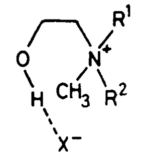
Infrared Studies of Intramolecular Interactions including Ionic Hydrogen Bonding in Tertiary and Quaternary Ammonium Halides having a Hydroxy- or Acetoxy-group β to the Ammonium Function

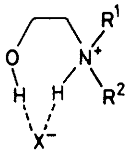
By **Mamoru Takasuka** * and **Yoshihiro Terui**, Shionogi Research Laboratories, Shionogi and Co. Ltd., Fukushima-ku, Osaka 553, Japan

I.r. measurements of a series of tertiary and quaternary ammonium halides having a hydroxy- or acetoxy-group β to the ammonium function showed the following characteristic i.r. behaviour. (i) Compared with the corresponding free stretching vibration band of the OH or the N⁺H group, marked shifts to lower wavenumbers ($\Delta\nu_{OH}$ 256—409 and $\Delta\nu_{N^+H}$ 567—860 cm^{-1} in CHCl$_3$) accompanied by large increases of integrated intensities ($10^{-4}A_{OH}$ 8.25—17.70 and 10^{-4} A_{N^+H} 8.76—21.14 mol^{-1} dm^3 cm^{-2} in CHCl$_3$) were found for ammonium halides. (ii) The shift ($\Delta\nu_{OH}$ or $\Delta\nu_{N^+H}$) and the intensity (A_{OH} or A_{N^+H}) increase as the ionic radius of the halide ion decreases in each series of ammonium halides. (iii) The $\Delta\nu_{OH}$ and $\Delta\nu_{N^+H}$ values are markedly influenced by the type of ammonium group and β-substituent, respectively. (iv) The $\Delta\nu_{OH}$ value of quaternary ammonium halides described above is larger than that found for intermolecular ionic hydrogen bonding between alcohols and tetra-n-butylammonium halides and shows a dependence upon the torsion angle N⁺CCO, τ, in the N⁺–C–C–OR system. (v) Compared with the corresponding $\nu_{C=O}$ found in the free amine, considerable shifts to higher wavenumber, $\Delta\nu_{C=O}$, were found for the C=O stretching band of the acetoxy-group in ammonium halides; in CHCl$_3$, $\Delta\nu_{C=O}$ is 14—32 cm^{-1}. (vi) In CHCl$_3$ and in D$_2$O, the $\Delta\nu_{C=O}$ and $\nu_{C=O}$ values also show dependence upon τ (*viz.* a dependence upon the spatial distance between acetoxy and ammonium groups). (vii) A fairly linear correlation exists between $\Delta\nu_{OH}$ of alcohols and $\Delta\nu_{C=O}$ of acetates. Points (i)—(iii) are attributed to intramolecular ionic hydrogen bonding between OH or N⁺H and halide ion. Points (iv)—(vii) can be understood by considering the factors influencing the polarization of the OH bond and the double-bond character of the acetoxy carbonyl, especially the through-space charge effect of the ammonium group.

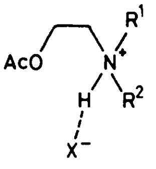
THE important role of hydrogen bonding has been frequently established in the fields of chemistry, molecular biology, and molecular pharmacology. For ionic hydrogen bonds formed between polar hydrogen and an anion, many i.r. studies have been conducted on intermolecular bonds formed in systems consisting of alcohols and alkylammonium salts,[1-9] but not on intramolecular bonding. If an ammonium salt, consisting of a cation and an anion, is considered to be one molecule, intramolecular ionic hydrogen bonding can be expected to occur in an aprotic solvent for molecules (I) and (II) with an OH group β to the ammonium function.



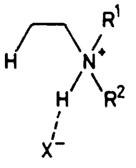
(I)



(II)



(III)



(IV)

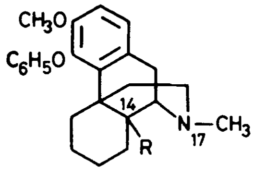
$R^1 = R^2 = $ alkyl

A preference for the *gauche*-conformation by choline and acetylcholine has been revealed by *X*-ray,[10] n.m.r.,[11-13] i.r.,[14,15] molecular mechanical calculations,[16,17] and molecular orbital calculations.[18] Although the importance [13,16] of electrostatic interactions in conformational control of choline and acetylcholine and the very high $\nu_{C=O}$ value of acetylcholine [14,15] have been reported, few i.r. studies have focused on intramolecular interactions in molecules with an OH or OAc group β to the ammonium function. Fellman and Fujita reported $\nu_{C=O}$ values for the molecules AcO-$[CH_2]_n$-$N^+(CH_3)_3X^-$.[14] They interpreted the change in $\nu_{C=O}$ as a reflection of the through-bond inductive effect of the ammonium cation, though the conformation of molecules which influences the through-space interaction is not known, except for acetylcholine ($n = 2$).

We report here i.r. studies on the model compounds (1a)—(11) which have spectra showing characteristic behaviour attributable to the influence of intramolecular interactions. Our main concerns in the present study were (1) measurement of frequency shifts and integrated intensities of OH and N⁺H stretching bands for intramolecular ionic hydrogen bonding in the title compounds, (2) inspection of the influence of neighbouring groups on the OH or N⁺H stretching band to obtain information on intramolecular interactions, and (3) detection of evidence for through-space interactions between the hydroxy- or acetoxy-group and the ammonium function.

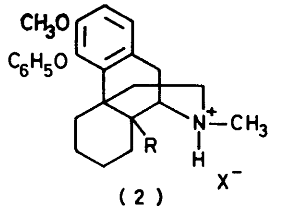
EXPERIMENTAL

I.r. spectra were recorded on a JASCO DS-403G grating spectrometer calibrated in the usual manner. The solvent chloroform was purified by distillation. Compounds (1a)—(3f), (11), and (4a)—(10b) were dissolved in chloroform at concentrations (*c*) 0.008—0.011, 0.005, and below 0.001 mol dm^{-3}, respectively. Matched cells (cell length *l* 0.025—1.0 cm) with NaCl windows and KRS-5 plates were used. All operations, except those for the heavy-water solution,



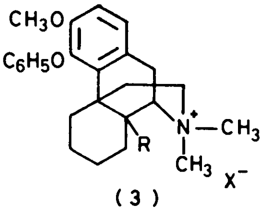
(1)

a; R = OH
b; R = OAc



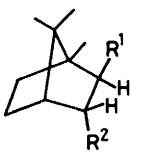
(2)

a; R = H, X = Cl
b; R = H, X = Br
c; R = H, X = I
d; R = OH, X = Cl
e; R = OH, X = Br
f; R = OAc, X = Cl
g; R = OAc, X = Br
h; R = OAc, X = I

