Infrared Spectra and Intramolecular Hydrogen Bonding of *p*-(Substituted phenoxy)-*α*-(dialkylamino)acetanilides

Kazuhisa ABE,* Minoru HIROTA, Michiharu SUGIURA,** and Yoshiki HAMADA**

Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240

***Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468*

(Received June 28, 1979)

Synopsis. The title compounds were synthesized with pharmaceutical interests, and their infrared spectra in the NH and carbonyl stretching regions were measured. By comparing the spectra with those of *p*-phenoxyacetanilide, intramolecular hydrogen bonds are shown to exist between the amide NH and the α-dialkylamino groups.

The structures and the conformations of many amides and peptides have been discussed on the basis of their infrared spectra and several absorption bands are shown to be characteristic of amide functional group.[1] Among these characteristic absorptions, NH stretching bands and carbonyl stretching bands (amide I bands) are most extensively studied, and the former bands are proved to be very sensitive to the stereochemistry and to the participation in hydrogen bond formation.[2,3]

On pharmaceutical interests, a series of *p*-(substituted phenoxy)-*α*-(dialkylamino)acetanilides (**1**) were synthesized[4] and their hydrogen bonding behaviors were studied by measuring their infrared spectra in the NH and carbonyl stretching regions. Since the intra- and intermolecular hydrogen bonds often have remarkable effect on solubility, it can also affect on their biological activities.

Experimental

Syntheses of the *p*-(substituted phenoxy)-*α*-(dialkylamino)-acetanilides were reported previously.[4] Infrared spectra in solutions were measured with a Hitachi 225 recording spectrophotometer. Concentrations of the solutions were about 1×10^{-3} mol/l for the measurements in NH stretching region and about 5×10^{-4} mol/l for the measurement in C=O stretching region, at which concentrations the association of the solute is negligible. Measurement of ^{1}H-NMR spectra were carried out by a JOEL JNM C60-H spectrometer with solutions of which concentrations were about 0.5 mol/l. The chemical shifts (in ppm) of the NH proton siginals are rather insensitive to the changes in concentrations probably due to the formation of strong intramolecular hydrogen bonds.

Results and Discussion

Their infrared spectra were measured in a carbon tetrachloride solution enough dilute to avoid the effect of association in practice and were given in Tables 1 (NH stretching region) and 2 (C=O stretching region). The NH absorption bands of all amides in Table 1 are located at considerably lower frequencies and rather broad with half-widths ranging from 70 to 120 cm^{-1}. On the other hand, *p*-phenoxyacetanilide (**2**) has an NH band at 3448 cm^{-1} ($\varepsilon=188$), being by far a narrower band with a half-width of 10.3 cm^{-1}. In general, the amide group takes predominantly the trans conformation in which NH and C=O groups are anti to each other, and the NH band of trans conformer appears at a higher frequency than that of cis conformer. For example, the trans conformer of acetanilide absorbs at 3446 cm^{-1}, while the cis at 3402 cm^{-1}.[2,5] However the low frequency shifts observed with **1**'s are more than 100 cm^{-1} with reference to the NH frequency of **2**, being too large to attribute to the privileged cis con-

Table 1. NH stretching absorptions of $RC_6H_4OC_6H_4NHCOCH_2Y$ (**1**)[a] in CCl_4

R	Y: $-N(CH_3)_2$	$-N(C_2H_5)_2$	$-N$	$-N(CH_3)$	$-N$ O
H	3329 (109)	3311 (117)	3320 (93)	—	3337 (93)
2-CH_3	—	3310 (114)	3320 (83)	3309 (82)	3338 (107)
3-CH_3	—	3309 (111)	3320 (91)	3303 (95)	3336 (99)
4-CH_3	—	3307 (141)	3319 (116)	3300 (112)	3334 (121)
2-Cl	3330 (95)	3304 (94)	3310 (68)	3302 (86)	3337 (78)
3-Cl	3327 (130)	3309 (99)	3318 (100)	3302 (99)	3333 (99)
4-Cl	3328 (86)	3309 (122)	3314 (91)	3304 (101)	3333 (81)

a) Wave numbers (in cm^{-1}) of the absorption maxima are given together with their intensities ε_{max} (in l mol^{-1} cm^{-1}) in parentheses.

Table 2. C=O stretching absorptions of $RC_6H_4OC_6H_4NHCOCH_2Y$ (**1**)[a] in CCl_4

R	Y: $-N(CH_3)_2$	$-N(C_2H_5)_2$	$-N$	$-N(CH_3)$	$-N$ O
H	1695 (676)	1695 (769)	1697 (579)	—	1697 (532)
2-CH_3	—	1695 (637)	1699 (462)	1694 (496)	1698 (656)
3-CH_3	—	1695 (608)	1698 (569)	1695 (583)	1698 (561)
4-CH_3	—	1699 (754)	1703 (722)	1699 (669)	1703 (636)
2-Cl	1696 (700)	1696 (651)	1697 (392)	1696 (505)	1697 (615)
3-Cl	1697 (740)	1696 (577)	1700 (593)	1697 (562)	1700 (522)
4-Cl	1699 (499)	1699 (719)	1702 (672)	1698 (659)	1702 (550)

a) See footnote of Table 1.

