Deshielding of *Ortho* Proton of *N*-Acylanilines

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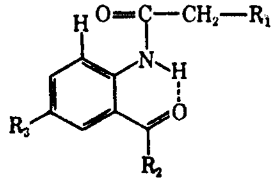
Unusual proton magnetic resonance deshielding is reported for 2-carboxy-*N*-acylaniline (I), *N*-acyl-2-aminobenzophenones (II–IX), and *N*-acyl-2-aminoalkylphenones (XI–XVI). A preferred conformation which brings the deshielded proton in close vicinity to the acylcarbonyl group is invoked to account for the noted effect.

Recently, several publications have appeared in which deshielding of an *ortho* proton on *ortho*-substituted benzene has been reported (*4, 12*). Zanger (*12*) has reported unusual *ortho* deshielding of *ortho*-substituted acylanilines, while Faller (*4*) reported a similar effect on the 4-proton of 3-acylsubstituted benzo[*b*]thiophenes. In this note, additional examples of this deshielding are reported for 2-carboxy-*N*-acylaniline (I), *N*-acyl-2-aminobenzophenones (II–IX), and *N*-acyl-2-aminoalkylphenones (XI–XVI). Additional information concerning the nature of this deshielding is discussed.

RESULTS AND DISCUSSION

The nmr spectra of a number of substituted *N*-acylanilines were determined, and the chemical shifts of the protons assigned (Table I). As shown in Table I, H_α consistently appears as the most deshielded proton. Table II lists the assigned chemical shifts of the protons of the substituted anilines. The most shielded proton in these compounds is the H_α proton. The assignment of the H_α proton is made simple in the 1,2,4-trisubstituted anilines by the characteristic coupling pattern for this proton, a doublet with a J of 8 to 10 Hz.

The noted deshielding is caused, in part, by the electronic change produced in going from the amine to the amide. The magnitude of this effect was approximated by determining the change in chemical shift of the *para* proton—that is, where R_3 = H, in compounds V and XX and compounds XII and XXIII. In compound V, 2-bromo-2′-benzoylacetanilide, the proton *para* to the nitrogen could not be specifically identified, but was located between 7.30 and 7.67 δ. The nmr spectrum of compound XIX, 4-chloro-2-benzoylaniline, when compared with the spectrum of compound XX, 2-benzoylaniline, showed a new multiplet centered in the region of 6.5 δ. This multiplet was assigned to the *para* proton of XX. Thus, the maximum chemical shift difference caused by the electronic change in going from an amine to an amide is 1.17 ppm. In compound XII, 2-bromo-2′-acetylacetanilide, the *para* proton is assigned to a multiplet centered at 7.45 δ; while in compound XXIII, 2-acetylaniline, the *para* proton shifted to approximately 6.50 δ, a difference in chemical shift of 0.95 ppm. Table III lists the chemical shift difference between the acylanilines and anilines. The ΔH_β is in the range of 0.05 to 0.44 ppm. The $\Delta H'_\alpha$ is in the range of 0.10 to 0.34 ppm. Thus, the electronic effect in such a change on the *meta* protons is small. With the exception of compound IX, the ΔH_α is in the range of 1.62 to 2.34 ppm. This shift is considerably greater than might have been expected by electronic considerations. As discussed above, a change in the range of 1.0 ppm might be reasonable for an electronic effect. An enhanced deshielding for this proton caused by the acetamide carbonyl group is invoked, which is in agreement with Zanger (*12*). The influence of the carbonyl group on the H_α proton may be twofold. Due to the steric effect of the *ortho* substituent and the hydrogen bonding between the carbonyl group of this substituent and the hydrogen on the nitrogen, the acetamido group is held in a preferred conformation. In this conformation, the anisotropy of the carbonyl group operates so as to cause deshielding. This effect, in itself, probably does not account for the total deshielding. An additional force that may be operating results from the highly electronegative carbonyl oxygen. The negative change tends to repel the bonding electrons of the H_α toward the carbon to which it is attached thereby deshielding this proton (*3*). This effect is dependent on the internuclear distance between the two atoms.



