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Intramolecular Hydrogen Bonds. XVIII.[1] Intramolecular Hydrogen Bonding in Ethyl α- and β-Alkylamino-alkanoates[2]

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The intramolecular hydrogen bonding in ethyl ω-alkylamino-acetates and -propionates in dilute carbon tetrachloride solutions has been investigated through the measurement of the NH and CO stretching absorption spectra. In the α-esters, the spectral data give no evidence regarding the hydrogen-bond formation. In the β-esters, though, the hydrogen bonding occurs, probably predominantly between the NH and the CO group.

It is known[3] that the hydrogen-donating nature of an amino group is much lower than that of a hydroxyl group, but higher than that of a mercapto group. Infrared spectroscopic investigations indicate that ethyl α- and β-hydroxyalkanoates[4,5] form an intramolecular hydrogen bond, exclusively between the OH and the CO group: thereby, their absorption bands are largely shifted to the lower-frequency side. In the corresponding mercapto-esters,[1] however, there is no spectral evidence for any hydrogen-bond formation between the SH and the ester group, indicating the very poor hydrogen-donating nature of the mercapto group, which is generally recognized.[6] These results have prompted us to investigate the intramolecular hydrogen bonding in the corresponding alkylaminoalkanoates as well.

Experimental

Samples. Ethyl alkylamino- and dialkylamino-acetates were prepared from the corresponding alkylamino-acetonitriles[7] by the usual method.[8] Ethyl β-alkylamino- and β-dialkylamino-propionates were synthesized by the addition of alkylamines to ethyl acrylate in ethanol.[9] The ethyl ethers of ω-ethylaminoalkanols were obtained by the reaction of ω-ethoxyalkyl bromides with ethylamine. They were then purified by several fractional distillations in an atmosphere of nitrogen immediately before the infrared measurement; their purity was checked by means of IR and/or NMR spectroscopy. Some of the samples are unknown compounds, whose analytical data and physical constants are summarized in Table 1. The solvents used were dried over phosphorus pentoxide and distilled.

Infrared Measurements. This was carried out at 20°C, using a grating spectrophotometer of the Japan Spectroscopic Co.[7] The concentrations used were 0.003 mol/*l* (NH spectra; cell-thickness: 5.0 cm) and 0.001 or 0.01 mol/*l* (CO spectra; cell-thickness: 1.1 or 0.1 cm), unless otherwise noted. The calculated spectral slit width was 1.5 cm^{-1} at the wave numbers of 3300 and 1700 cm^{-1}.

Results and Discussion

The analytical data of the unknown compounds are summarized in Table 1.

Table 1. Analytical data of unknown compounds

Compound	R	Bp °C/mmHg	n_D^{20}	Anal. of N, % Found	Anal. of N, % Calcd
$RNHCH_2$-COOEt	*i*-Pr	71/21	1.4204	9.70	9.65
	t-Bu	75/18	1.4230	9.00	8.80
$RNH(CH_2)_2$-COOEt	*i*-Pr	87/20	1.4232	8.78	8.80
	t-Bu	76/6	1.4254	8.07	8.09

In order to determine the level of concentration below which the intermolecular association is negligible, the concentration dependence has been examined. Figures 1 and 2 show the spectra of two esters in various concentrations in carbon tetrachloride in the NH stretching region. At higher concentrations, three absorptions appear. On dilution, the lowest-frequency band practically disappears, the middle-frequency band increases in its intensity and frequency, and the highest-frequency band remains almost unchanged. Below a certain concentration, the relative intensity of the last two bands remains constant; from their frequencies and intensities, the

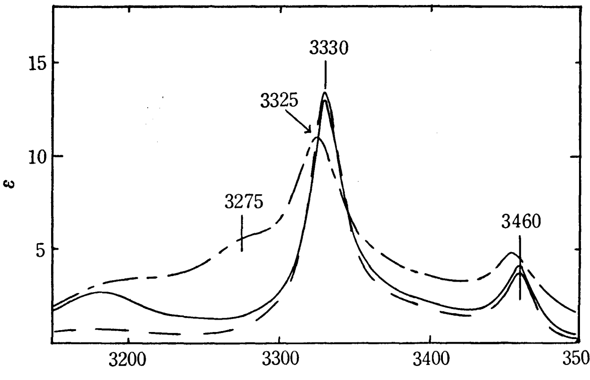

Fig. 1. NH spectra of ethyl *N*-isopropylaminoacetate in various concentrations: neat (----), 0.1 mol/*l* (——), and 0.01 and 0.003 mol/*l* (—-—).

