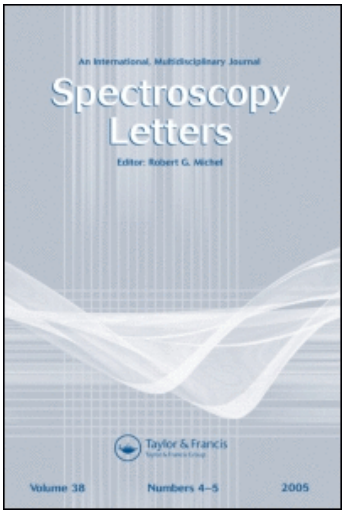


Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

FTIR Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Antagonist S-145 and Related Compounds. Part 4

Mamoru Takasuka[a]; Fumihiko Watanabe[a]; Masumi Yamakawa[a]
[a] Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan

To cite this Article Takasuka, Mamoru , Watanabe, Fumihiko and Yamakawa, Masumi(1993) 'FTIR Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Antagonist S-145 and Related Compounds. Part 4', Spectroscopy Letters, 26: 6, 1023 — 1037
To link to this Article: DOI: 10.1080/00387019308011590
URL: http://dx.doi.org/10.1080/00387019308011590

SPECTROSCOPY LETTERS, 26(6), 1023-1037 (1993)

FTIR SPECTRAL STUDY OF INTRAMOLECULAR HYDROGEN BONDING IN THROMBOXANE A_2 RECEPTOR ANTAGONIST S-145 AND RELATED COMPOUNDS. PART 4

Key Words: Intramolecular Hydrogen Bonding, Carboxylic Acid, Large-membered Ring, FTIR Spectra, Curve-fitting Calculation

MAMORU TAKASUKA,* FUMIHIKO WATANABE and MASUMI YAMAKAWA

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

ABSTRACT

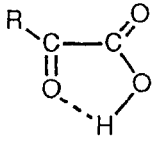
An *N*-methylated compound of S-145, (±)-(5Z)-7-[3-*endo*-[*N*-methyl)phenylsulphonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic acid **1**, its chain analogue 12-[*N*-methyl(phenylsulphonyl)amino]dodecanoic acid **3**, (±)-(5Z)-7-[3-*endo*-(benzoylamino)bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic acid **5** and related compounds were synthesized in order to study the formation of a new class of intramolecular hydrogen

bond IX (*cis*-$CO_2H\cdots O=Y$). Their FTIR spectra were measured in dilute CCl_4 solution and subjected to curve analysis in order to separate overlapping absorption bands. For compounds 1, 3 and 5, the intramolecular hydrogen bonds of the IX type involving 14-, 17- and 14-membered rings were found between a carboxyl group, which takes a *cis*-structure IV, and an oxygen atom of a sulphonyl or benzoylamino group, respectively. The C=O stretching vibration bands of these carboxyl groups shifted to lower wavenumbers (*ca.* 19 cm^{-1}). The direction of these shifts was contrary to that found for α-keto and α-alkoxycarboxylic acids in which carboxyl groups take a *trans*-structure III due to the formation of intramolecular hydrogen bonds I and II, respectively.

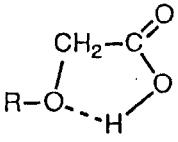
INTRODUCTION

The OH and C=O stretching (ν_{OH} and $\nu_{C=O}$) bands in carboxylic acids RCO_2H in dilute CCl_4 solution provide useful information not only on the nature of the substituent R, but also on the molecular conformation.[1-4] For only compounds with n = 1 in $RCO(CH_2)_{n-1}CO_2H$ and $RO(CH_2)_nCO_2H$, the ν_{OH} bands have been reported to shift to lower wavenumbers because their carboxyl groups form intramolecular hydrogen bonds I and II to the proton accepting groups at the α-position, respectively.[1-4] The $\nu_{C=O}$ bands of these carboxyl groups which take a *trans*-structure III have been also reported to shift to higher wavenumbers (*ca.* 30 cm^{-1}), compared with those at *ca.* 1760 cm^{-1} observed for aliphatic acids which take the *cis*-