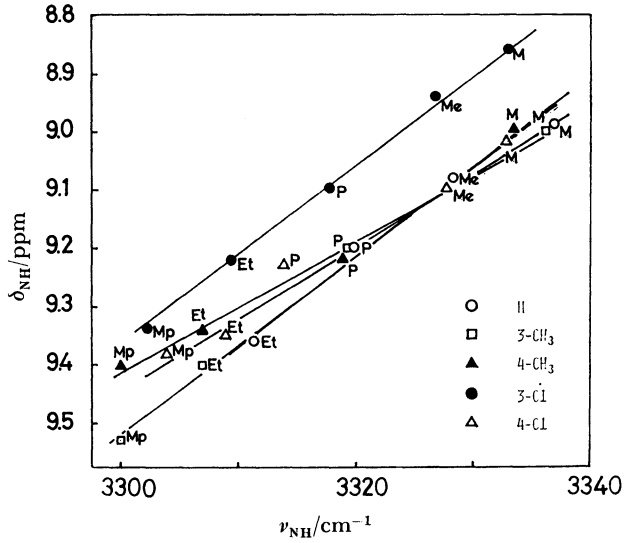
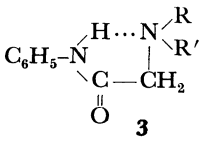


Fig. 1. The ν_{NH} *vs.* δ_{NH} plot.

former. Thus the NH group of **1** is suspected to be involved in a strong hydrogen bond. Since the NH absorptions of these amide are not concentration dependent and measured at very low concentrations, the hydrogen bond must be intramolecular (as illustrated by **3**).



3

The NH stretching frequencies of **1**'s are mainly controlled by the nature of the α-dialkylamino groups. As shown in Table 1 and also in Fig. 1, the NH stretching frequencies generally decrease in the order: morpholino >dimethylamino>piperidino>diethylamino >2-methylpiperidino derivatives. The pK_a values of the parent amines are 8.33 for morpholine, 10.77 for dimethylamine, 11.22 for piperidine, and 10.93 for diethylamine.[6,7] Stronger base usually acts as stronger hydrogen acceptor and will cause larger low frequency shift of the stretching vibration of hydrogen donating NH group in hydrogen bond formation. The effect of the α-dialkylamino group is in line with this interpretation. The anomalously low frequency shifts observed with diethylamino derivatives, and presumably with 2-methylpiperidino derivatives, are explained that the bases are weakened by the so-called B strain probably operating when the ammonium ions are formed from these nitrogen bases. Hydrogen bonds are formed without considerable change in geometries of the acceptor molecules, the effect being negligible. The

Table 3. NH proton chemical shifts of $RC_6H_4OC_6H_4NHCOCH_2Y$ (**1**) in $CDCl_3$[a)]

R	Y: $-N(CH_3)_2$	$-N(C_2H_5)_2$	$-N$	$-N$ (CH$_3$)	$-N$ O
H	9.08	9.36	9.20	—	8.99
2-CH$_3$	9.02	9.28	9.18	9.32	8.98
3-CH$_3$	9.15	9.40	9.20	9.53	9.00
4-CH$_3$	9.05	9.34	9.22	9.40	9.00
2-Cl	9.08	9.38	9.24	9.36	9.04
3-Cl	8.94	9.22	9.10	9.34	8.86
4-Cl	9.10	9.35	9.23	9.38	9.02

a) Chemical shifts (in ppm downfields from internal TMS reference) are given.

pK_a's of diethylamine and 2-methylpiperidine are lower than expected from the electronic effect alone.

The hydrogen bond was also proved by ^{1}H-NMR spectra of **1**'s in chloroform-*d* (Table 3). The amide NH signals resonate in the range 8.9—9.5 ppm (downfield from TMS reference signal), which is obviously lower fields than the NH chemical shift of **2** (7.85 ppm) which is impossible to form intramolecular hydrogen bond. The NH stretching frequency (ν_{NH}) *vs.* NH chemical shift (δ_{NH}) plots in Fig. 1 are almost linear in all cases illustrated, and support evidently the fact that the low frequency shifts of ν_{NH} and the low field shifts of δ_{NH} are both due to the hydrogen bond formation, and the hydrogen bonds are formed with the α-dialkylamino group intramolecularly.

The NH stretching absorption bands of free amide group was not observed with any of **1**'s, and the α-dialkylamino-*p*-phenoxyacetanilides are supposed to exist solely as the intramolecularly hydrogen bonded conformers.

References

1) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," pp. 175—198.
2) I. Suzuki, M. Tsuboi, T. Shimanouchi, and S. Mizushima, *Spectrochim. Acta*, **16**, 467 and 471 (1960).
3) Y. Senda and Y. Kudo, *Kagaku No Ryoiki, Suppl.* **68**, 115—138 (1965).
4) Y. Hamada, M. Sugiura, T. Nishina, K. Araki, K. Horigome, and Z. Henmi, *Yakugaku Zasshi*, **98**, 1597 (1978).
5) H. W. Russell and R. A. Thompson, *Spectrochim. Acta*, **8**, 138 (1956).
6) A. Albert and E. P. Serjeant, "The Determination of Ionization Constants," Chapman and Hall, London (1971).
7) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).