3 516.6	42.7	52.9	25.9		2.8491
	$\nu_{C=O}(\alpha)$	F	1 755.2	55.8	20.4	14.3	11.1		1 744.4	178.9	32.8	73.6	44.7	
	$\nu_{asCO_2^-}(\alpha)$	H	1 659.9	208.8	23.6	*c*			1 653.4	187.9	31.2	~71		
	$\nu_{NH}(\omega)$	F	3 367.6	79.4	40.8	52.8			3 366.6	109.5	47.0	76.5		
	$\nu_{NH}(\omega)$	H	3 232.5	95.2	110.4	148.1			~3 226	*c*				
	$\nu_{NH_2^+}(\omega)$	H	3 073.3	67.4	131.9	108.1			*c*					
		H	2 634	24	287	*c*			*c*					
	$\nu_{C=O}(\omega)$	F	1 709.0	619.7	20.4	175.1			1 703.8	412.0	29.8	165.7		
		F	1 684.2	87.2	15.3	16.4			1 679.2	126.4	35.6	57.5		
(5)	$\nu_{OH}(\alpha)$	F	*g*					3.1604	3 513.1	56.6	45.6	34.0		2.8684
	$\nu_{C=O}(\alpha)$	F	1 757.0	19.0	17.0	4.0	3.8		1 744.5	228.6	33.3	95.0	57.2	
	$\nu_{asCO_2^-}(\alpha)$	H	1 659.7	434.3	21.7	*c*			1 655.4	185.8	28.3	65.8		
	$\nu_{NH}(\omega)$	F	3 379.4	130.7	28.2	50.4			3 386.0	111.2	31.5	47.6		
		H[h]							3 358.2	58.1	24.2	20.6		
		H	3 210.4	133.2	91.5	190.0			*c*					
	$\nu_{NH^+}(\omega)$	H	2 900	90	250	285			*c*					
		H	2 564	60	228	*c*			*c*					
	$\nu_{C=O}(\omega)$	F	1 706.6	1 254.8	13.9	264.9			1 698.9	651.2	31.4	259.6		

[a] α and ω in parentheses show two side chains, respectively, and F, H, and D also show free, intramolecular hydrogen-bonded, and dimer bands, respectively. [b] Ratio of non-intramolecular hydrogen-bonded molecules ($N = \varepsilon/501.9 \times 100$ in CCl_4 and $N = \varepsilon/399.9 \times 100$ in $CHCl_3$), where 501.9 and 399.9 are the ε values of 100% free $\nu_{C=O}$ band of (**10**) in CCl_4 and $CHCl_3$ solutions, respectively.[5] [c] The parameters were not obtained because the band was overlapped by solvent absorptions. [d] The ε and A values were estimated to be approximately 14.6% of the parameters in (±)2-*exo*-propylbicyclo[2.2.1]hept-3-*endo*-(phenylsulphonyl) amine[5] because the band is weak and was overlapped by intramolecular hydrogen-bonded ν_{OH} and ν_{NH} bands. [e] The value given in parenthesis is the ratio of dimers ($\sigma = \varepsilon/822.6 \times 100$), where 822.6 are the true per $\nu_{C=O}$ band of dimer in CCl_4 solution.[5] [f] The parameters could not be obtained because the band was very weak and broad. [g] The parameters could not be obtained because the N value was very small. [h] The peak was assigned to the intramolecular hydrogen-bonded ν_{NH} band of urea group as in (**VIII**) as well as in (**9**).

Table 2. FTIR spectral data of compounds (**6**), (**8**), and (**9**) in CCl_4 and $CHCl_3$ solutions.

			CCl_4 (cell length = 5.0 cm)						$CHCl_3$ (cell length = 1.0 cm)					
Compound	Assignment[a]		ν/cm^{-1}	ε/dm^3 mol^{-1} cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	A/10^{-8} cm^2 s^{-1} molecule^{-1}	N^b (%)	c/10^{-5} mol dm^{-3}	ν/cm^{-1}	ε/dm^{3}mol^{-1} cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	A/10^{-8} cm^2 s^{-1} molecule^{-1}	N^b (%)	c/10^{-4} mol dm^{-3}
(**6**)	$\nu_{C=O}(\alpha)$	F	1 741.2	393.6	16.1	83.7	71.6	2.9587	1 730.8	375.5	23.8	114.8	92.3	2.6853
		H	1 725.3	165.6	14.9	34.7			1 718.8	85.3	17.4	23.6		
	$\nu_{OH}(\omega)$	F	3 629.9	41.2	20.2	10.6			3 618.6	49.3	29.6	16.7		
		H	3 445	23	126	36			3 424	20	127	30		
	$\nu_{NH}(\omega)$	F	3 419.9	73.4	21.6	26.7			3 413.4	80.7	27.3	26.5		
	$\nu_{C=O}(\omega)$	F	1 674.1	567.4	18.6	~124			1 669.1	331.5	18.2	88.2		
		F							1 656.1	303.1	19.1	70.5		
(**8**)	$\nu_{C=O}(\alpha)$	F	1 741.0	400.8	16.0	86.5	72.9	3.0037	1 729.5	420.7	27.3	150.1	103.5	2.7297
		H	1 724.2	188.5	18.6	42.8								
	$\nu_{NH}(\omega)$	F	3 407.2	26.9	21.1	8.0								
		H[c]	3 378.4	94.6	34.1	46.2			3 371.7	116.5	50.0	78.6		
		H	3 346	20	102	24								
	$\nu_{C=O}(\omega)$	F	1 706.7	427.1	19.0	107.9			1 692.0	447.3	30.0	170.9		
		F	1 687.5	195.3	22.0	54.5			1 666.9	104.2	32.2	40.9		
(**9**)	$\nu_{C=O}(\alpha)$	F	1 741.3	420.4	16.2	85.7	76.4	3.0137	1 730.1	416.7	25.4	133.3	102.5	3.0086
		H	1 724.9	150.3	20.4	40.3								
	$\nu_{NH}(\omega)$	F	3 394.5	142.3	27.9	52.1			3 387.5	139.2	30.2	56.4		
		H	3 361.2	61.1	18.3	17.0			3 356.8	84.0	22.1	29.0		
		H	3 315.6	13.6	50.2	8.9								
	$\nu_{C=O}(\omega)$	F	1 711.0	679.8	23.9	211.3			1 703.3	349.6	24.9	120.5		
		F							1 691.1	532.0	19.7	146.6		