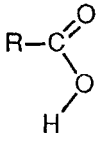
structure IV.[2-4] A similar higher shift of the $\nu_{C=O}$ band was observed for pyruvic acid,[5] glyolic acid[6] and glycolic acid[7] in the Ar matrix and *o*-phenoxybenzoic acids in dilute CCl_4 solution.[8] The *cis*-carboxyl group IV is more stable than the *trans*-one III unless carboxylic acids form the intramolecular hydrogen bond of the I or II type.[1-4] This was theoretically supported by the ab initio MO calculations.[9]



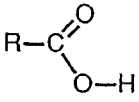
I



II

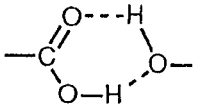


III

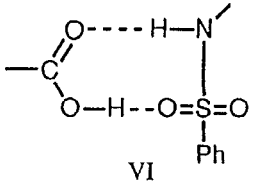


IV

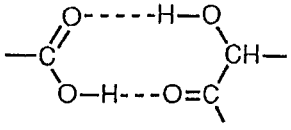
Recently, we found[10-14] that a thromboxane A_2 receptor agonist U-46619,[15,16] its antagonists S-145[17] and ONO-3807,[18] chain analogues of S-145 [$PhSO_2NH(CH_2)_nCO_2H$ (n = 6-11)] and ω-alkanedicarboxylic acids [$HO_2C(CH_2)_nCO_2H$ (n = 10-14)] in dilute CCl_4 solution form cyclic intramolecular hydrogen bonds V-VII, VI and VIII involving large rings of more than 9 members which link between the



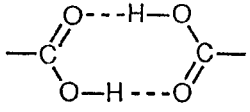
V



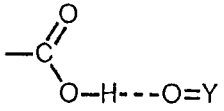
VI



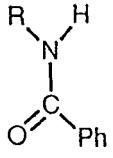
VII



VIII

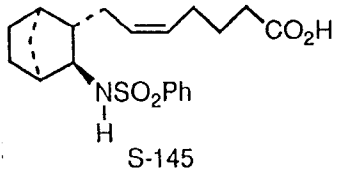


IX

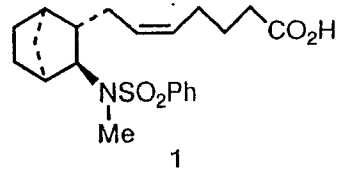


X

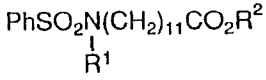
cis-carboxyl and functional or *cis*-carboxyl groups, respectively. The hydrogen-bonded ν_{OH} and $\nu_{C=O}$ band of these carboxyl groups shifted to lower wavenumbers, analogous to the case of the carboxylic acid dimer.[19] Furthermore, we have taken an interest in chain compounds containing the non-vicinal carboxyl group and a Y=O bond such as prostaglandin-related compounds because they are expected to form an intramolecular hydrogen bond of the IX type in which the carboxyl group takes the *cis*-structure. However, no information is available on the intramolecular hydrogen bond of this type except for the intermolecular hydrogen bond mentioned below.[20] Thus, in order to study the intramolecular hydrogen bond of the IX type, we synthesized S-145 and **1**-**5** and measured FTIR spectra of **1** and **3**-**5** in dilute CCl_4 solution. Full optimization curve analysis was applied to all spectra for separation of the overlapping absorption bands.