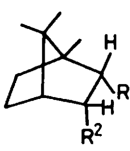


(3)

a; R = OH, X = Cl
b; R = OH, X = Br
c; R = OH, X = I
d; R = OAc, X = Cl
e; R = OAc, X = Br
f; R = OAc, X = I

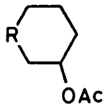


(4)



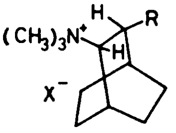
(5)

a; R^1 = OH, R^2 = $N(CH_3)_2$
b; R^1 = OH, R^2 = $N^+(CH_3)_3Br^-$
c; R^1 = OH, R^2 = $N^+(CH_3)_3I^-$
d; R^1 = OAc, R^2 = $N(CH_3)_2$
e; R^1 = OAc, R^2 = $N^+(CH_3)_3I^-$

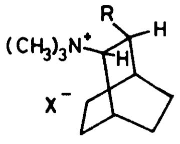


(9)

a; R = NCH_3
b; R = $N^+(CH_3)_2I^-$

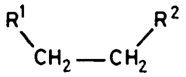


(6b)



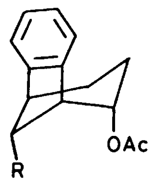
(7a,b)

a; R = OH, X = Cl
b; R = OAc, X = I



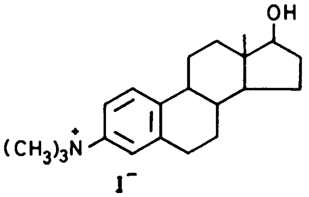
(8)

a; R^1 = OH, R^2 = $N(CH_3)_2$
b; R^1 = OH, R^2 = $N^+(CH_3)_3Cl^-$
c; R^1 = OH, R^2 = $N^+(CH_3)_3Br^-$
d; R^1 = OAc, R^2 = H
e; R^1 = OAc, R^2 = $N(CH_3)_2$
f; R^1 = OAc, R^2 = $N^+(CH_3)_3Cl^-$
g; R^1 = OAc, R^2 = $N^+(CH_3)_3Br^-$
h; R^1 = OAc, R^2 = $N^+(CH_3)_3I^-$



(10)

a; R = $N(CH_3)_2$
b; R = $N^+(CH_3)_3I^-$



(11)

were performed in a dry box. The integrated intensity A was calculated by Ramsay's method,[19] with $A = (\pi/2)[\ln(I_0/I)/c\cdot l]\cdot\Delta\nu_{\frac{1}{2}}$ (mol^{-1} dm^3 cm^{-2}), where $\ln(I_0/I)/c\cdot l$ is the absorption coefficient (mol^{-1} dm^3 cm^{-1}) at the band maximum and $\Delta\nu_{\frac{1}{2}}$ is the band width (cm^{-1}) at half-intensity. The accuracies of ν_{OH} and A_{OH} for the hydroxy-group were within ± 3 cm^{-1} and $\pm 5\%$ and those for ν_{N^+H} and A_{N^+H} were within ± 5 cm^{-1} and $\pm 10\%$, respectively. The accuracies of $\nu_{C=O}$ and $A_{C=O}$ for the acetoxy-group in $CHCl_3$ were within ± 0.3 cm^{-1} and $\pm 3\%$, respectively, and that in D_2O was within ± 1 cm^{-1}. All measurements were carried out at room temperature (*ca.* 27 °C). The ratio of the monomeric form, $m(\%)$, was determined using a vapour osmometer (Mecrolab model 301) in $CHCl_3$ solutions (c 0.01 mol dm^{-3}) at 37 °C, assuming the equilibrium $M \rightleftharpoons \frac{1}{2}$M-M occurs. The accuracy of m was within $\pm 5\%$. Compounds (1b), (2d, e) and (3a—f), (2a—c), (4a—e), (5a—e), (9a, b), (10a, b), and (11) were synthesized in the usual manner from (1a),[20] 3-methoxy-4-phenoxy-*N*-methylmorphinane,[21] 2-*exo*- and 2-*endo*-hydroxy-3-*endo*-methylaminobornane,[22] 3-hydroxy-*N*-methylpiperidine,[16b] *syn*-12-aminotricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-*exo*-9-ol,[23] and 3-aminoestra-1,3,5(10)-trien-17β-ol,[24] respectively. Compound (8), 3-hydroxy-*N*-methylpiperidine, tetra-n-butylammonium halides, and the alcohols were obtained commercially. Compounds (6b) and (7a, b), prepared [25] and provided by Nelson and Wilson, were dried before their i.r. spectra were taken.

RESULTS AND DISCUSSION

(a) *Behaviour of* OH *and* N$^+$H *Stretching Bands and Ionic Hydrogen Bonding.*—The i.r. parameters obtained for dilute $CHCl_3$ solutions of morphinane derivatives are listed in Table 1, together with the ratio of the monomeric form estimated by vapour osmometry. The band parameters of bicyclic compounds and choline analogues are shown in Table 2. Typical spectra of the ν_{OH} and ν_{N^+H} bands are shown in Figure 1.

The parameters $\Delta\nu_{OH}$ and $\Delta\nu_{N^+H}$ represent the magnitude of a shift to a lower wavenumber from the standard value. As the standard values of the tertiary free ν_{OH} band for morphinane derivatives and of the primary free ν_{OH} band for choline analogues, 3 608 and 3 623 cm^{-1} were used, respectively; the former is the free ν_{OH} band of t-butyl alcohol [26] and the latter is that of ethanol. The ν_{OH} values observed for compounds (1a), (5a), and (8a) indicate the existence of intramolecular hydrogen bonding between the hydroxy- and the amino-groups,[27]

TABLE 1

I.r. spectral data for OH, N^+H, and AcO groups of 3-methoxy-4-phenoxy-*N*-methylmorphinane derivatives in chloroform [a]