[a] See Table 1, footnote *a*. [b] Ratio of non-intramolecular hydrogen-bonded molecules ($N = \varepsilon/550.0 \times 100$ in CCl_4 and $N = \varepsilon/406.7 \times 100$ in $CHCl_3$), where 550.0 and 406.7 are the ε values of methyl stearate in CCl_4 and $CHCl_3$ solutions, respectively.[5] [c] The peak was assigned to the free ν_{NH} and intramolecular hydrogen-bonded ν_{NH} bands of urea group as in (**VI**) (see text).

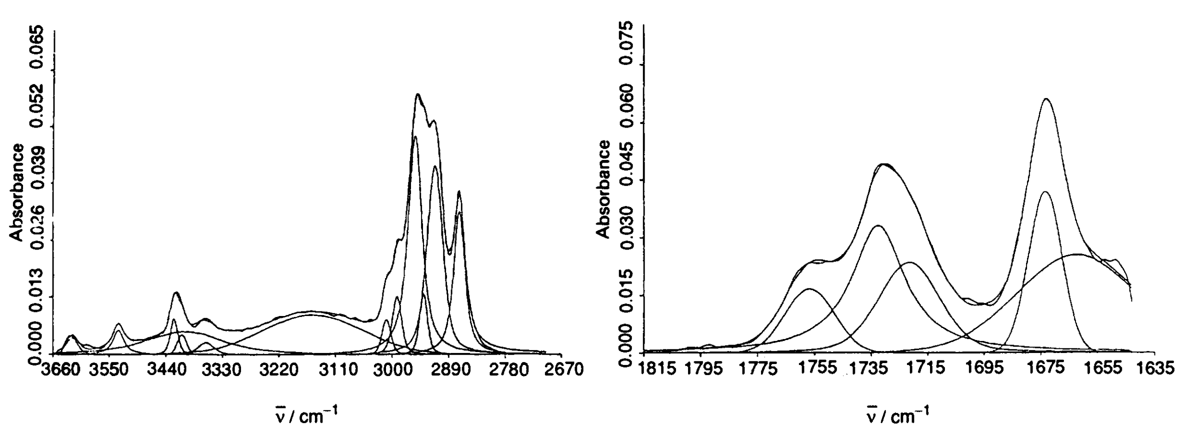
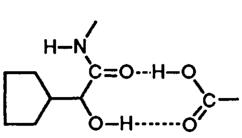


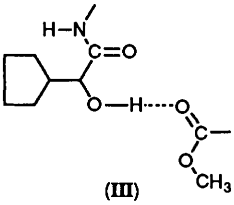
Figure 3. FTIR spectra of (**2**) at 3.0392 × 10^{-5} mol dm^{-3} in CCl_4 solution in a 5.0 cm cell and the results of peak separation of their spectra.

3 627 cm^{-1} for a hydroxy group remarkably decreased and new broad bands appeared at 3 154 and 3 403 cm^{-1}, respectively. The basis of this assignment is as follows: the latter broad band is analogous to that of the intramolecular hydrogen-bonded hydroxy group in the ω-side chain as in (**6**) described below. The intensities of the free $\nu_{C=O}$ bands at 1 757 cm^{-1} for the carboxy group and at 1 674 cm^{-1} for the amido group in (**2**) also decreased and a new band appeared at 1 733 and 1 722 cm^{-1} and at 1 663 cm^{-1}, respectively. The latter free $\nu_{C=O}$ band agreed with that in (**6**). From these findings, it is obvious that (**2**) in CCl_4 solution exists in a conformation with a fourteen-membered ring formed by intramolecular hydrogen bonds of (**II**) between the α- and the ω-side chains. In CCl_4 solution, (**2**) exhibits two intramolecular hydrogen-bonded $\nu_{C=O}$ bands for the carboxy group, suggesting that an equilibrium exists between two conformers in the fourteen-membered ring. The split free ν_{NH} bands at 3 424 and 3 410 cm^{-1} for the amido group of (**2**) were presumed to be due to the conformational change in this ring. The weak ν_{NH} band in (**2**) was further observed at 3 363 cm^{-1}, indicative of the existence of other intramolecular hydrogen bonding. As its amount was estimated to be very small, the hydrogen bonding was neglected.



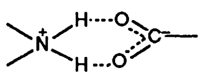
(**II**)

For (**6**) in CCl_4 solution, the intensities of the free $\nu_{C=O}$ band at 1 741 cm^{-1} for the methyl ester and the free ν_{OH} band at 3 630 cm^{-1} for the hydroxy groups decreased and new bands were observed at 1 725 and 3 445 cm^{-1}, respectively. The latter new peak was assigned to the intramolecular hydrogen-bonded ν_{OH} band, because its peak has a higher wavenumber than that of the free ν_{NH} band of the amido group. In addition, the free $\nu_{C=O}$ band of the amido group was observed at 1 674 cm^{-1}. These results indicate that intramolecular hydrogen bond (**III**) involving a fifteen-membered ring in (**6**) is formed between the α- and ω-side chains. Since the spectral behaviours of (**2**) and (**6**) in $CHCl_3$ solution are similar to those in CCl_4 solution, their compounds are anticipated to form intramolecular hydrogen bonds (**II**) and (**III**) in $CHCl_3$ solution, respectively. The ρ values of (**2**) and (**6**) are estimated to be 78 and 28% in CCl_4 and 25 and 8% in $CHCl_3$ solutions, respectively. The value of (**6**) is smaller than that of (**2**) because there is only one hydrogen bond in (**6**).