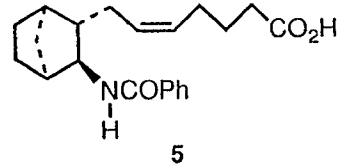
S-145



1



2: R^1 = H, R^2 = H
3: R^1 = Me, R^2 = H
4: R^1 = Me, R^2 = Me



5

EXPERIMENTAL

S-145, 2 and 5 were prepared as reported elsewhere.[12, 17] Compound 2 was treated with sodium hydride and methyl iodide to obtain 4. Compound 3 was obtained by hydrolysis of 4. Compound 1 was synthesized from S-145 by the same method. Compounds 1 and 3-5 were dissolved in CCl_4 at a concentration (c) below 5×10^{-5} mol dm^{-3} (cell length (l) = 5.0 cm), which does not lead to the formation of intermolecular hydrogen bonds between functional groups, except for the carboxylic acid dimer.[10,11] FTIR spectra were recorded on a Nicolet 20 SXB FTIR spectrometer at 27°C. Purification of CCl_4, operation for the solution and curve-fitting calculation for peak separation were as previously described.[10] The percentages (N) of non-hydrogen-bonded molecules and (σ) of dimers for 1, 3 and 5 were estimated by the following approximation: the values of the molar absorption coefficients (ε/mol^{-1} dm^3 cm^{-1}) of the free and dimer $\nu_{C=O}$ bands for the carboxyl group in these compounds are equal to those of lauric acid [$CH_3(CH_2)_{10}CO_2H$]. In CCl_4 solution, the ε values of the free ν_{OH} band at 3533 cm^{-1} and the free $\nu_{C=O}$ band at 1759 cm^{-1} and the ε value per $\nu_{C=O}$ band of the dimer at 1711 cm^{-1} for lauric acid are 178.4, 501.9 and 822.6, respectively.[10]

RESULTS AND DISCUSSION

The spectral data in 1 and 3-5 and their assignments are listed in Table 1, together with the $\Delta\nu$, N, σ, ρ and S values, where ρ is the percentage of the intramolecular hydrogen-bonded molecules and S is

TABLE 1. FTIR Data[a] for 1 and 3-5 in CCl_4 Solution

Compd.	Assign.[b]		ν / cm^{-1}	ϵ / $mol^{-1}\,dm^3\,cm^{-1}$	$\Delta\nu_{\frac{1}{2}}$ / cm^{-1}	A / $10^{-8}\,cm^2\,s^{-1}\,molecule^{-1}$	N[c] / %	ρ[d] / %	σ[e] / %	S[f]	c / $10^{-5}\,mol\,dm^{-3}$
1	ν_{OH}	F	3531.9	133.9	24.0	42.7				14	3.0138
		H	[g]								
	$\nu_{C=O}$	F	1758.2	412.0	18.0	98.4	82.1	7.6			
		F[h]	1740.4	69.1	17.3	17.5					
		D	1709.8	84.7	13.9	14.7			10.3		
3	ν_{OH}	F	3533.2	131.1	23.1	39.8				17	3.2474
		H	3336.4	27.7	93.1	34.3					
	$\nu_{C=O}$	F	1758.8	367.7	18.5	88.1	73.3	15.7			
		F[h]	1739.2	107.0	20.0	26.1					
		D	1710.7	90.4	14.3	17.2			11.0		
	$\nu_{as\,SO_2}$	F	1351.7	425.0	11.7	68.6					
4	$\nu_{C=O}$	F	1741.6	536.8	16.0	121.8					4.6096
	$\nu_{as\,SO_2}$	F	1352.0	508.5	12.1	85.3					

5	ν_{OH}	F	3532.1	63.6	24.4	21.0				14	3.1688
		H	3196.1	52.3	276.9	176.4					
	ν_{NH}	F	3452.6	52.8	22.1	16.9					
	$\nu_{C=O}$	F	1760.0	237.9	16.4	51.8	47.4	49.1			
		F[h]	1740.7	202.2	29.8	76.1					
		D	1709.8	28.7	15.0	5.8			3.5		
	($\nu_{C=O}$)	F	1669.2	317.5	15.7	59.7					
		H	1646.8	288.4	18.7						

[a] $\nu, \varepsilon, \Delta\nu_{\frac{1}{2}}$ and A are the band frequency, the molar absorption coefficient, the band width at half-intensity and the integrated intensity, respectively. [b] ν_{OH}, $\nu_{C=O}$, ν_{as} SO_2, and ν_{NH} show OH, C=O, antisymmetric SO_2 and NH stretching vibration, respectively, $\nu_{C=O}$ in parenthesis is the C=O stretching vibration of the benzoylamino group and F, H and D also show free, intramolecular hydrogen-bonded and dimer bands, respectively. [c] Percentage (N) of non-hydrogen-bonded molecules, N = (ε/501.9)100, where 501.9 is the ε value of 100% free $\nu_{C=O}$ band of lauric acid.[10] [d] Percentage (ρ) of intramolecular hydrogen-bonded molecules, $\rho = 100 - (N + \sigma)$. [e] Percentage ($\sigma$) of dimer molecules, $\sigma = (\varepsilon/822.6)100$, where 822.6 is the ε value per $\nu_{C=O}$ band of dimer for lauric acid.[10] [f] Size of the ring formed by the intramolecular hydrogen bond. [g] The exact parameters could not be obtained because the band was weak. [h] Type IX.