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[1] Part XVII: N. Mori, S. Kaido, K. Suzuki, M. Nakamura, and Y. Tsuzuki, This Bulletin, **44**, 1858 (1971).

[2] A part of this report was presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, 1968, No. 1109.

[3] See, for example, G. C. Pimental, and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco (1960), p. 92.

[4] N. Mori, S. Ōmura, N. Kobayashi, and Y. Tsuzuki, This Bulletin, **38**, 2149 (1965).

[5] N. Mori, Y. Asano, and Y. Tsuzuki, *ibid.*, **41**, 1871 (1968).

[6] For example, Ref. 3, p. 201.

[7] N. Mori, Y. Asabe, J. Tatsumi, and Y. Tsuzuki, This Bulletin, **43**, 3227 (1970).

[8] N. J. Leonard and E. Barthel, *J. Amer. Chem. Soc.*, **72**, 3632 (1950).

[9] R. W. Holley and A. D. Holley, *ibid.*, **71**, 2124 (1949); they used methanol as the solvent. We have found that the products obtained in methanol are contaminated with considerable amounts of the corresponding methyl esters.

Table 2.[a] Apparent spectral data of ethyl alkylaminoalkanoates

Compound	In CCl_4						In CH_3CN		
	ν_{NH} cm^{-1}	$\Delta\nu_{1/2}$	ε	ν_{CO} cm^{-1}	$\Delta\nu_{1/2}$	ε	ν_{CO} cm^{-1}	$\Delta\nu_{1/2}$	ε
CH_3NHCH_2COOEt	3348	29	16	1742	17	620	1738	20	450
				(1736)		(100)	(1727)		(80)
$C_2H_5NHCH_2COOEt$	(3348)			1742	17	620	1738	20	450
	3330	40	12	(1736)		(100)	(1728)		(80)
i-$C_3H_7NHCH_2COOEt$	3330	33	13	1742	17	620			
				(1736)		(100)			
t-$C_4H_9NHCH_2COOEt$	3325	30	13	1742.5	17	630			
				(1736)		(100)			
$(CH_3)_2NCH_2COOEt$				1756		250	1746		380
				1738		275	1731		280
$(C_2H_5)_2NCH_2COOEt$				1756		240			
				1740		390			
$CH_3NH(CH_2)_2COOEt$	(3360)			1736	17	500	1730	18	470
	3338	38	13						
$C_2H_5NH(CH_2)_2COOEt$	(3338)			1736	17	520	1730	18	480
	3318	43	10						
i-$C_3H_7NH(CH_2)_2COOEt$	(3341)			1736	17	570			
	3320	46	8						
t-$C_4H_9NH(CH_2)_2COOEt$	(3332)			1736	17	560			
	3314	39	8						
$(C_2H_5)_2N(CH_2)_2COOEt$				1740	17	570	1729	19	480
$C_2H_5NH(CH_2)_2OEt$	3338		3						
	3322		7						
$C_2H_5NH(CH_2)_3OEt$	3330		6						
	3300		3						

a) The numerical values in parentheses are those estimated approximately by band reflection.

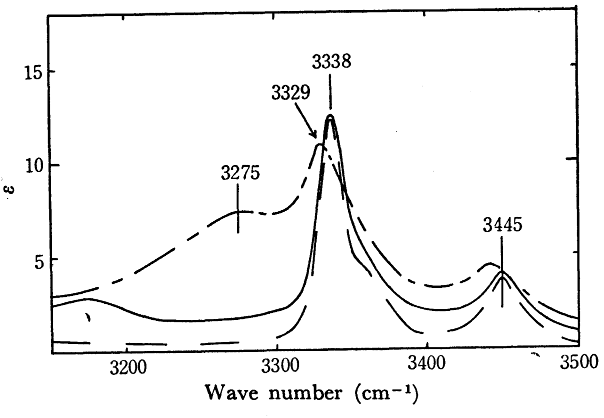

Fig. 2. NH spectra of ethyl β-(N-methylamino)-propionate in various concentrations: neat (– – –), 0.1 mol/l (——), and 0.01 and 0.003 mol/l (—·—).