(**III**)

Intramolecular Hydrogen Bonds in (**3**) *and* (**7**).—For (**3**) in CCl_4 solution as shown in Figure 4, the intensities of the free ν_{OH} band at 3 531 cm^{-1} and the free $\nu_{C=O}$ band at 1 759 cm^{-1} for the carboxy group remarkably decreased and new weak bands appeared at *ca.* 2 700 and 1 707 cm^{-1}. For (**3**) in $CHCl_3$ solution, the intensities of these bands at 3 515 and 1 744 cm^{-1} also decreased and new weak bands appeared at *ca.* 2 700, 1 690, and 1 636 cm^{-1}. The ν_{OH} and $\nu_{C=O}$ bands due to the carboxy group almost disappeared. In (**3**) with the carboxy and the amino groups in one molecule, intramolecular ionic hydrogen bonds as in the zwitterion form (**IV**) can be expected to occur. Therefore, in order to explain the changes in these spectra, we made assignments for the new weak bands of (**3**).



(**IV**)

As the intermolecular ionic hydrogen bonds would be formed in the mixture of (**10**) and (**13**) as in (**IV**), the concentration dependence of FTIR spectra of this mixture was measured in CCl_4 solution. The spectra and the spectral parameters obtained are shown in Figure 5 and Table 3, respectively. In a highly concentrated CCl_4 solution, the intensities of the free ν_{OH} band at 3 532 cm^{-1} and the free $\nu_{C=O}$ band at 1 759 cm^{-1} for the carboxy group remarkably decreased and new weak bands were observed at *ca.* 2 700, 1 699, and 1 621 cm^{-1} in this mixture. The FTIR spectral data of the mixture of (**10**) and (**13**), and (**3**) to (**5**) and the ^1H NMR spectral data of its mixture and (**3**) observed at a concentration above 1 × 10^{-2} mol dm^{-3} are given in Table 4. The free ν_{OH}, the free $\nu_{C=O}$, and the dimer $\nu_{C=O}$ bands for the carboxy group of these compounds almost disappeared in the CCl_4, $CHCl_3$, and $CDCl_3$ solutions examined, respectively.

For the mixture of (**10**) and (**13**) and for (**3**), three new bands were observed in the range between 1 750 and 1 500 cm^{-1} and the middle bands disappeared on substitution of the deuterium atom by evaporating the acetone–D_2O solution. Furthermore, ^1H chemical shifts for NH_2^+ groups of the mixture and (**3**) were

Table 3. FTIR spectral data of compounds **(10)**–**(14)** and 1:1 mixtures of **(10)** and **(11)**, **(10)** and **(12)**, **(10)** and **(7)**, **(10)** and **(13)**, and **(10)** and **(14)** in CCl_4 and $CHCl_3$ solutions.

			CCl_4 (cell length = 5.0 cm)						$CHCl_3$ (cell length = 1.0 cm)					
Compound	Assignment[a]		ν/cm^{-1}	$\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$	$\Delta\nu_{1/2}/cm^{-1}$	$A/10^{-8}\ cm^2\ s^{-1}\ molecule^{-1}$	N^b (%)	$c/10^{-5}$ mol dm^{-3}	ν/cm^{-1}	$\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$	$\Delta\nu_{1/2}/cm^{-1}$	$A/10^{-8}\ cm^2\ s^{-1}\ molecule^{-1}$	N^b (%)	$c/10^{-4}$ mol dm^{-3}
(10)	ν_{OH}	F	3 532.9	54.2	22.9	46.8		3.2248	3 514.4	106.7	45.7	61.5		3.0051
	$\nu_{C=O}$	F	1 758.5	434.8	19.4	108.9	86.6		1 745.4	381.4	32.2	154.8	95.4	
		D	1 711.0	113.8	13.2	21.0	(13.8)[c]		1 707.1	59.0	16.9	12.2	(8.6)[c]	
(11)	ν_{OH}	F	3 627.4	51.9	22.2	16.1		4.0251	3 614.0	51.6	35.1	21.7		3.1444
(12)	ν_{NH}	F	3 475.6	100.1	17.1	24.3		3.1739	3 467.6	103.9	22.7	32.0		2.9815
	$\nu_{C=O}$	F	1 679.1	637.2	14.6	117.7			1 669.6	210.3	17.2	44.2		
		F							1 658.3	378.5	17.1	96.9		
(13)	ν_{NH}	F	*d*					3.1613	*d*					3.3342
(14)	ν_{NH}	F	3 443.7	73.3	11.4	10.3		3.1283	3 437.4	69.8	12.3	10.5		3.0200
		F	3 428.3	198.0	13.8	38.0			3 421.2	260.9	19.3	70.0		
	$\nu_{C=O}$	F	1 728.6	183.7	9.6	21.6			1 722.2	83.1	16.7	16.9		
		F	1 707.2	488.8	17.9	117.5			1 701.4	308.1	16.8	70.2		
		F							1 683.7	400.9	25.4	127.3		
(10)[e] and	ν_{OH}	F	3 532.4	149.6	23.0	49.6		3.9935	3 514.2	105.3	44.5	61.5		3.1349
	$\nu_{C=O}$	F	1 758.3	414.3	20.3	113.2	82.5		1 745.5	372.4	31.9	148.7	93.1	
		D	1 710.9	163.0	14.5	35.8	(19.8)[c]		1 707.2	60.7	16.2	12.0	(8.9)[c]	
(11)[e]	ν_{OH}	F	3 629.2	54.0	18.9	13.4		4.0251	3 615.4	50.7	36.6	20.0		3.1444
(10)[e] and	ν_{OH}	F	3 532.5	153.0	23.3	48.3		3.1749	3 514.6	110.4	45.1	60.9		3.0950
	$\nu_{C=O}$	F	1 758.6	417.0	19.3	110.6	83.1		1 745.6	371.7	31.4	147.2	92.9	
		D	1 710.8	90.1	11.6	12.8	(11.0)[c]		1 707.3	53.7	15.4	12.3	(7.9)[c]	
(12)[e]	ν_{NH}	F	3 475.6	95.3	18.1	27.3		3.1812	3 467.5	112.1	23.6	32.9		3.1369
	$\nu_{C=O}$	F	1 679.2	589.0	14.1	108.4			1 669.2	225.5	17.2	47.4		
		F							1 658.0	385.1	16.9	101.1		
(10)[e] and	ν_{OH}	F	3 532.4	149.5	23.8	49.6		4.0934						
	$\nu_{C=O}$	F	1 758.8	425.8	18.8	106.1	84.8							
		D	1 710.9	143.4	13.6	27.2	(17.4)[c]							
(7)[e]	$\nu_{C=O}$	F	1 741.4	555.4	16.1	121.4	(101.0)[f]	3.8455						