Compound	ν_{OH} or $\nu_{C=O}$/ cm^{-1}	$\Delta\nu_{OH}$ [b] or $\Delta\nu_{C=O}$ [c]/ cm^{-1}	$10^{-4} A_{OH}$ or $10^{-4} A_{C=O}$/ $mol^{-1} dm^3 cm^{-2}$	ν_{N^+H}/ cm^{-1}	$\Delta\nu_{N^+H}$ [d]/ cm^{-1}	$10^{-4} A_{N^+H}$/ $mol^{-1} dm^3 cm^{-2}$	*m* [e] (%)
(1a)	3 408 [f]	200	1.86				
(2a)				2 380	860	21.14	100
(2b)				2 493	747	20.43	
(2c)				2 576	664	19.92	
(2d)	3 270	338	10.95	2 625	615	11.16	53
(2e)	3 305	303	9.03	2 673	567	8.76	44
(3a)	3 201	407	12.13				69
(3b)	3 263	345	10.75				55
(3c)	3 313	295	8.25				
(1b)	1 720.5		2.74				
	1 706.9		0.77				
	(1 717.5) [g]	0					
(2f)	1 739.3	21.8	3.50	2 407	833	17.74	100
(2g)	1 739.6	22.1	3.20	2 553	687	15.56	
(2h)	1 740.1	22.6	3.08	2 635	605	11.80	
(3d)	1 741.7	24.2	2.88				86
(3e)	1 742.2	24.7	2.78				
(3f)	1 742.8	25.3	2.74				

[a] *c* 0.011—0.008 mol dm^{-3}. [b] $\Delta\nu_{OH} = 3\,608 - \nu_{OH}$; 3 608 cm^{-1} is the wavenumber of the free ν_{OH} band of t-butyl alcohol.[26] [c] $\Delta\nu_{C=O} = \nu_{C=O} - 1\,717$ (1b). [d] $\Delta\nu_{N^+H} = 3\,240 - \nu_{N^+H}$; 3 240 cm^{-1} is the wavenumber of the free ν_{N^+H} band estimated for the tertiary ammonium cation.[6] [e] Ratio of the monomer (see text). [f] ν_{OH} Band in the system forming the intramolecular hydrogen bond, OH · · · N.[27] [g] The value in parentheses is the centre of gravity frequency for the $\nu_{C=O}$ band of the acetoxy-group.

and therefore cannot be used for the standard value. On the other hand, the ν_{OH} values of compounds (4a) and (11) refer to the free ν_{OH} band and the former can be used for the standard value of the secondary free ν_{OH} band in bicyclic analogues. The standard value corresponding to the free N^+H band [6] of the tributylammonium ion has been reported to be 3 240 cm^{-1}. The integrated intensities of the free bands are also known: $10^{-4}A^f_{OH}$ (Bu^tOH) [26] 0.59 and $10^{-4}A^f_{N^+H}$ (Et_3N^+H) [4] 0.6 mol^{-1} dm^3 cm^{-2}. The $10^{-4}A^f_{OH}$ value of bicyclic compound (4a) is 0.71 mol^{-1} dm^3 cm^{-2}.

Compared with the free band, marked shifts to lower wavenumber, $\Delta\nu_{OH}$ and $\Delta\nu_{N^+H}$, accompanied by a large increase in the integrated intensities were observed for ammonium halides, except for compound (11): $\Delta\nu_{OH}$ 256—409 cm^{-1} (A_{OH}/A^f_{OH} 14—25), $\Delta\nu_{N^+H}$ 567—860 cm^{-1} ($A_{N^+H}/A^f_{N^+H}$ 15—35). The $\Delta\nu_{OH}$, $\Delta\nu_{N^+H}$, A_{OH}, and A_{N^+H} are very much influenced by the counter halide ion, X^-, in each series of ammonium halides; their magnitude increases as the ionic radius [28] of X^- decreases, as shown in Figure 2. Similar i.r. behaviour has been reported for intermolecular hydrogen-bonding systems, as in mixtures of alcohols and alkylammonium halides,[1-9] though interest has not been shown in the integrated intensity.

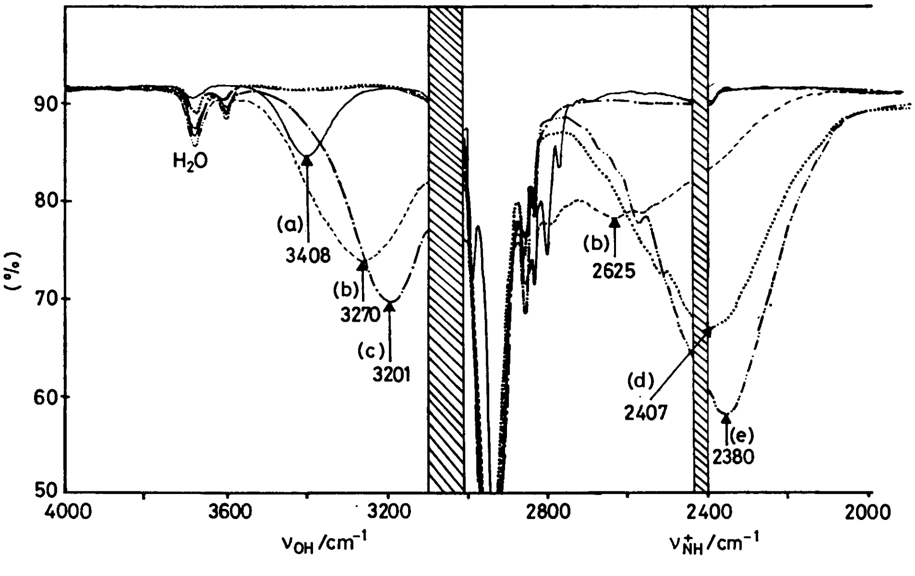


FIGURE 1 I.r. spectra of morphinane derivatives having OH and/or N^+H in $CHCl_3$. Spectra were obtained using a 1 mm cell. The hatched regions could not be measured because of the solvent absorption. (a), * (1a) (1.0524 × 10^{-2} mol dm^{-3}); (b), (2d) (1.0517 × 10^{-2} mol dm^{-3}); (c), (3d) (0.9489 × 10^{-2} mol dm^{-3}); (d), (2f) (0.9950 × 10^{-2} mol dm^{-3}); (e), (2a) (0.9023 × 10^{-2} mol dm^{-3}). * ν_{OH} Band ascribable to the intramolecular hydrogen bond, OH · · · N [27]

Thus, the characteristic i.r. behaviour described above is attributed to the ionic hydrogen bonding, $OH \cdots X^-$ or $N^+H \cdots X^-$.