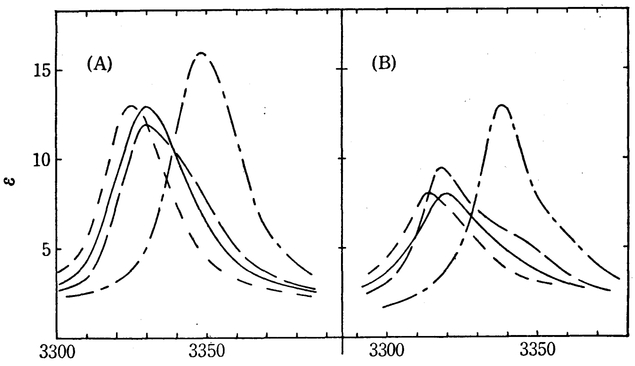

Fig. 3. NH spectra of ethyl N-alkylaminoacetates (A) and β-N-alkylaminopropionates (B); alkyl=methyl (— — —), ethyl (– – –), isopropyl (——) and t-butyl (—·—·—) (concentration 0.003 mol/l; cell 5.0 cm).

band near 3350 cm^{-1} can be assigned to the monomeric NH species, and the other, near 3450 cm^{-1}, probably to the carbonyl overtone.[10] Furthermore, these esters are practically monomeric in concentrations of 0.01 mol/l or less.

The NH Spectra. As Fig. 3A shows, the bands of ethyl alkylaminoacetates, when the alkyl group is methyl, isopropyl, or t-butyl, are very slightly broadened on the higher-frequency side, while the ethyl-

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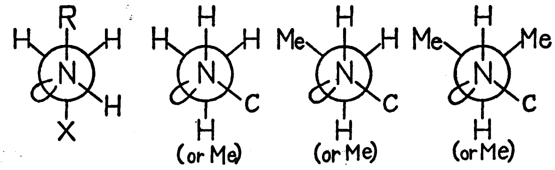
[10] L. Joris and P. von R. Schleyer, *ibid.*, **90**, 4599 (1968).

amino-ester shows a highly unsymmetric band. On the other hand, the band of each β-alkylamino-propionate is very much broadened at a frequency higher by *ca.* 20 cm^{-1} than the maximum position (Fig. 3B). The apparent spectral data are summarized in Table 2.

In discussing the data, it may be convenient to examine the molecular model with respect to the rotational isomerism around the N–C bonds. In this examination, the following assumptions were made:7) (1) the tricovalently-bound nitrogen atom takes a tetrahedron-like structure, (2) the molecule exists in a staggered conformation, but not in an eclipsed one, and (3) the lone electron-pair on the nitrogen atom is practically equal in steric size to the hydrogen atom.

In Fig. 4, the projections, IA and IB, are made along the N–C$_{\alpha}$ bond of ethyl alkylaminoacetates and along the N–C$_{\beta}$ bond of ethyl β-alkylaminopropionates respectively, while the projections, II, III, and IV, are those along the N–C$_{R}$ bond, where C$_{R}$ denotes the carbon atom of an alkyl group, R, directly attached to the amino-nitrogen atom; the circle denotes the C$_{\alpha}$ atom in IA, the C$_{\beta}$ atom in IB, or the C$_{R}$ atom in II, III, and IV.



IA: X=COOEt II III IV
IB: X=CH$_2$COOEt

Fig. 4. Projections along the N–C$_{\alpha}$ (IA) or the N–C$_{\beta}$ bond (IB) and along the N–C$_{R}$ bond (II, III and IV).

All the acetates may sterically prefer the same conformation, IA, with respect to the C$_{\alpha}$–N bond, in which the bulky groups, R and X, are *trans*. The observed differences in peak frequencies may be explained by the steric effect of R, as has previously been done for similar phenomena observed in alkylmethylamines7) and *N*-alkylanilines.11) When R is methyl or *t*-butyl, the amino-hydrogen atom always exists in the environment, II or IV respectively, in any rotational position about the N–C$_{R}$ bond to be favored. In the case of *t*-butyl, thus, the lowering of the NH frequency by 23 cm^{-1} seems attributable to the presence of the two methyl groups *skew* to the NH group. When R is ethyl, there are two steric environments, II and III, around the NH group; the latter may be sterically preferable because of the methyl and the C-group being *trans*. In view of the steric preference, thus, the major component of the unsymmetric band can be assigned to III, and the minor component at the higher frequency can be assigned to II and may correspond to the band of ethyl methylaminoacetate. Finally, when R is isopropyl, two environments, III and IV, are likewise possible; they are practically indiscriminative in steric preference. Thus, the observed, almost symmetric band probably consists of two bands corresponding to these environments, III and IV. The same explanation can apply to the case of the β-esters, because the same steric environments around the NH group are expected.