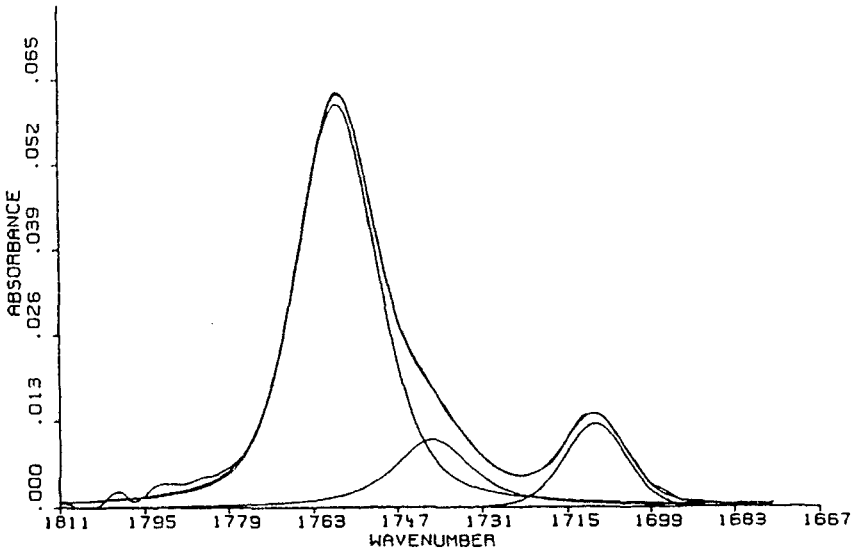


FIG. 1. FTIR spectrum of 1 at 3.0138 x 10^{-5} mol dm^{-3} in CCl_4 solution in a 5.0-cm cell and the result of peak separation of the spectrum.

the size of the ring formed by the hydrogen bond. The FTIR spectra of **1**, **3** and **5** and the results of the peak separation of their spectra are shown in Figures 1-3, respectively. In general, the formation of the intramolecular hydrogen bond Z-H···O=Y causes a shift of the ν_{ZH} and $\nu_{Y=O}$ bands to lower wavenumber.

Since S-145 which forms the cyclic intramolecular hydrogen bonds VI showed the high ρ value of 89% in CCl_4 solution,[10] it is presumed that its *N*-methylated compound **1** also forms a certain amount of intramolecular hydrogen bond of the IX type, although there is only one hydrogen bond in IX. As shown in Figure 1, **1** exhibits the $\nu_{C=O}$ band at 1740 cm^{-1} other than the free $\nu_{C=O}$ band

at 1758 cm^{-1} and the dimer $\nu_{C=O}$ band at 1710 cm^{-1} for the carboxyl group. This suggests that 1 forms an intramolecular hydrogen bond of the IX type. In order to confirm this result, the FTIR spectra of *N*-methylated compound 3 of chain analogue 2 was investigated because 2 (ρ = 95%), which forms a cyclic intramolecular hydrogen bond VI similar to that of S-145, shows the highest ρ value in the compounds examined.[12]

For 3 as shown in Figure 2, the intensities of the free ν_{OH} band at 3533 cm^{-1} and the free $\nu_{C=O}$ band at 1759 cm^{-1} for the carboxyl group decreased and new bands appeared at lower wavenumbers (3336 and 1739 cm^{-1}), respectively. In addition, compared with the ϵ value of the $\nu_{as\ SO_2}$ band at 1352 cm^{-1} for the sulphonyl group in 4 which is incapable of hydrogen bonding, a decrease of 16% was found for the corresponding band of 3. This value agrees well with the ρ value. For 1 and 3, the $\nu_{C=O}$ bands were not observed at wavenumbers higher than 1760 cm^{-1}, indicative of the *trans*-carboxyl group.[1-4] From these findings, it is clear that an intramolecular hydrogen bond of the IX type involving the 14-membered ring in 1 and the 17-membered one in 3 in CCl_4 solution is formed between the OH bond of the carboxyl group and the oxygen atom of the sulphonyl group. In 1 and 3, the ρ values of 8 and 16% were much smaller than those of S-145 and 2, respectively, because there is only one hydrogen bond in both 1 and 3.

