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Infrared Spectra and Intramolecular Hydrogen Bonding of 4-(Haloacetylamino)diphenylamines

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Synopsis. Infrared NH stretching absorptions and ^{1}H NMR chemical shifts of a series of 4-(haloacetylamino)diphenylamines were reported. The halogen atoms in haloacetamido groups are shown to participate in the intramolecular NH···X hydrogen bond. The hydrogen bond tends to be strengthened in the increasing order of atomic number of the acceptor halogen atoms.

The conformations of the molecules of pharmaceutical interest are often perturbed by intramolecular hydrogen bonding. Thus the hydrogen bonding sometimes affects the biological activity. Previously the authors had determined conformations of a series of substituted salicylanilides by infrared spectroscopy and found a correlation between the preference to the hydrogen-bonded conformation and the antibacterial activities.[1] In this connection, intramolecular hydrogen bonding of a series of 4-(haloacetylamino)diphenylamines were characterized by infrared and NMR spectroscopy in search for the structure-activity correlation.

Results and Discussion

The infrared NH and C=O absorptions, as well as the chemical shifts of NH protons, are given in Table 1. Parent 4-(acetylamino)diphenylamine has two NH stretching absorptions at 3448 and 3430 cm^{-1}. These bands were assigned to the amide and diphenylamine NH groups, respectively, by comparing to the NH absorptions of several reference compounds.[2,3] ^{1}H NMR spectra in chloroform-*d* also showed to NH signals. The one at the higher field appears at around 5.5 ppm and assigned to the NH group in diphenylamine structure. The assignment was certified by showing that the signal shifts down-field when a nitro group was introduced at the ortho position.[4] The signal at the lower field (appearing at 7.25 ppm in the spectrum of 4-acetyldiphenylamine) was assigned to the NH group of secondary amide.

The low frequency shift of the amide NH stretching absorption was observed when a halogen substituent was introduced on the acetyl group, which suggests the presence of intramolecular hydrogen bonding. Formation of the five-membered hydrogen bonded chelate ring can be expected to cause a low frequency shift of the NH band to a varying degree dependent on the hydrogen accepting ability of halogen atom (X). Hydrogen bond including fluorine atom as a hydrogen acceptor is generally weak, resulting the least low

Table 1. Infrared Spectra (in CCl_4) and ^{1}H NMR Spectra (in $CDCl_3$) of 4′-Substituted 4-(Haloacetylamino)diphenylamines $RC_6H_4NH(d)C_6H_4NHH(a)COCH_2X$

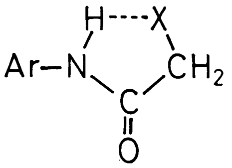
Substituent		Infrared spectra (cm^{-1})			^{1}NMR (δ/ppm)			MIC (μg ml^{-1})[c]	
R	X	NH(*d*)	NH(*a*)	C=O	NH(*d*)	NH(*a*)	CH_2	S. aureus	M. gypseum
H	H	3430	3448	1703	5.36	7.25	—	>100	>10
H	F	3431[a]		1697	5.69	7.86	4.920	>100	>10
F	F	3431[a]		1697	5.59	7.82	4.917	>100	>10
Cl	F	3432[a]		1703	5.60	7.84	4.926	>100	>10
F	Cl	3429	3411	1691	5.59	8.14	4.182	>100	>10
CH_3	Cl	3434	3412	1689	5.50 (5.27)[b]	8.12 (11.09)	4.164 (4.433)	>100	10
CH_3O	Cl	3434	3413	1691	5.50	8.11	4.176	>100	10
C_2H_5O	Cl	3433	3412	1690	5.39	8.10	4.176	—	—
H	Br	3434	3404	1686	5.50	8.03	4.008	>100	1
F	Br	3432	3403	1686	5.50	8.02	4.024	10	1
Cl	Br	3434	3402	1689	5.58	8.03	4.013	10	1
CH_3	Br	3433	3404	1685	5.59 (5.86)[b]	8.03 (11.09)	4.018 (4.356)	10	1
C_2H_5O	I	3433	3396	1691	5.50	7.66	3.833	10	1

a) The two NH bands merge into a slightly asymmetric band having a nearly twice intensity. b) The chemical shifts in pyridine solutions. c) Minimum inhibitory concentration (Ref. 7).