TABLE 2

I.r. spectral data of OH stretching bands of compounds other than morphinane derivatives in chloroform[a]

Compd.	Form	ν_{OH}/cm^{-1}	$\Delta\nu_{OH}$/cm^{-1}	10^{-4} A_{OH}/ mol^{-1} dm^3 cm^{-2}
(4a)	*trans*	3 616	0	0.71
(4b)	*trans*	3 325	291[c]	
(4c)	*trans*	3 360	256[c]	
(5a)	*cis*	3 402[b]	214[c]	1.81
(5b)	*cis*	3 242	374[c]	
(5c)	*cis*	3 284	332[c]	12.81
(7a)	*cis*	3 207	409[c]	17.70
(8a)		3 469[b]	154[d]	
(8b)	*gauche*	3 266	357[d]	
(8c)	*gauche*	3 345	278[d]	
(11)		3 611	0	0.91

[a] c <0.001 mol dm^{-3}, expect (11); c (11) 0.005 mol dm^{-3}. [b] ν_{OH} band in the system forming the intramolecular hydrogen bond, $OH \cdots N$. [c] $\Delta\nu_{OH}$ = 3 616 (4a) − ν_{OH}. [d] $\Delta\nu_{OH}$ = 3 623 (ethanol) − ν_{OH}.

Besides the monomeric forms shown in (I)—(IV), polymeric forms which aggregate through interaction between ion pairs or intermolecular ionic hydrogen bonding must be taken into consideration. To obtain information on the aggregation state, we used vapour osmometry with $CHCl_3$ solutions of morphinane derivatives. Based on the apparent molecular weight observed, the monomer ratio, *m*, was calculated by assuming an equilibrium between monomer and dimer, $M \rightleftharpoons \frac{1}{2}M\text{-}M$, though contributions of other polymeric forms such as a trimer or a tetramer are also possible. If contributions by a trimer or a tetramer are postulated, the *m* value will be larger than the listed one. The concentration used for i.r. measurement of morphinane derivatives was similar to that for vapour osmometry, and that used for i.r. measurements of the other compounds, except (11), was ten times lower. Accordingly, the *m* value of bicyclo-compounds or choline analogues is supposed to be larger than that of morphinane derivatives. The *m* values of (2a, f) are 100%, which indicate the existence of intramolecular hydrogen bonding as shown in (III) and (IV). With some compounds (2d, e) and (3a, b), a 31—56% contribution of the dimeric forms was found. However, the bands due to the monomer (I) or (II) and the dimer cannot be observed separately, nor can free ν_{OH} or free ν_{N^+H} bands in ammonium halides with a hydroxy-group, except for (11), be observed. This indicates that the difference between the i.r. parameters of the monomer and the dimer is very small. In addition, the fact that (11), which has hydroxy- and ammonium-groups far from each other, gives only a free ν_{OH} band at 3 611 cm^{-1} clearly shows that the ion pair $N^+ \cdots X^-$ has a stronger influence than ionic hydrogen bonding in controlling the position of the halide anion. The results suggest that aggregation of the monomer is primarily governed by the combining force between ion pairs rather than by an intermolecular hydrogen bond.

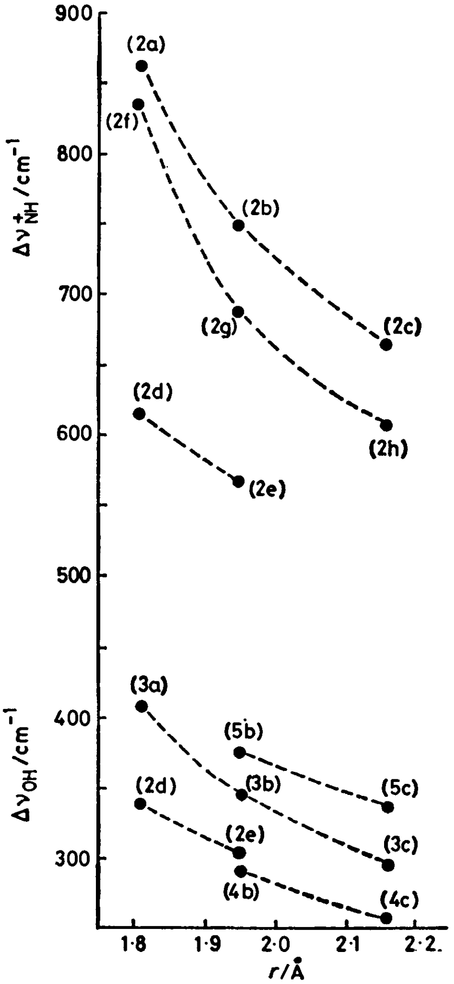


FIGURE 2 Correlation between the ionic radius (r)[28] of halide anions and $\Delta\nu_{OH}$ or $\Delta\nu_{N^+H}$ found in ionic hydrogen-bond systems

Further detailed comparison of the i.r. data of the molecules examined provides much useful information. When the same halide anion is present in morphinane derivatives, the $\Delta\nu_{OH}$ and A_{OH} values of the tertiary ammonium halide are smaller than those of the quaternary one. The $\Delta\nu_{N^+H}$ and A_{N^+H} of the tertiary ammonium halide having β-OH are the smallest of those of the three molecules having a different β-substituent (*viz.* β-OH, β-OAc, or β-H). This can be explained by considering the halide ion bridge, as shown in (II). The formation of a hydrogen bond with one side decreases the proton acceptor ability of the halide ion to attentuate the strength of the hydrogen bond with the other side. Consequently, plural hydrogen bonds with a common X^- weaken each other. Thus, the relatively small i.r. parameters of compounds (2d, e) can be rationalized. While the $\Delta\nu_{N^+H}$ and A_{N^+H} values of (2f—h) with β-OAc are relatively smaller than those of (2a—c) with β-H, this is never attributable to the through-bond inductive effect of the β-substituent. Further, the $\nu_{C=O}$ value of the acetoxy-group of ammonium halides (2f—h) shifts to higher wavenumbers than that of the corresponding amine (1b). These facts imply a through-space interaction between the ammonium group and the acetoxy-group, which is detailed in the next paragraph.

For the ν_{OH} band behaviour in the system N^+–C–C–OH, a geometric dependence is found, as shown in Figure 3.