In addition to the steric stabilization, the conformations, IA and IB, can probably involve a further stabilization resulting from the possible hydrogen bonding between the NH and the COOEt group, as would be expected from a similar situation in the corresponding α- and β-hydroxyalkanoates, which are exclusively internally bonded.4,5) In the case of the aminoacetates, however, the NH spectral data give no striking evidence for the hydrogen-bond formation. That is, (1) there is no appreciable band-shift from the ν_{NH} values of alkylmethylamines7) to the lower-frequency side, (2) the half-band widths are very close to those of alkylmethylamines,7) and (3) the high band-intensites, as compared with those of the latter amines,7) may also be caused by the electron-attractive nature of the ethoxycarbonyl group. On the other hand, ethyl β-alkylaminopropionates may be internally bonded, as can be evidenced by their lower NH frequencies and high band intensities. A similar result is found in α- and β-alkylaminoalkanonitriles.7) These findings, particularly the absence of hydrogen bonding in the α-esters, are not expected from the fact that the ethyl ethers of ω-ethylamino-ethanol and -propanol are internally bonded, with similar 5- and 6-membered rings being formed through the bonding.

Recent infrared investigations indicate that an intramolecular hydrogen bonding occurs in *o*-substituted anilines,12) pyrrolic esters,13) 2-methylamino-ethanol,14) acetylureas,15) and *N*-ω-phenoxyalkyl-anilines.16) In these cases, the shifts observed in the NH frequencies are very small as compared with those in the corresponding OH bondings, indicating a considerably weaker hydrogen bond, although the frequency shifts of the hydrogen-acceptor groups are larger than those which would be expected from the NH shifts, indicating a considerably strong bond. For example, in methyl *N*-methylanthranilate,17) the $\Delta\nu_{NH}$ is 81 cm^{-1} from the free ν_{NH} assumed to be equal to the ν_{NH} of 3442 cm^{-1} of *N*-methylaniline, while the $\Delta\nu_{CO}$ is 45 cm^{-1} from the ν_{CO} of 1730 cm^{-1} of methyl *N,N*-dimethylanthranilate (*cf.*, in methyl salicylate, $\Delta\nu_{OH}$: *ca.* 430 cm^{-1}; $\Delta\nu_{CO}$: *ca.* 40 cm^{-1}).17,18) In the present case, accordingly, an examination of the carbonyl spectra has been carried out.

The Carbonyl Spectra. Ethyl dialkylamino-

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11) M. Ōki and K. Mutai, This Bulletin, **33**, 784 (1960).

12) A. N. Hambly and B. V. O'Grady, *Aust. J. Chem.*, **15**, 626 (1963); P. J. Krueger, *Can. J. Chem.*, **41**, 363 (1963); J. D. Scribner and J. A. Miller, *J. Org. Chem.*, **32**, 2348 (1967).

13) R. Grigg, *J. Chem. Soc.*, **1965**, 5149.

14) P. J. Krueger and H. D. Mettee, *Can. J. Chem.*, **43**, 2970 (1965).

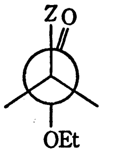
15) C. I. Jose and P. R. Pabrai, *Spectrochim. Acta*, **23A**, 736 (1967).

16) M. Ōki and K. Mutai, *ibid.*, **25A**, 1941 (1969).

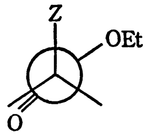
17) R. S. Rasmussen and R. R. Brattain, *J. Amer. Chem. Soc.*, **71**, 1073 (1949).