Table 2. Hydrogen Bond Shifts in The $N–H\cdots X$ Hydrogen Bonds

X	F	Cl	Br	I
$\Delta\nu/\mathrm{cm}^{-1}$	17	36	45	52
$\Delta\delta/\mathrm{ppm}$	0.59	0.87	0.78	0.41

frequency shift of amide NH band. Hydrogen bond shift ($\Delta\nu_{NH}$) increases in the increasing order of atomic number; i.e., F<Cl<Br<I (Table 2), which suggests the major contribution of polarizability effect. In other words, the $\Delta\nu$ is controlled by the strength of the N–H bond, which comes from the contribution of charge-transfer resonance structure (**2b**). The secondary amide moiety of the intramoecularly hydrogen-bonded conformer is enforced to take a trans geometry as depicted by **1**. The trans conformer usually absorbs in the frequency region higher than 3640 cm^{-1} (3480—3440 cm^{-1}) in contrast to the cis absorption in the lower frequency region (3435—3395 cm^{-1}).[5] Thus the NH absorption at 3448 cm^{-1} of 4-(acetylamino)diphenylamine showed the fact that it takes a trans conformation preferably. The carbonyl stretching absorptions at relatively high frequencies supported the trans-conformation in the *o*-haloacetyl derivatives.[6]



(**1**)

(Formula of the hydrogen-bonded conformation **1**)

N–H :X (**2a**)

N:$^-$ H–X$^+$ (**2b**)

The ^{1}H NMR spectra also support the intramolecularly hydrogen-bonded conformation (**1**), showing considerable low field shifts of amide NH signals. The hydrogen bond shift ($\Delta\delta$) increases in the following order of halogen substituent: I<F<Br<Cl. The sequence of $\Delta\delta$ is quite different from that of infrared $\Delta\nu$. The hydrogen bond shifts ($\Delta\delta$) of NH proton chemical shifts should be controlled by the electron density plus charge displacement effects, which can be evaluated by the second and the first terms of Buckingham's equation ($\sigma_E = -2\times10^{-12}\,E_z + 10^{-18}\,E^2$). Thus the electronegativity effect might affect the chemical shift considerably in addition to the delocalization effect. As a result of two opposite effects the NH protons of chloroacetanilides resonate at the lowest fields. In short, the two hydrogen bond shifts $\Delta\nu$ and $\Delta\delta$, some from different origins.

The strength of hydrogen bonding can be more properly evaluated by using the infrared hydrogen bond shift ($\Delta\nu$) as a measure. Since antibacterial activity can be governed by the nature of halogen atoms as is the case of hydrogen bonding, we could not conclude very definitely, but the general tendency that the strength of intramolecular hydrogen bond is in line with the inverse of minimal inhibitory concentration[7] was observed. Thus the possible contribution of the intramolecular hydrogen bonding to the activity was suggested by this research.

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3) Assignment of the amide NH band was based on the fact that acetanilide absorbs at 3448 and 1703 cm^{-1} in carbon tetrachloride solution.

4) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," Chapman and Hall, London (1975), Vol. 1, p. 233.

5) p. 240 of Ref. 4.

6) 4,4′-Dichloro-2-nitrodiphenylamine absorbs at 3357 cm^{-1} in the NH region. The absorption frequency is considerably lower than the normal NH frequencies for *o*-unsubstituted diphenylamines (3432 cm^{-1} for 4,4′-dichlorodiphenylamine).

7) Y. Hamada and H. Matsuoka, *Yakugaku Zasshi,* **96**, 447 (1976).