It was presumed that 5 does not form cyclic intramolecular hydrogen bond similar to S-145 but forms intramolecular hydrogen

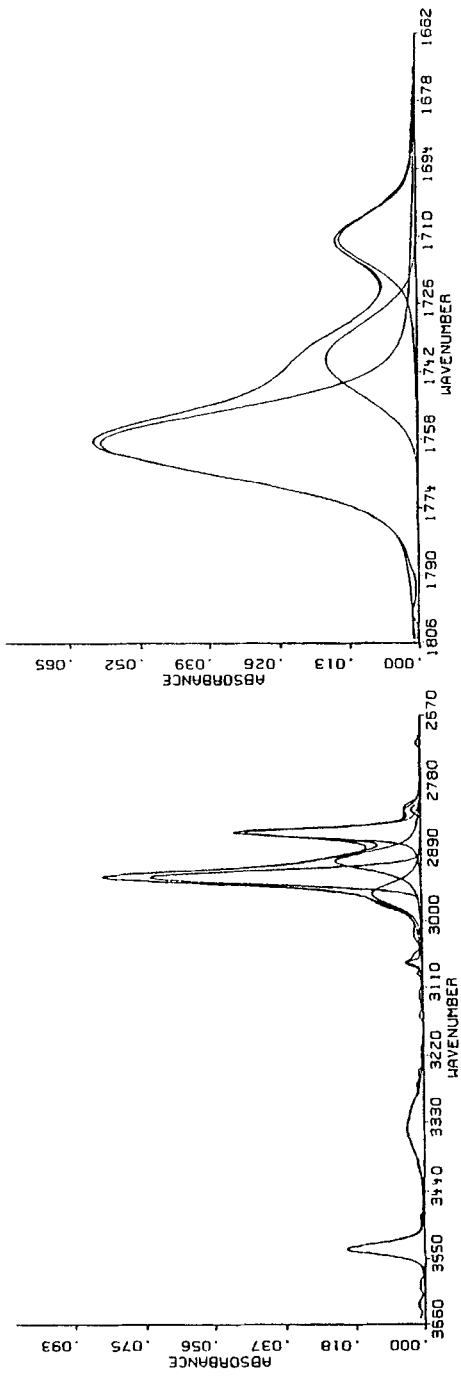


FIG. 2. FTIR spectra of **3** at 3.2474 x 10^{-5} mol dm^{-3} in a 5.0-cm cell and the results of peak separation of their spectra.

bond of the IX type, because *N*-monosubstituted benzamides take the *trans*-structure X.[21] The integrated intensity ($A/10^{-8}$ cm^2 s^{-1} molecule^{-1}) of 16.9 and the ε value of 53 were observed for the free ν_{NH} band at 3453 cm^{-1} for the benzoylamino group in **5**. The former value agrees well with 18.3 (3456 cm^{-1}) for *p*-$MeOC_6H_4CONHPr^i$ and 17.9 (3450 cm^{-1}) for *p*-$ClC_6H_4CONHPr^i$.[22] The latter value is also in close agreement with 56 (3462 cm^{-1}) for $PhCONHBu^n$, 55 (3466 cm^{-1}) for $PhCONHBu^i$ and 55 (3452 cm^{-1}) for $PhCONHBu^t$.[23] These results indicate that the NH bond of the benzoylamino group in **5** is not intramolecularly hydrogen-bonded to oxygen atoms of the carboxyl group.