Table 3 (*continued*)

Compound	Assignment[a]		CCl$_4$ (cell length = 5.0 cm)						CHCl$_3$ (cell length = 1.0 cm)					
			ν/cm^{-1}	ε/dm^3 mol^{-1} cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	A/10^{-8} cm^2 s^{-1} molecule^{-1}	N^b (%)	c/10^{-5} mol dm^{-3}	ν/cm^{-1}	ε/dm^3 mol^{-1} cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	A/10^{-8} cm^2 s^{-1} molecule^{-1}	N^b (%)	c/10^{-4} mol dm^{-3}
(10)^e and	ν_{OH}	F	3 532.8	152.9	24.0	51.3		3.5842	3 514.4	79.4	46.2	46.5		2.9752
	$\nu_{C=O}$	F	1 758.6	413.4	19.3	112.3	82.4		1 745.3	293.9	32.0	122.4	73.5	
		D	1 710.6	116.3	12.3	19.5	(14.1)^c		1 707.6	34.3	15.8	6.7	(5.0)^c	
	$\nu_{asCO_2^-}$	H							1 688	27	50	16		
(13)^e	ν_{NH}	F	*d*					3.9517	*d*					3.2601
(10)^e and	ν_{OH}	F	3 532.1	11.5	23.3	3.4		454.46^g						
	$\nu_{C=O}$	F	1 759.2	32.7	18.8	8.8	6.5							
		D	1 711.2	94.8	14.0	18.4	(11.5)^c							
	$\nu_{asCO_2^-}$	H	1 698.5	99.5	62.1	75.1								
(13)^e	$\nu_{NH_2^+}$	H	~2 700	*h*				493.96^g						
	$\delta_{NH_2^+}$	H	1 621.4	88.1	36.4	*i*								
(10)^e and	ν_{OH}	F	3 532.2	152.2	22.8	44.0		3.1310	3 514.4	108.5	46.9	63.2		3.0900
	$\nu_{C=O}$	F	1 758.4	406.6	19.7	106.5	81.0		1 745.3	378.7	32.3	154.7	94.7	
		D	1 709.8	135.6	15.0	28.3	(16.5)^c		1 707.2	62.6	16.8	12.9	(9.2)^c	
(14)^e	ν_{NH}	F	3 444.3	79.1	9.5	9.2		3.1001	3 438.0	73.6	11.8	13.8		3.1263
		F	3 428.1	195.7	15.0	38.9			3 421.4	254.2	19.6	70.6		
	$\nu_{C=O}$	F	1 728.7	187.8	10.1	23.3			1 721.8	74.9	17.4	15.9		
		F	1 707.2	477.2	17.8	113.4			1 701.2	326.6	16.9	78.1		
		F							1 683.8	399.7	25.6	132.8		

[a] See Table 1, footnote *a*. [b] See Table 1, footnote *b*. [c] The values given in parentheses are the 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 true ε value per $\nu_{C=O}$ band of dimer of **(10)** in CCl$_4$ and CHCl$_3$ solutions, respectively.[5] [d] The parameters could not be obtained because the band was very weak. In neat sample the hydrogen-bonded ν_{NH} band was barely observed at 3 286 cm^{-1}. [e] Mixture. [f] See Table 2, footnote *b*. [g] Cell length = 0.5 cm. [h] The parameters could not be obtained because the band was very weak and broad. [i] The parameter could not be obtained because the band was overlapped by solvent absorptions.

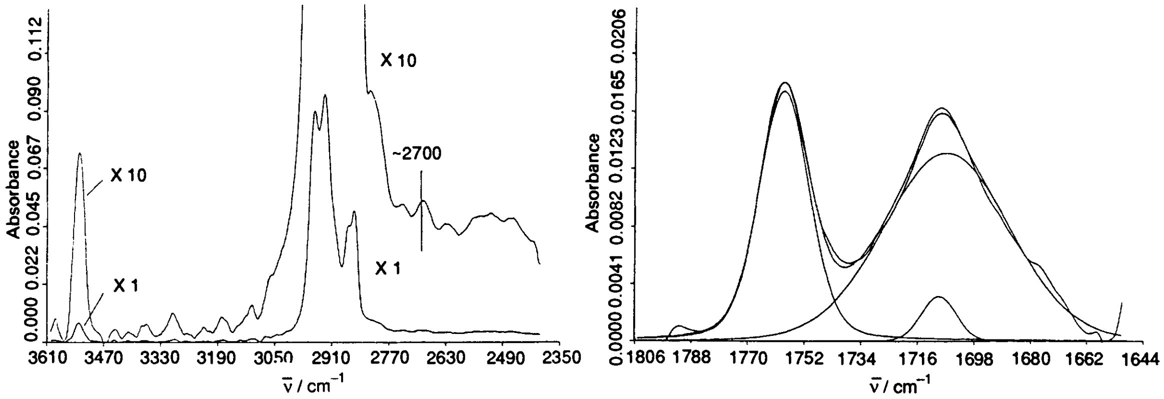


Figure 4. FTIR spectra of (3) at 3.1818 × 10^{-5} mol dm^{-3} in CCl_4 solution in a 5.0 cm cell and the result of peak separation of a spectrum.