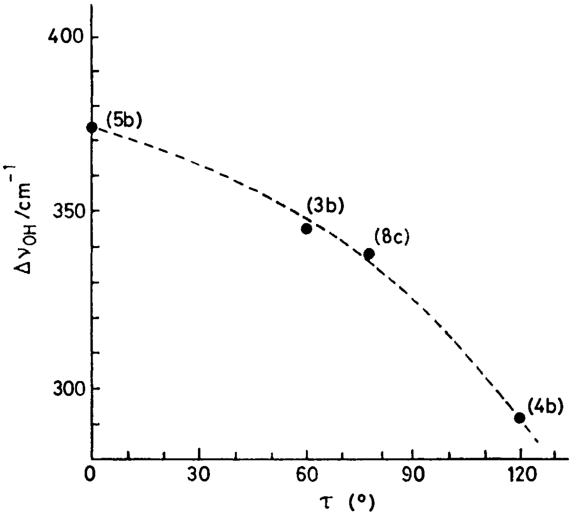


FIGURE 3 Correlation between $\Delta\nu_{C=O}$ and torsion angle N^+CCO (τ) in quaternary ammonium bromides having a β-OH group. See Table 4, footnote *b*

The $\Delta\nu_{OH}$ value decreases as the torsion angle N^+CCO, τ, increases (see footnote *b* in Table 4). The relation strongly implies that the intramolecular interaction exerts an influence. The distance between the hydroxy- and ammonium-groups increases with the increase of the torsion angle. Therefore, we considered, at first, that the strength of the intramolecular ionic hydrogen bond, $OH \cdots X^-$, decreases with the increase in the torsion angle (*i.e.* the increase of internal distance between the hydroxy-group and the halide ion), because ion pairing has a stronger influence than hydrogen bonding in controlling the position of the halide ion as mentioned above. However, molecular model examinations showed that a suitable distance (*e.g.* $R_{O \cdots Br^-}$ 3.07 and $R_{N^+ \cdots Br^-}$ 4.37 Å) [29] can be assumed for quaternary ammonium halides without significant interference by steric factors, when 0° $\lesssim \tau \lesssim$ 120°. In addition, a similar torsion angle dependence was also seen for $\nu_{C=O}$ of the β-acetoxy-group (see next paragraph), in spite of the fact that there were no participating ionic hydrogen bonds. The key point is that although we cannot clearly show a significant variation in the distance between the hydroxy-group and the halide ion in the range 0° $\lesssim \tau \lesssim$ 120°, the internal distance between the oxygen atom of the β-hydroxy-group and the ammonium cationic head clearly increases with an increase of the torsion angle. Based on the above data, we deduce that the intramolecular charge interaction is a very important factor in controlling the ν_{OH} or $\Delta\nu_{OH}$ value. The ammonium cationic head and the halide anion facilitate polarization of the O–H bond. The degree of polarization is much influenced by the distance between the oxygen and the ammonium cationic head. The more polar the OH bond, the stronger the hydrogen bond. The strong hydrogen bond causes a large shift, $\Delta\nu_{OH}$. For the same halide ion, the $\Delta\nu_{OH}$ value of the intramolecular ionic hydrogen bonding in the quaternary ammonium halides with an OH group is larger than that of the intermolecular one found for a system consisting of saturated alcohol and tetra-n-butylammonium halide; the $\Delta\nu_{OH}$ values found for intermolecular hydrogen bonds are listed in Table 3. Thus, the geometric dependence of ν_{OH} is supported. The characteristic behaviour of the ν_{OH} and the ν_{N^+H} bands found in ammonium halides can be interpreted by considering the ionic hydrogen bonding and the factors influencing its strength.

(b) *Behaviour of the* C=O *Stretching Band found in Acetates.*—I.r. parameters of acetoxy-carbonyls observed in dilute $CHCl_3$ solution of morphinane derivatives are presented in Table 1. The i.r. parameters observed for bicyclic compounds and acetylcholine analogues in $CHCl_3$ and those in D_2O are listed in Tables 4 and 5, respectively.

Compared with the standard $\nu_{C=O}$ value found in the corresponding free amine, a characteristic shift was seen for the ammonium salt. Unlike the shift found in ν_{OH} or ν_{N^+H}, a shift to higher wavenumber, $\Delta\nu_{C=O}$, was observed. The frequency of the carbonyl stretching vibration is thought to depend strongly upon the double-bond character of the carbonyl group.[30,31] The larger the

TABLE 3

I.r. spectral data of OH stretching bands found in intermolecular hydrogen bonding systems [a]

No.	Proton [b] donor	Proton [c] acceptor	Free ν_{OH}/ cm^{-1}	Hydrogen-bonded ν_{OH}/cm^{-1}	$\Delta\nu_{OH}$/ cm^{-1}	$\Delta\nu_{OH}$(phenol) /$\Delta\nu_{OH}$
($^{12}Cl^-$)	Cyclohexanol	Cl^-	3 612	3 334	278	1.7
($^{13}Cl^-$)	t-Butyl alcohol	Cl^-	3 607	3 336	271	1.8
($^{14}Cl^-$)	Phenol	Cl^-	3 593	3 110	483	1.0
($^{12}Br^-$)	Cyclohexanol	Br^-	3 607	3 376	231	1.8
($^{13}Br^-$)	t-Butyl alcohol	Br^-	3 605	3 381	224	1.9
($^{14}Br^-$)	Phenol	Br^-	3 597	3 175	422	1.0
($^{12}I^-$)	Cyclohexanol	I^-	3 606	3 407	199	1.9
($^{13}I^-$)	t-Butyl alcohol	I^-	3 603	3 422	181	1.9
($^{14}I^-$)	Phenol	I^-	3 597	3 258	339	1.0

[a] Data were obtained using chloroform solutions of a mixture of the alcohol and tetra-n-butylammonium halide. [b] *c* 0.0087—0.0113 mol dm^{-3}. [c] *c* 0.0314—0.0347 mol dm^{-3}.

contribution of the canonical structure (Va) [equation (1)], the higher is the $\nu_{C=O}$ value. Here, let us consider the factors influencing the double bond character of the acetoxy-carbonyl group. For the free amines examined, there are no factors to prevent the polarization of the acetoxy-carbonyl group, except the weak inductive effect of the β-amino-group. For ammonium halides, however, there is a potent factor which decreases the contribution of polarized structure (Vb). In the rigid molecules examined, the ester oxygen atom, O*, of the O*Ac group is fixed in a position close to the ammonium cationic head. Thus, the polarized structure (Vb) is destabilized by the effect of the charge (*i.e.* electrostatic) interaction. In other words, the ammonium cationic head close to O* suppresses the polarization of the acetoxy-group and therefore increases the double-bond character of the acetoxy-carbonyl, causing a shift to higher wave-number. A similar situation is also considered for acetylcholine assuming the overwhelming predominance of the *gauche*-form. With the β-substituted system, N^+CCO^*Ac, a dependence of $\Delta\nu_{C=O}$ upon the torsion angle N^+CCO^*, τ, was found (see Figure 4). This supports the importance of the effect of the through-space charge interaction. The internal distance between O* and the ammonium function increases with an increase of τ in the range of $0° \lesssim \tau \lesssim 180°$; the charge interaction is attentuated as the distance increases.