For **5** as shown in Figure 3, the intensities of the free ν_{OH} band at 3532 cm^{-1} and the free $\nu_{C=O}$ band at 1760 cm^{-1} for the carboxyl group and of the free $\nu_{C=O}$ band at 1669 cm^{-1} for the benzoylamino group appreciably decreased and new bands appeared at lower wavenumbers (3196, 1741 and 1647 cm^{-1}), respectively. It is obvious from these results that an intramolecular hydrogen bond of the IX type involving the 14-membered ring in **5** in CCl_4 solution is formed between the OH bond of the carboxyl group and the oxygen atom of the benzoylamino group. The ρ value of **5** is estimated to be 49%, which is much larger than that of **1** in spite of the 14-membered ring. For **1**, **3** and **5**, the $\nu_{C=O}$ band of the carboxyl group was found to shift to lower wavenumber (*ca.* 19 cm^{-1}) due to formation of an intramolecular hydrogen bond of the IX type. This trend is contrary to that of $RCOCO_2H$ and $ROCH_2CO_2H$ mentioned in the Introduction.[1-4]

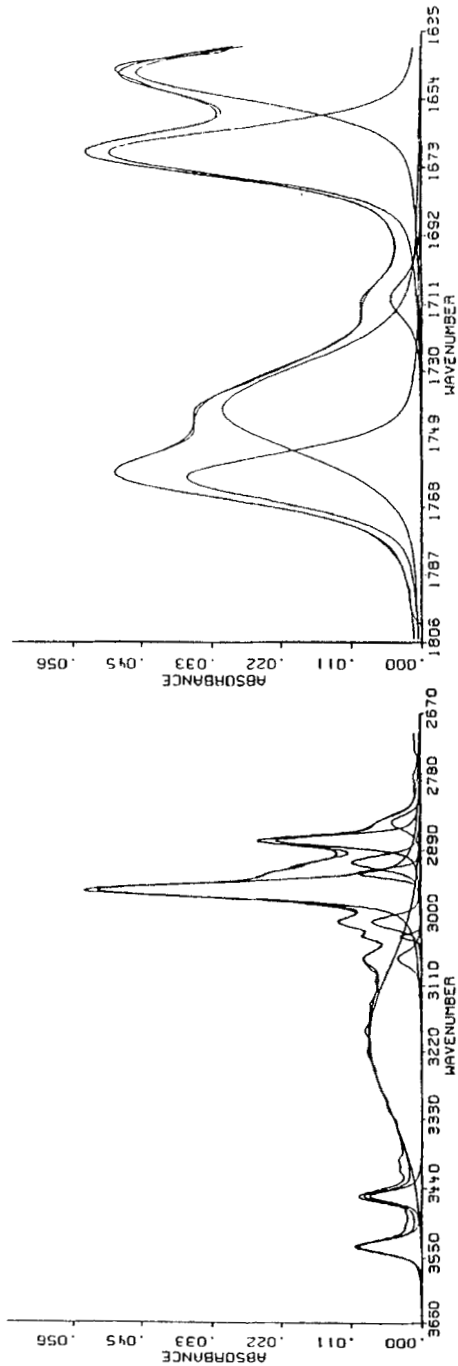
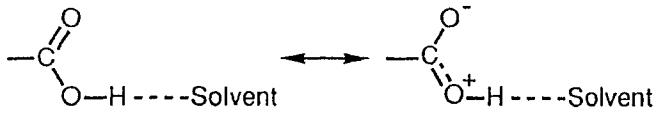


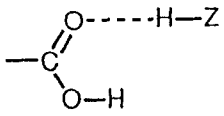
FIG. 3. FTIR spectra of **5** at 3.1688×10^{-5} mol dm^{-3} in CCl_4 solution in a 5.0-cm cell and the results of peak separation of their spectra.

When an intermolecular hydrogen bond of the IX type is formed between CCl_3CO_2H and a hydrogen-bonding solvent, its $\nu_{C=O}$ band is shifted to lower wavenumbers.[20] This shift has been also reported to be attributable to resonance, as can be seen in the following equation, where the double-bond character of the C=O bond decreases, causing to a shift of the $\nu_{C=O}$ band to lower wavenumbers.[20] Accordingly, the

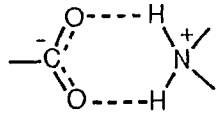


main factor for the shift to lower wavenumbers of *ca.* 19 cm^{-1} observed for **1**, **3** and **5** is considered to be due to a similar resonance.