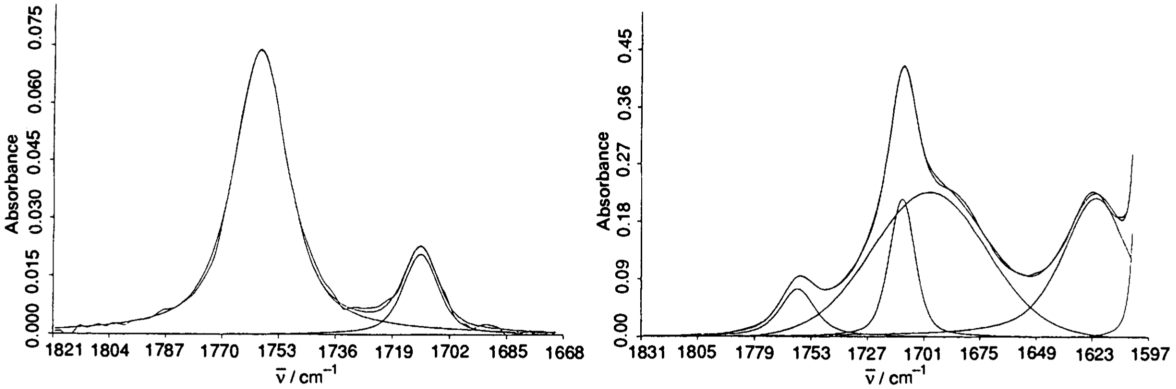


Figure 5. FTIR spectra of 1:1 mixtures of (10) and (13) in CCl_4 solution and the results of peak separation of their spectra. Spectra were obtained using a 5.0-cm cell; (10) 3.5842 × 10^{-5} and (13) 3.9517 × 10^{-5} mol dm^{-3} (left) and a 0.5 cm cell; (10) 4.5446 × 10^{-3} and (13) 4.9396 × 10^{-3} mol dm^{-3} (right).

Table 4. FTIR spectral data of 1:1 mixture of (10) and (13) and compounds (3)–(5) and ^{1}H NMR spectral data of 1:1 mixture of (10) and (13) and compound (3).

Compound	$\nu_{asCO_2^-}$/cm^{-1}	$\delta_{NH_2^+}$[a]/cm^{-1}	$\nu_{sCO_2^-}$/cm^{-1}	$\delta_{H(NH_2^+)}$[b]/ppm	c/10^{-2} mol dm^{-3}	Solvent[c]
(10) + (13)	1 711.2	1 622.8	1 549.2		~4[d]	CCl_4
(10) + (13)	1 687.4	1 622.8	1 549.2		~5[d]	$CHCl_3$
(10) + (13)	1 687.7	1 622.9	1 548.6	6.02	1.2[d]	$CDCl_3$
(3)	1 685.3	1 623.7	1 551.7	5.68	1.3	$CDCl_3$
(3)	1 685.9	1 621.6	1 554.9		~4	$CHCl_3$
(4)[e]	~1 655		1 541.0		~2	$CHCl_3$
(5)[f]	1 655.0		1 540.8		~2	$CHCl_3$

[a] On substitution of the deuterium atom, the band disappears. [b] Chemical shift of the NH_2^+ protons from TMS. [c] Cell length is 0.1 cm for $CDCl_3$ and 0.025 cm for $CHCl_3$ and CCl_4. [d] The value is the concentration of (10) and (13). [e] The $\nu_{C=O}$ bands of the urea group were observed at 1 706 and 1 687 cm^{-1}. [f] The $\nu_{C=O}$ band of the urea group was observed at 1 699 cm^{-1}.

the peaks in the region of 1 623 cm^{-1} were assigned to the $\delta_{NH_2^+}$ band. However, the peaks in the region of 1 700 cm^{-1} are thought to be at wavenumbers generally considered too high for the $\nu_{asCO_2^-}$ band. It has been reported[25] that the $\nu_{asCO_2^-}$ bands for $CF_3CO_2^-$ and $CCl_3CO_2^-$ ions, which form a very strong hydrogen bond in $CHCl_3$ solution, appear at wavenumbers above 1 747 and 1 732 cm^{-1}, respectively, and that the formation of the $CO_2^- \cdots HB^+$ bond causes the shift of the $\nu_{asCO_2^-}$ band to a higher wavenumber. Based on these findings, the three peaks observed in our mixture and (3) were assigned to the bands as shown in Table 4. The broad peaks in the region of *ca.* 2 700 cm^{-1} in these compounds were also assigned to the hydrogen-bonded $\nu_{NH_2^+}$ band. Clearly, (3) and the mixture of (10) and (13) in the highly concentrated CCl_4 and $CHCl_3$ solutions form intermolecular hydrogen bonds of the zwitterion form (IV), in spite of the fact that they are scarcely formed in dilute solutions.

Since the new bands observed for (3) in dilute CCl_4 and $CHCl_3$ solutions are similar to those for the mixture and (3) in the highly concentrated solutions, their bands were assigned as shown in Table 3. This indicates that the intramolecular ionic hydrogen bonds (IV) involving the twelve-membered ring in (3) are formed between the α- and ω-side chains in these solutions. The ρ values of (3) are estimated to be 75% in CCl_4 and 82% in $CHCl_3$ solutions. The latter is larger than the former and different from those in (1), (2), (4), and (5). Thus, intermolecular ionic hydrogen bonding might occur in the $CHCl_3$ solution of (3) as mentioned above. For the mixture of (10) and (7) in CCl_4 solution, the methyl ester group of (7) revealed only the free $\nu_{C=O}$ band at 1 741 cm^{-1} and the spectral parameters of the mixture agreed well with the sum of those of the two compounds as shown in Table 3. This suggests that this mixture does not form the intermolecular hydrogen bond between (10) and (7) in the CCl_4 solution measured and (7) does not form the intramolecular one between the α- and ω-side chains.