TABLE 4

I.r. spectral data of the C=O stretching band of acetates in chloroform [a]

Compound	Form	$\nu_{C=O}$/cm^{-1}		$\Delta\nu_{C=O}$/cm^{-1}	10^{-4} $A_{C=O}$/ mol^{-1} dm^3 cm^{-2}	τ [b] (°)
(4d)	*trans*	1 725		0		
(4e)	*trans*	1 742	(1 739) [c]	14 [d]	2.47	120
		1 726			0.58	
(6b)	*trans*	1 748	(1 742) [c]	17 [d]		108
		1 732				
(5d)	*cis*	1 730	(1 727) [c]	0		
		1 721				
(5e)	*cis*	1 759		32 [e]	2.38	0
(7b)	*cis*	1 753		26 [e]		12
(8d)		1 732 [f]	1 733 [g]	0		
(8e)			1 733 [g]			
(8f)	*gauche*	1 750.5	1 749.0 [h]	18.5 [i]		
(8g)	*gauche*	1 753.5	1 749.5 [h]	21.5 [i]		77
(8h)	*gauche*	1 754.5	1 750.0 [h]			
(3f)		1 742.8		25.3	2.74	60
(9a)		1 726		0	3.93	
(9b)		1 750		24 [j]	3.56	60
(10a)		1 722		0	4.11	
(10b)		1 750		28 [k]	3.77	
Isopropyl acetate (15)		1 723 [f]		0		
t-Butyl acetate (16)		1 721.5 [f]		0		
Phenyl acetate (17)		1 763.5	(1 755) [c]	32 [l]		
		1 743.0				

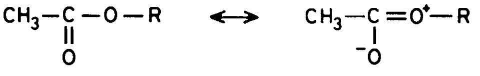
[a] c < 0.001 mol dm^{-3}. [b] Torsion angle N^+CCO, τ, was estimated on the basis of electron diffraction (A. Yokozeki, K. Kuchitsu, and Y. Morino, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 2017; A. Yokozeki and K. Kuchitsu, *ibid.*, 1971, **44**, 2356) and *X*-ray data (ref. 29; W. Fedeli, G. Giacomello, S. Cerrini, and A. Vaciago, *J. Chem. Soc. B*, 1970, 1190; L. Gylbert and D. Carsbtröm, *Acta Crystallogr.*, 1977, **B33**, 2833) of analogous compounds, except for (8g).[10] [c] The values in parentheses are the centre of gravity frequencies for the $\nu_{C=O}$ band. [d] $\Delta\nu_{C=O} = \nu_{C=O} - 1\,725$ (4d). [e] $\Delta\nu_{C=O} = \nu_{C=O} - 1\,725$ (5d). [f] In $CHCl_3$; value from K. J. Morge and N. Unwin, *J. Chem. Soc. B*, 1968, 880. [g] In DMSO; values from ref. 14. [h] In CH_3CN. [i] $\Delta\nu_{C=O} = \nu_{C=O}$ (in $CHCl_3$) $- 1\,732$ (8d). [j] $\Delta\nu_{C=O} = \nu_{C=O} - 1\,726$ (9a). [k] $\Delta\nu_{C=O} = \nu_{C=O} - 1\,722$ (10a). [l] $\Delta\nu_{C=O} = \nu_{C=O} - 1\,732$ (15).

TABLE 5

I.r. spectral data of the C=O stretching band of acetates in D_2O

Compound	Form	$\nu_{C=O}$/cm^{-1}	
(4e)	*trans*	1 719	
(6b)	*trans*	1 721	
(5e)	*cis*	1 749	(1 735) [a]
		1 731	
(7b)	*cis*	1 735	(1 731) [a]
		1 718	
(3f)		1 732	
(8f)	*gauche*	1 732	
(8g)	*gauche*	1 732	
(9b)		1 728	

[a] The values in parentheses are the centre of gravity frequencies for the $\nu_{C=O}$ band.



$$\mathrm{CH_3-\underset{\underset{O}{\|}}{C}-O-R} \longleftrightarrow \mathrm{CH_3-\underset{\underset{^-O}{|}}{C}=O^{+}-R} \qquad (1)$$

(Va) (Vb)

Very small differences (1—2 cm^{-1}) in $\Delta\nu_{C=O}$ depending on the type of halide ion were also found (in the order $I^- > Br^- > Cl^-$). With different halide anions, some difference in the distance between X^- and OAc can be presumed to exist, and this perhaps has a weak influence on the polarization of the acetoxy-carbonyl through the charge interactions.

To diminish the effect of the halide ion, i.r. measurements were made of representative molecules in D_2O, in which the halide ion is released from the ammonium cation. Observation of the same $\nu_{C=O}$ value, **1 732 cm^{-1}**, for (8f, g) indicates that the effect of the halide ion is excluded in D_2O. The data listed in Table 5 also show i.r. behaviour similar to that observed in $CHCl_3$, except for the neglibible effect of halide ion. This shows that the geometric relationship in the ammonium cation is a very important factor controlling the $\nu_{C=O}$ value.

The influence of electrostatic interaction in acetylcholine was proposed by Canepa,[15,29] but the through-bond inductive effect in a series of salts, AcO-$[CH_2]_n$-$N^+(CH_3)_3X,^-$ was considered by Fellman and Fujita to be the most important factor controlling $\nu_{C=O}$.[14] When n is 0 or 1, we agree that the inductive effect is very important. However, with molecules having $n = 2$, our data suggest the importance of the geometric factor which influences the through-space interaction. The inductive effect cannot be neglected even at $n = 2$, because the ammonium group is extremely electron withdrawing. The values of 1 722 and 1 750 cm^{-1} obtained for (10a, b), respectively, offer useful information for comparing the contribution of the through-space charge effect with that of the through-bond inductive effect. Compound (10b) has the γ-substituted system N^+–C–C–C–O*Ac, in which a clear decrease of the inductive effect can be expected by comparison with the β-substituted relationship. On the other hand, the relationship for N^+ and O* is especially close; according to molecular models, the shortest distance between the N^+ and O* atoms in the molecules examined is that for (10b). The large shift to higher wavenumber ($\Delta\nu_{C=O}$ 28 cm^{-1}) observed for (10b), which is comparable to that for the *cis*-relationship in the β-substituted system [$\Delta\nu_{C=O}$ (*cis*) 26—32 cm^{-1}] and larger than that for the *gauche*- or *trans*-relationship [$\Delta\nu_{C=O}$ (*gauche*) 18.5—21.5, $\Delta\nu_{C=O}$ (*trans*) 14—17 cm^{-1}], clearly indicates the important contribution of through-space interaction. However, the largest $\Delta\nu_{C=O}$ value (32 cm^{-1}) in the molecules examined is that for (5e), in spite of the fact that the distance $R_{N^+\cdots O^*}$ in (5e) is slightly larger than that in (10b). This suggests that other factors including the through-bond inductive effect have some influence on $\Delta\nu_{C=O}$.