18) C. J. W. Brooks, G. Eglinton, and J. F. Morman, *J. Chem. Soc.*, **1961**, 661; N. Mori, Y. Asano, and Y. Tsuzuki, This Bulletin, **42**, 488 (1969).

acetates show, in carbon tetrachloride, two overlapped bands with a spacing of about 15 cm^{-1}, and the intensity of the higher-frequency band increases in acetonitrile relative to that of the lower-frequency band (Fig. 5A). By analogy with the cases of α-halogeno-[19] and α-alkoxy-carbonyl compounds,[5,20] this band splitting can be suitably explained by the rotational isomerism around the C_1–C_2 bond. Thus, the two bands can be assigned to the *cis* and the the *gauche* forms respectively:



cis-Form with a higher ν_{CO}



gauche-Form with a lower ν_{CO}

In carbon tetrachloride, the relative intensity (*cis* to *gauche*) increases with the α-substituents in the order: Et_2N (0.6)<Me_2N (0.9). Thus, the diethylamino group is larger in steric size than the dimethyl amino group if the steric size of the α-substituent is the most important factor in determining the *cis-gauche* equilibrium[20]

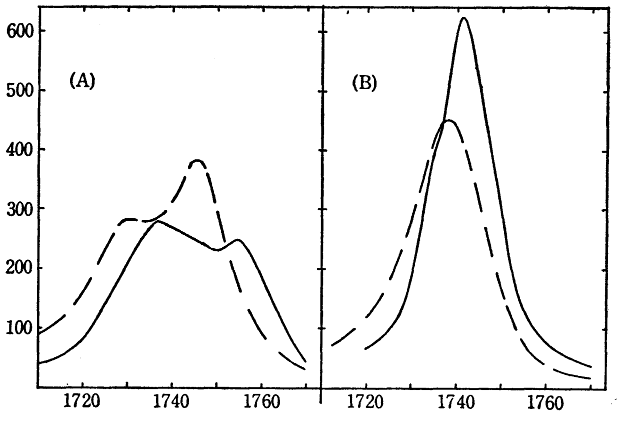


Fig. 5. Carbonyl spectra of ethyl dimethylaminoacetate (A) and of ethyl monomethylaminoacetate (B) in acetonitrile (– – –) and carbon tetrachloride (——): concentration 0.01 mol/*l*; cell 0.11 cm.

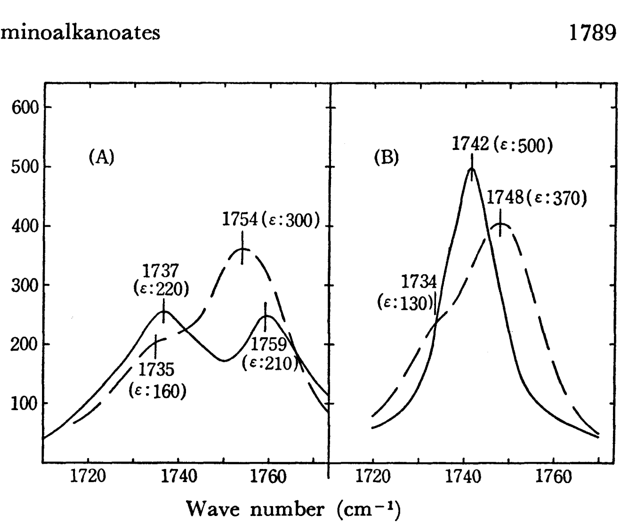


Fig. 6. Carbonyl spectra of ethyl methoxyacetate (A) and of ethyl glycolate (B) in acetonitrile (– – –) and carbon tetrachloride (——): concentration 0.01 mol/*l*; cell 0.11 cm. The ε values of the band components are given in parentheses.

On the other hand, ethyl monoalkylaminoacetates show, in carbon tetrachloride, a strong band at 1742 cm^{-1}, with a very weak shoulder centered near 1736 cm^{-1}. In acetonitrile, a single, somewhat broadened band appears at 1738 cm^{-1}; this band corresponds to the higher-frequency band observed in carbon tetrachloride, since a more polar solvent has the effect of decreasing the ν_{CO}. If no intramolecular hydrogen bonding occurs in carbon tetrachloride, as has been suggested from the NH data, the unsymmetry of the band may again be attributed to the *cis-gauche* isomerism. If this is true, the following two points should be noticed: (1) the band spacing in each solvent is smaller than those of the corresponding dialkylaminoacetates, or the peak-frequency in each solvent is lower than those of the *cis* form of the latter esters (the same trend is found in the cases of ethyl glycolate and methoxyacetate), and (2) the intensity ratio (*cis* to *gauche*) of *ca.* 6 is so high as to be not expected, unless an intramolecular hydrogen bonding or attractive interaction occurs to stabilize the *cis* form. The first point can, at least in part, be explained in terms of the lower electron density on the monoalkylamino-nitrogen atom, since the C–N dipole with a lower electron density on the N atom should have the lower field effect of decreasing the double-bond character (or ν_{CO}) of the carbonyl group in the *cis* form.