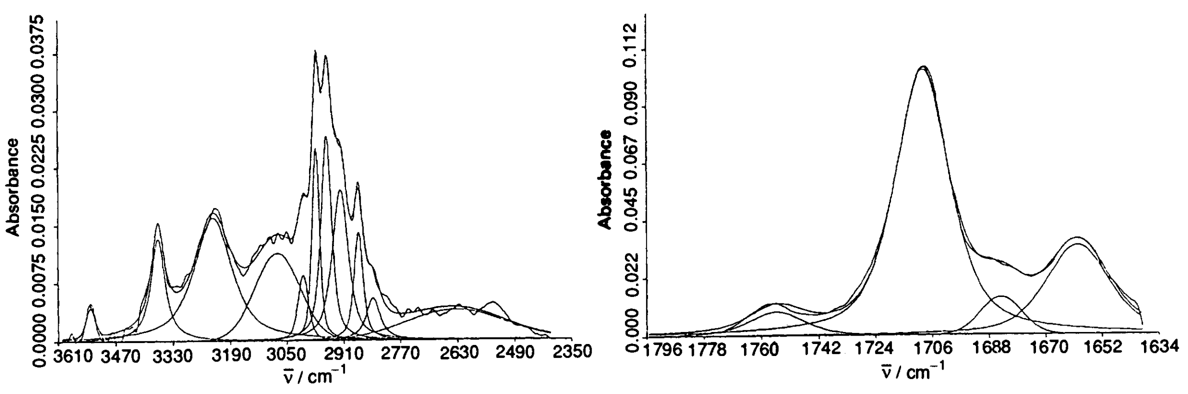
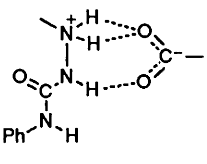
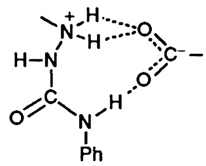


Figure 6. FTIR spectra of (4) at 3.3395 × 10^{-5} mol dm^{-3} in CCl_4 solution in a 5.0 cm cell and the results of peak separation of their spectra.

Intramolecular Hydrogen Bonds in (**4**) *and* (**8**).—For (**4**) in CCl_4 solution as shown in Figure 6, the intensities of the free ν_{OH} band at 3 531 cm^{-1} and the free $\nu_{C=O}$ band at 1 755 cm^{-1} for the carboxy group remarkably decreased and new bands appeared at 3 073, 2 634, and 1 660 cm^{-1}. Furthermore, the free ν_{NH}, the intramolecular hydrogen-bonded ν_{NH}, and two free $\nu_{C=O}$ bands of the urea group were observed at 3 368, 3 233, and 1 709 and 1 684 cm^{-1}, respectively. These free $\nu_{C=O}$ bands correspond to those at 1 707 and 1 688 cm^{-1} for the urea group of (**8**). This indicates that a C=O bond of the urea in (**4**) does not take part in the intramolecular hydrogen bonding. In $CHCl_3$ solution at *ca.* 2 × 10^{-2} mol dm^{-3}, the free $\nu_{C=O}$ band of the carboxy group in (**4**) disappeared and new bands were observed at *ca.* 1 655 and 1 541 cm^{-1}. Because this spectral behaviour resembles that of the mixture of (**10**) and (**13**), the former and the latter peaks were assigned to the $\nu_{asCO_2^-}$ and $\nu_{sCO_2^-}$ bands, respectively. In dilute $CHCl_3$ and CCl_4 solutions, (**4**) gave peaks at 1 653 and 1 660 cm^{-1}, respectively, which correspond to the former band. Therefore, these peaks were assigned to the $\nu_{asCO_2^-}$ band and the new bands at 3 073 and 2 634 cm^{-1}, to the $\nu_{NH_2^+}$ bands. From these results, we inferred that the intramolecular hydrogen bonds of the zwitterion form (**Va**) or (**Vb**) involving the thirteen-membered ring in (**4**) are formed between the α- and ω-side chains.



(**Va**)

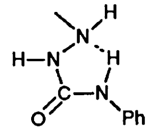


(**Vb**)

In general, 1,3-disubstituted ureas exist in *Z*/*Z* conformation as in (**Va**) and the free ν_{NH} bands of their compounds appear at wavenumbers above 3 410 cm^{-1} in CCl_4 solution,[26] but the band is shifted to a lower wavenumber by a conformational change from *Z*/*Z* to *E*/*Z* as in (**Vb**).[26a,27] Since (**4**) gives the free ν_{NH} band at 3 368 cm^{-1}, it seems reasonable to assume that its intramolecular hydrogen-bonded structure is (**Vb**) rather than (**Va**), but no direct evidence is available on these structures. The spectral behaviour of (**4**) in $CHCl_3$ solution is similar to that in CCl_4 solution. This suggests that in $CHCl_3$ solution, the intramolecular hydrogen-bonded structure of (**4**) is the same as that described above. The ρ value of (**4**) is estimated to be 89% in CCl_4 and 55% in $CHCl_3$ solutions.

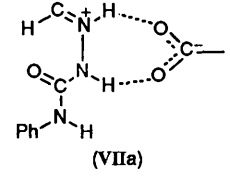
For (**8**) in CCl_4 solution, the intensity of the free $\nu_{C=O}$ band at 1 741 cm^{-1} for the methyl ester group decreased, a new band appeared at 1 724 cm^{-1}, and the intramolecular hydrogen bonded ν_{NH} band of the urea group was observed at 3 346 cm^{-1}. These indicate that the intramolecular hydrogen bond in (**8**) is formed between a C=O bond of the methyl ester and either of the NH bonds of the urea group. In $CHCl_3$ solution, (**8**) does not form the intramolecular hydrogen bonding because only the free $\nu_{C=O}$ band for the methyl ester group was observed at 1 730 cm^{-1}. The ρ value of (**8**) is also estimated to be 27% in CCl_4 and 0% in $CHCl_3$ solutions.

In addition, the ν_{NH} bands of the urea group in (**8**) were observed at 3 407 and 3 378 cm^{-1} in CCl_4 and 3 372 cm^{-1} in $CHCl_3$ solution; the band at 3 407 cm^{-1} is small. Compared with the free ν_{NH} bands of 1,3-disubstituted ureas,[26] these bands were shifted to lower wavenumbers. This suggests that the ω-side chain of (**8**) forms the intramolecular hydrogen bond as in (**VI**), when (**8**) does not form the intramolecular hydrogen bond between the α- and ω-side chains.