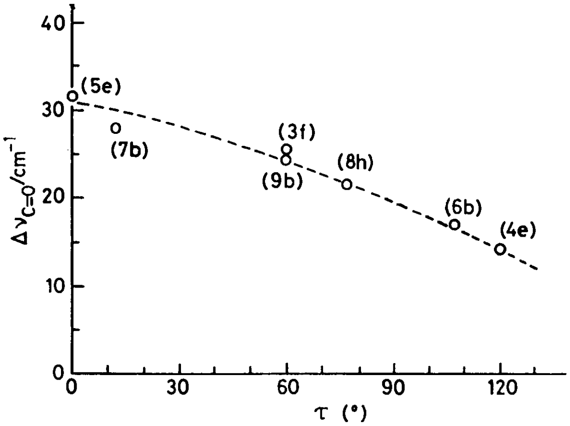
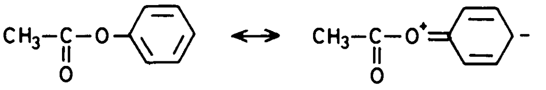


FIGURE 4 Correlation between $\Delta\nu_{C=O}$ of the O*Ac group and torsion angle NCCO* (τ) in quaternary ammonium iodides having a β-OAc group. Because of the lack of *X*-ray data for (8h), the τ value observed for bromide (8g) was used[10]

Savage *et al.*[32] reported that the shifts to higher wavenumber found in 3α,17β-diacetoxy-2β,16β-dipiperidino-5α-androstane bismethobromide [$\Delta\nu_{C=O}$ (3-OAc) 21, $\Delta\nu_{C=O}$ (17-OAc) 29 cm^{-1}] are ascribable to an intramolecular hydrogen bond, CH · · · O*Ac, between CH in the ammonium group and O* of O*Ac. They attributed the disparity in $\Delta\nu_{C=O}$ between 3- and 17-OAc to the difference in interatomic distance [$R_{C\cdots O^*}$ (3-OAc) 2.96, $R_{C\cdots O^*}$ (17-OAc) 2.95 and 3.02 Å]. However, in spite of the fact that 3α-acetoxy-5α-hydroxycholestane has a hydroxy-group which is a stronger proton donor than CH and the interatomic distance $R_{O\cdots O^*}$ (*ca.* 2.55 Å) is shorter than $R_{C\cdots O^*}$ in the above compound, the $\Delta\nu_{C=O}$ value (13 cm^{-1}) observed for 3α-acetoxy-5α-hydroxycholestane[33] is smaller than that for the above compound. This suggests that the shift to higher wavenumber of acetoxy-carbonyl is primarily governed by the charge interaction discussed rather than the CH · · · O*Ac hydrogen bonding.

The $\Delta\nu_{C=O}$ values of tertiary ammonium halides (2f—h) are smaller than those of the quaternary ones (3d—f) by 2.4—2.7 cm^{-1} (see Table 1). This may be ascribable to the decrease of the positive charge of the tertiary ammonium group, which is caused by the strong hydrogen bond, $N^+H \cdots X^-$, and attenuates the charge interaction effect on the acetoxy-group. Thus, we propose an important contribution by through-space charge interaction in controlling $\Delta\nu_{C=O}$ on the basis of the observations of the torsion angle dependence of $\Delta\nu_{C=O}$ in the β-substituted system and a large $\Delta\nu_{C=O}$ value in the γ-substituted system (10b).

(c) *Correlation between* $\Delta\nu_{OH}$*(alcohol) and* $\Delta\nu_{C=O}$*(acetate).*—The shifts to lower wavenumber, $\Delta\nu_{OH}$, attributed to intermolecular hydrogen bonding, $OH \cdots X^-$, between cyclohexanol (12), t-butyl alcohol (13), or phenol (14), and tetra-n-butylammonium halide in $CHCl_3$ are shown in Table 3. Because of the resonance between the benzene ring and one of the lone pair electrons of the oxygen atom in the hydroxy-group, the $\Delta\nu_{OH}$ value of phenol is about two times greater than that for a saturated alcohol such as cyclohexanol or t-butyl alcohol; by the resonance effect, the OH bond of the former is more polarized than that of the latter. Compared with the $\nu_{C=O}$ value (*ca.* 1 723 cm^{-1}) of a saturated acetate such as isopropyl acetate (15), the $\nu_{C=O}$ value (1 755 cm^{-1}) observed for phenyl acetate (17) is *ca.* 32 cm^{-1} higher.



(2)

Again, the most important factor for this shift is considered to be the resonance effect.[30,31] The resonance shown in equation (2) suppresses the π-bond polarization of the C=O bond, and increases the double-bond character of the C=O bond to cause the shift to higher wavenumber.

As shown in Figure 5, a plot of $\Delta\nu_{OH}$ for saturated alcohols, alcohols with a β-ammonium function, and phenol *versus* $\Delta\nu_{C=O}$ for saturated acetates, acetates with a β-ammonium function, and phenyl acetate indicates fairly linear correlations differentiated by the type of halide ion. The plotted points for the saturated alcohols and acetates and those for phenol and phenyl acetate are located at the terminals of the lines, and those for alcohols and acetates having the β-ammonium function are at intermediate positions, reflecting the geometric relationship of the β-substituents (*viz. cis*, *gauche*, or *trans*). Figure 5 indicates that the polarization of the OH bond in (5b or c), which is due to the β-ammonium function, is comparable to that caused by the resonance effect in phenol and that the suppressive effect of the ammonium function on polarization of the carbonyl π-bond in acetate (5e) is also comparable to the resonance effect in phenyl acetate (17). In conclusion, we rationalize this result by through-space interaction between the ammonium function and the lone pair electron of the β-oxygen atom.