As for the second point, if the *cis-gauche* equilibrium is determined predominantly by the size of the α-substituent,[20] and if the nonomethylamino group is smaller in size than the dimethylamino group, the former group can be expected to give an intensity ratio higher than the 0.9 of the latter. This expectation agrees with our observation, but the observed ratio of 6 seems too high to be attributed to the decreased steric effect only,[1] since such a high ratio is generally found in internally-bonded carbonyl compounds such as α-hydroxyalkanoates.[5] The high ratio in carbon tetrachloride may be suitably explained by taking account of an attractive interaction which may be operative between the NH and the CO group in the *cis* form in that solvent, but not in acetonitrile, which associates with the NH group to prevent the intramolecular interaction (observed ν_{NH}: 3340 cm^{-1} lower by 8 cm^{-1} than in CCl_4).[21] It is not evident whether the interaction is the usual hydrogen bonding or the electrostatical attraction, but it is probably the latter, because no lowering of the NH frequency is observed. In this connection, it should be mentioned that ethyl glycolate shows, in carbon tetrachloride, an unsymmetric band, because a

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[19] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., London (1958), p. 400.

[20] T. L. Brown, *J. Amer. Chem. Soc.*, **80**, 3513 (1958).

[21] Aliphatic secondary amines have spectral shifts of at most 10 cm^{-1} in acetone from the free ν_{NH}'s in CCl_4.[22]

[22] D. Hagži (Ed.), "Hydrogen Bonding," Pergamon Press, New York (1959), p. 181.

strong hydrogen bond is formed exclusively between the OH and the CO group in the *cis* form (ν_{OH}: 3550 cm^{-1}).[4] In acetonitrile, the bonding to the carbonyl is prevented by the intermolecular association with the solvent (observed ν_{OH}: 3480 cm^{-1}), and two carbonyl bands appear with an intensity ratio of 2.8 (Fig. 6): this ratio is larger than the value of 2 of ethyl methoxyacetate (probably because of the smaller size of the hydroxyl group), but it is only half of the 5.5 of ethyl monomethylaminoacetate, although the hydroxyl group is expected to be smaller in size (hence, to give a higher intensity ratio) than the methylamino group. As one of the reasons for this, there can be considered an electrostatic repulsion between the dipoles in the *cis* form;[23] this repulsion is expected to be less operative between the C–N and the C=O dipole than between the C=O and the C–O dipole, because the C–N, especially the C–N(HCH$_3$), dipole may have a lower field effect on the C=O dipole, as is suggested by the order in which the band spacing in acetonitrile increases with the α-substituents: NHCH$_3$ (11 cm^{-1}) < N(CH$_3$)$_2$ (15 cm^{-1}) = OH (14 cm^{-1}) < OCH$_3$ (19 cm^{-1}). It is, of course, not evident whether this repulsion has such a high effect on the *cis-gauche* equilibrium.

Finally, β-dialkylamino, and also β-monoalkylamino, groups have practically no field effect on the carbonyl group, since ethyl β-diethylaminopropionate shows a single, symmetric CO band at the usual position of 1740 cm^{-1}. Furthermore, the ν_{CO} values, lower by 4 cm^{-1}, of ethyl monoalkylaminopropionates indicate that internal bonding to the carbonyl group occurs.

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[23] S. Mizushima, T. Shimanouchi, I. Ichishima, T. Miyazawa, I. Nakagawa, and T. Araki, *J. Amer. Chem. Soc.*, **78**, 2038 (1956). The importance of the steric factor in determining the equilibrium was indicated by Brown[20] for highly electronegative groups, such as halogens and alkoxy groups, but the electrostatic factor should be further considered when the electronegativities of the substituents are very different (*cf.*, usually, μ_{C-N}: 0.22; μ_{C-O}: 0.74).