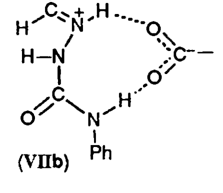


(**VI**)

Intramolecular Hydrogen Bonds in (**5**) *and* (**9**).—For (**5**) in CCl_4 solution as shown in Figure 7, the free ν_{OH} and $\nu_{C=O}$ bands of the carboxy group almost disappeared, new bands appeared at 2 900, 2 564, and 1 660 cm^{-1}, and the free ν_{NH}, the intramolecular hydrogen-bonded ν_{NH}, and the free $\nu_{C=O}$ bands of the urea group were observed at 3 379, 3 210, and 1 707 cm^{-1}, respectively. The last band corresponds to the free $\nu_{C=O}$ band at 1 711 cm^{-1} for the urea group of (**9**) in CCl_4 solution. In $CHCl_3$ solution at *ca.* 2 × 10^{-2} mol dm^{-3}, the free $\nu_{C=O}$ band of the carboxy group in (**5**) disappeared and new peaks were observed at 1 655 and 1 541 cm^{-1}, indicative of the $\nu_{asCO_2^-}$ and the $\nu_{sCO_2^-}$ bands, respectively. Based on these findings and the results described above, the peak at 1 660 cm^{-1} was assigned to the $\nu_{asCO_2^-}$ band and the peaks at 2 900 and 2 564 cm^{-1} to the ν_{NH^+} bands. These results suggest that the intramolecular hydrogen bonds of the zwitterion form (**VIIa**) or



(**VIIa**)



(**VIIb**)

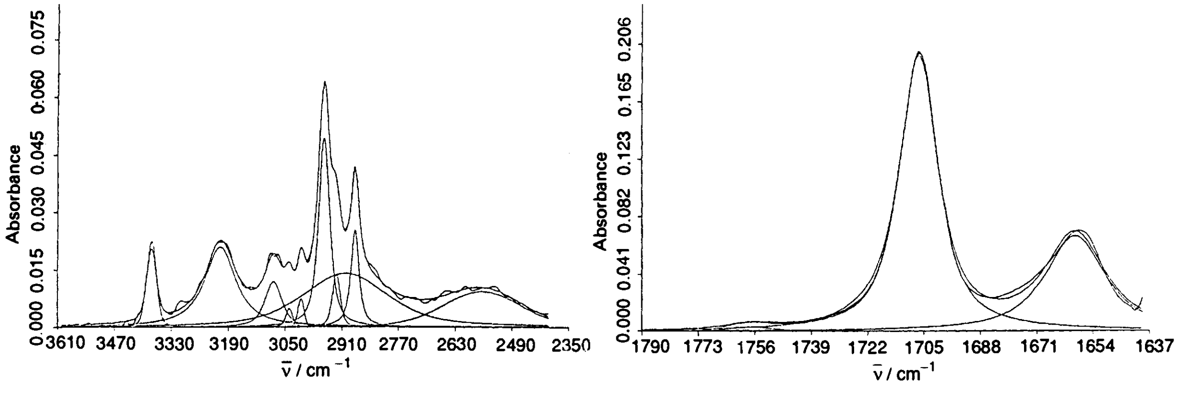


Figure 7. FTIR spectra of (5) at 3.1604×10^{-5} mol dm^{-3} in CCl_4 solution in a 5.0 cm cell and the results of peak separation of their spectra.

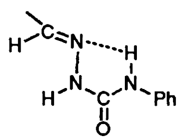
Table 5. Energy difference (ΔE) between the conformers and torsion angle H–C_a–C_b–H (τ) for model compound (**15**) by MINDO/3 and AM1 calculations.

	MINDO/3		AM1	
Form[a]	ΔE/kJ mol^{-1}	τ/°	ΔE/kJ mol^{-1}	τ/°
T_1	0.0	179	0.0	−173
T_2	0.5	161	0.02	175
G_1	4.3	98	3.3	93
C_1	4.8	58	5.0	43
C_2	4.9	−57	6.4	−28
G_2	5.4	−87	2.5	−95

[a] T, G, and C show *trans*, *gauche*, and *cis* forms, respectively.

(**VIIa**) involving the thirteen-membered ring in (**5**) are formed between the α- and ω-side chains. Since the shift to a lower wavenumber of the free ν_{NH} band for the urea group was observed for (**5**), it seems reasonable to assume that the intramolecular hydrogen-bonded structure is (**VIIb**) rather than (**VIIa**), as described above, but no direct evidence is available on these structures. The spectral behaviour of (**5**) in $CHCl_3$ solution is analogous to that in CCl_4 solution. This suggests that the intramolecular hydrogen bonds of (**5**) in $CHCl_3$ solution are identical to those in CCl_4 solution. The ρ value is estimated to be 96% in CCl_4 and 43% in $CHCl_3$ solutions.

For (**9**) in the CCl_4 solution, the free $\nu_{C=O}$ band at 1 741 cm^{-1} for the methyl ester group decreased and the intramolecular hydrogen-bonded $\nu_{C=O}$ and ν_{NH} bands were observed at 1 725 cm^{-1} for the ester group and 3 316 cm^{-1} for the urea group, respectively, but no change was observed for the $CHCl_3$ solution. This indicates that the intramolecular hydrogen bond in (**9**) is formed between the C=O bond of the methyl ester and either of the NH bonds of the urea group in CCl_4 solution and does not form in $CHCl_3$ solution. The ρ value of (**9**) is estimated to be 27% in CCl_4 and 0% in $CHCl_3$ solutions. Furthermore, the ν_{NH} bands of the urea group in (**9**) were observed at 3 395 and 3 361 cm^{-1} in CCl_4 and 3 388 and 3 357 cm^{-1} in $CHCl_3$ solutions. Compared with the ν_{NH} band of 1,3-disubstituted ureas,[26] these bands were shifted to lower wavenumbers. This suggests that an NH bond adjacent to the phenyl group of the ω-side chain in (**9**) is intramolecularly hydrogen-bonded to a lone pair electrons of N atom as in (**VIII**) as well as in 3-methyl-1,5-diphenylformazan[28] when (**9**) does not form the intramolecular hydrogen bond between the α- and ω-side chains.