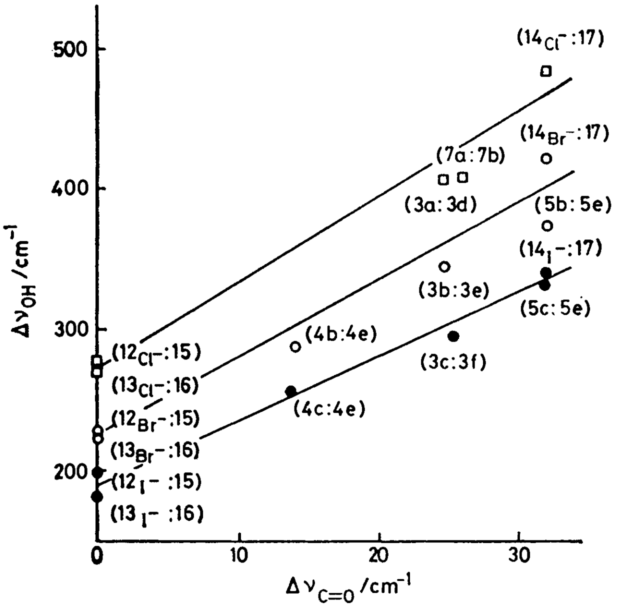


FIGURE 5 Correlation between $\Delta\nu_{OH}$ for OH · · · X^- in alcohols and $\Delta\nu_{C=O}$ for acetates: $X^- = Cl^-$ (□), Br^- (○), and I^- (●). Because of the lack of model compounds, a substitute (halide) was used. Fortunately, the halide ion has a very small effect on $\Delta\nu_{C=O}$ (see the text and Tables 1 and 4)

The information obtained in the present study should be useful for understanding the i.r. behaviour found in analogous systems such as phosphonium salts and for investigating intra- and inter-molecular interactions.

We thank Drs. T. Kubota of Gifu College, Y. Matsui, K. Tori, and M. Yamakawa, and Mr. K. Ezumi for helpful discussions, and Drs. W. L. Nelson and R. S. Wilson, University of Washington, Drs. Y. K. Sawa, H. Tada, Y. Takano, and Y. Hamashima, and Mr. S. Maeda for providing samples.

[1/1423 *Received, 10th September*, 1981]

REFERENCES

[1] H. Lund, *Acta Chem. Scand.*, 1958, **12**, 298.

[2] J. B. Hyne and R. M. Levy, *Can. J. Chem.*, 1962, **40**, 692.

[3] A. Allerhand and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1963, **85**, 371, 1233.

[4] V. P. Glazunov, A. A. Mashkovsky, and S. E. Odinokov, *J. Chem. Soc., Faraday Trans. 2*, 1979, 629.

[5] P. C. Dwivedi and C. N. R. Rao, *Spectrochim. Acta*, 1970, **26A**, 1535.

[6] E. Moreno-Gonzalez, M. Marraud, and J. Neel, *J. Chim. Phys.*, 1977, **74**, 563.

[7] R. R. Ryall, H. A. Strobel, and M. C. Symons, *J. Phys. Chem.*, 1977, **81**, 253.

[8] P. Bacelon, J. Corset, and C. de Lozé, *Chem. Phys. Lett.*, 1975, **32**, 458.

[9] J. B. Rulinda and T. Zeegers-Huyskens, *Bull. Soc. Chim. Belg.*, 1978, **87**, 329.

[10] F. G. Canepa, P. J. Pauling, and H. Sörum, *Nature (London)*, 1966, **210**, 907.

[11] C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, 1966, 537.

[12] R. J. Cushley and H. G. Mautner, *Tetrahedron*, 1970, **26**, 2151.

[13] Y. Terui, M. Ueyama, S. Satoh, and K. Tori, *Tetrahedron*, 1974, **30**, 1465.

[14] (*a*) J. H. Fellman and T. S. Fujita, *Nature (London)*, 1966, **211**, 848; (*b*) J. H. Fellman and T. S. Fujita, *Biochim. Biophys. Acta*, 1962, **56**, 227; 1963, **71**, 701.

[15] F. G. Canepa and E. F. Mooney, *Nature (London)*, 1965, **207**, 78.

[16] (*a*) Y. Terui, *J. Chem. Soc., Perkin Trans. 2*, 1975, 119; (*b*) Y. Terui and K. Tori, *ibid.*, p. 127.

[17] M. Froimowitz and P. J. Gaus, *J. Am. Chem. Soc.*, 1972, **94**, 8020.

[18] (*a*) A. Pullman and G. N. J. Port, *Theor. Chim. Acta*, 1973, **32**, 77; (*b*) B. Pullman and P. Courriére, *ibid.*, 1973, **31**, 19; (*c*) D. Ajö, M. Bossa, R. Fidenzi, S. Gigli, G. Jeronimidis, A. Damiani, and A. Lapiccirella, *ibid.*, 1973, **30**, 275; (*d*) D. L. Beveride and R. J. Radna, *J. Am. Chem. Soc.*, 1971, **93**, 3759; (*e*) H. Johansen and S. Rettrup, *Theor. Chim. Acta*, 1980, **55**, 267.

[19] D. A. Ramsay, *J. Am. Chem. Soc.*, 1952, **74**, 72.

[20] Y. K. Sawa and H. Tada, *Tetrahedron*, 1968, **24**, 6185.

[21] Y. K. Sawa, M. Horiuchi, and K. Tanaka, *Tetrahedron*, 1965, **21**, 1133.

[22] (*a*) Y. Hamashima, K. Tori, and A. Takamizawa, *Chem. Pharm. Bull.*, 1963, **13**, 1052; (*b*) Y. Terui, K. Aono, and K. Tori, *J. Am. Chem. Soc.*, 1968, **90**, 1069.

[23] K. Kitahonoki, Y. Takano, and H. Takahashi, *Tetrahedron*, 1968, **24**, 4605.

[24] K. Tsuda, S. Nozoe, T. Takazawa, and S. M. Sharif, *J. Org. Chem.*, 1963, **28**, 795.

[25] W. L. Nelson and R. S. Wilson, *J. Med. Chem.*, 1971, **14**, 169.

[26] A. R. H. Cole, L. H. Little, and A. J. Michell, *Spectrochim. Acta*, 1965, **21**, 1169.

[27] M. Takasuka, Y. Matsui, and T. Kubota, *Spectrosc. Lett.*, 1976, **9**, 821.

[28] L. Pauling, 'The Nature of the Chemical Bond,' Cornell Univ. Press, New York, 1960, p. 526.

[29] F. G. Canepa, *Nature (London)*, 1965, **207**, 1152.

[30] R. N. Jones and C. Sandorfy, 'Chemical Applications of Spectroscopy,' ed. W. West, Interscience, New York, 1956, p. 483.

[31] M. Takasuka and H. Tanida, *J. Chem. Soc., Perkin Trans. 2*, 1980, 486.

[32] D. S. Savage, A. F. Cameron, G. Ferguson, C. Hannaway, and I. R. Macky, *J. Chem. Soc. B*, 1971, 410.

[33] R. N. Jones and F. Herling, *J. Org. Chem.*, 1954, **19**, 1252.