An intramolecular hydrogen bond of the XI type can also be formed in chain compounds having a non-vicinal carboxyl group and a Z-H bond. However, these chain compounds formed cyclic intra-



XI



XII

molecular hydrogen bonds of the V and XII types when Z was an oxygen and a nitrogen atom, respectively.[10-12] In general, the smaller the electronegativity of the Z atom, the weaker is the hydrogen bonding interaction ability in the Z-H bond. From these findings, it is thought that little of the intramolecular hydrogen bond of the XI type is formed.

In conclusion, we found that **1**, **3** and **5** form intramolecular hydrogen bonds of the IX type and the $\nu_{C=O}$ bands of their carboxyl groups shift to lower wavenumbers in spite of the fact that the C=O bond of the carboxyl group does not form the hydrogen bond. This information should be helpful for elucidating the intramolecular hydrogen bonds of prostaglandin-related compounds such as 15-keto-prostaglandins.

REFERENCES

1. Ōki M., Hirota M. Bull. Chem. Soc. Jpn. 1960; 33: 119.
2. Ōki M., Hirota M. Bull. Chem. Soc. Jpn. 1961; 34: 374, 378.
3. Ōki M., Iwamura H. Bull. Chem. Soc. Jpn. 1962; 35: 283.
4. Ōki M., Hirota M. Spectrochim. Acta 1961; 17: 583.
5. Hollenstein H., Akermann F., Günthard H. H. Spectrochim. Acta 1978; A34: 1041.
6. Redington R. L., Liang Ch. K. J. J. Mol. Spectrosco. 1984; 104: 25.
7. Hollenstein H., Ha T.-K., Günthard H. H. J. Mol. Struct. 1986; 146: 289.
8. Ōki M., Hirota M. Bull. Chem. Soc. Jpn. 1964; 37: 209.
9. Wiberg K. B., Laidig K. E. J. Am. Chem. Soc. 1987; 109: 5935.
10. Takasuka M., Yamakawa M., Watanabe F. J. Chem. Soc., Perkin Trans. 2 1989; 1173.
11. Takasuka M., Yamakawa M., Ohtani M. J. Chem. Soc., Perkin Trans. 2 1990; 1467.
12. Takasuka M., Yamakawa M., Ohtani M. J. Med. Chem. 1991; 34: 1885 (Part 3).
13. Takasuka M., Ezumi K., Yamakawa M. J. Chem. Soc., Perkin Trans. 2 1992; 29.

14. Takasuka M., Saito T., Yamakawa M. J. Chem. Soc., Perkin Trans. 2 1991; 1513.

15. DiMinno G., Bertele V., Bionchi L., Barbieri B., Cerletti C., Dejana E., Gaetano G. D., Silver M. J. Thromb. Haemostasis 1981; 45: 103.

16. Bundy G. L. Tetrahedron Lett. 1975; 1957.

17. Narisada M., Ohtani M., Watanabe F., Uchida K., Arita H., Doteuchi M., Hanasaki K., Kakushi H., Otani K., Hara S. J. Med. Chem. 1988; 31: 1847.

18. Suga H., Hamanaka N., Kondo K., Miyake H., Ohuchida S., Arai Y., Kawasaki A. Adv. Prostal. Thromb. Leukotri Res. 1987; 17: 799.

19. Chang Y.-T., Yamaguchi Y., Miller W. H., Schaefer III H. F. J. Am. Chem. Soc. 1987; 109: 7245.

20. Nicolet P., Laurence C., Lucon M. J. Chem. Soc., Perkin Trans. 2 1987; 483.

21. Rao C. N. R., Rao K. G., Goel A., Balasubramanian D. J. Chem. Soc. (A) 1971; 3077.

22. Nyquist R. N. Spectrochim. Acta 1963; 19: 509.

23. Nikolić A. D., Rozsa-Trarjani M., Komaromi A., Csanadi J., Petrovic S. D. J. Mol. Struct. 1992; 267: 49.

Date Received: December 28, 1992

Date Accepted: January 15, 1993