(**VIII**)

Conformation in U-46619.—Previously, we have reported[5] that U-46619 with α- and ω-side chains and configuration that are the same as those of TXA_2 forms intramolecular hydrogen bonds involving the fifteen-membered ring in CCl_4 and $CHCl_3$ solutions as shown in Figure 8. The six conformers in U-46619 are possible by rotation along the C(12)–C(13) bond, but the geometry of this part is not clear. Accordingly, the geometries of these conformers for model compound (**15**) were optimized by MINDO/3[20] and AM1[21] methods.

As shown in Table 5, conformer T_1 with C_b–H bond *trans* to C_a–H bond is the most stable among them in both the calculations. From this result, we assumed that H-12 and H-13 atoms of U-46619 are *trans* to each other in the conformation with the fifteen-membered ring formed by the hydrogen bonds. MINDO/3 and AM1 calculations were done for several model systems of 1,3-disubstituted ureas to predict the stable geometries. However, these calculations cannot yield accurate geometries of the ω-side chains in (**4**), (**5**), (**8**), and (**9**) because the theoretical predictions produce different results based on the two methods.

Geometrical Resemblance of (**1**)–(**5**).—The intramolecular hydrogen-bonded structures found in (**1**)–(**5**) in dilute CCl_4 and $CHCl_3$ solutions are shown in Figure 8, together with the ρ values. Freedom in the conformation of a large ring formed by these hydrogen bonds is very restricted owing to a bicyclic ring, a double bond, and the hydrogen bonds in these compounds. If the conformations illustrated in Figure 8 are adopted for (**1**)–(**5**), the geometrical arrangements of the functional groups in their compounds strongly resemble each other, although an equilibrium in (**1**) and (**2**) exists between the two ring conformers. The same statement is true for U-46619. The illustrated conformation of (**1**) is similar to that reported for S-145.[5] Namely, we found a geometrical resemblance between the TXA_2 receptor antagonists S-145 and (**1**)–(**5**) and the agonist U-46619 in non-polar solvents.

In conclusion, the FTIR method used should be helpful for elucidating the conformation of analogous compounds such as TXA_2 receptor agonists and antagonists containing non-vicinal carboxy and other functional groups in non-polar solvents. The information obtained should be useful for designing drugs and for confirming the conformational analyses using theoretical calculations.

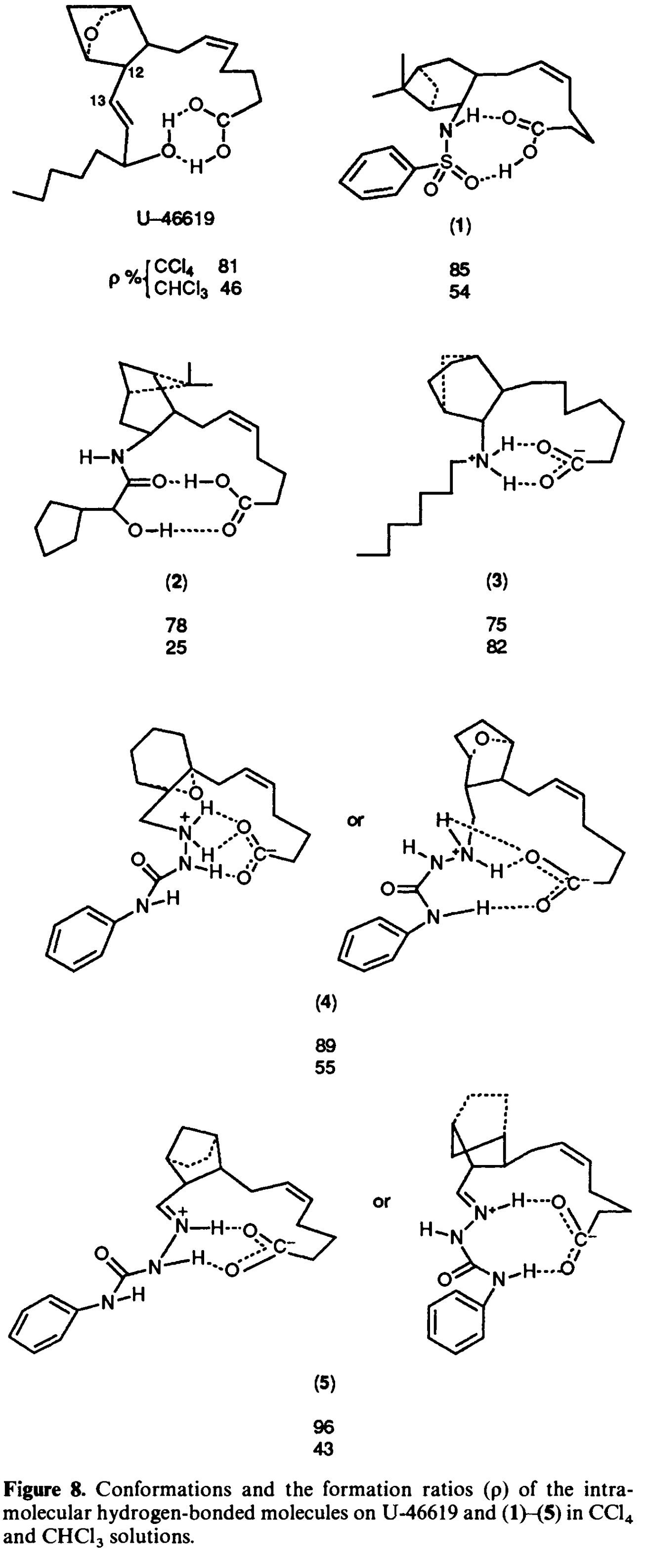


Figure 8. Conformations and the formation ratios (ρ) of the intramolecular hydrogen-bonded molecules on U-46619 and (1)–(5) in CCl_4 and $CHCl_3$ solutions.

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