One compound in this list, IX—the only tertiary amide—shows a chemical shift of 7.90 δ for the H_α proton. The ΔH_α of 1.22 ppm is in the range of a reasonable chemical shift difference in going from an amine to an amide. The lack of a large ΔH_α may be due to the steric effect of the methyl group which no longer allows a conformation such as depicted above. Also, the intramolecular hydrogen bonding as depicted for the secondary amides is not possible in this case.

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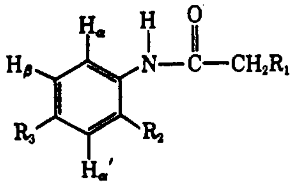
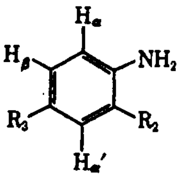
Table I. Chemical Shift Data of Acylanilines



				Chemical shift (δ)			Coupling constant (Hz)		
Compounds	R_1	R_2	R_3	H_α	H_β	H'_α	J_{ortho}	J_{meta}	Lit.
I[a]	H	COOH	Cl	8.44	7.61	7.92	9	...	(5)
II	NH_2	2-COC_6FH_4	Cl	8.79	...	...	9	...	*(10)*
III	Br	2-COC_6FH_4	Cl	8.68	...	...	~9	~1	*(10)*
IV	Br	COC_6H_5	Cl	8.57	...	...	10	...	*(10)*
V	Br	COC_6H_5	H (7.67 max.)	8.58	~7.17	...	9	1-2	*(10)*
VI	H	2,6-$COC_6F_2H_3$	Cl	8.87	7.13	...	8	1-2	(7)
VII	Br	2,6-$COC_6F_2H_3$	Cl	8.79	7.12	...	8	...	(7)
VIII	NH_2	2,6-$COC_6F_2H_3$	Cl	8.97	7.10	...	8	...	(7)
IX(N—CH_3)	Br	COC_6H_5	Cl	7.90	...	7.30	...	...	*(10)*
X	Br	COC_2H_5	Cl	8.69	7.51	7.90	9	...	...
XI	H	COC_2H_5	Cl	8.68	7.49	7.85	9	...	...
XII	Br	$COCH_3$	H (7.45)	8.73	7.25	7.95	8	1.5	...
XIII	Br	$COCH_3$	Cl	8.70	7.52	7.87	9	...	...
XIV	Br	$COCH_3$	NO_2	8.97	8.46	8.90	13	...	...
XV	H	COC_6H_{11}	Cl	8.77	7.47	7.86	9	2.5	(2)
XVI	Br	COC_6H_{11}	Cl	8.74	7.66	7.92	9	2.5	(2)

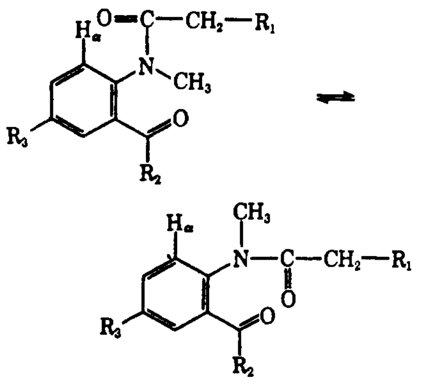
[a] Solvent was deuterated dimethylsulfoxide.

Table II. Chemical Shift of Substituted Anilines

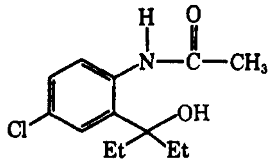


			Chemical Shifts (δ)			
Compound	R_2	R_3	H_α	H_β	H'_α	Ref.
XVII[a]	COOH	Cl	6.82	7.26	7.70	[b]
XVIII	2-COC_6FH_4	Cl	6.61	...	...	*(11)*
XIX	COC_6H_5	Cl	6.62	7.19	7.39	[b]
XX	COC_6H_5	H (~6.5)	~6.5	...	...	[b]
XXI	2,6-$COC_6F_2H_3$	Cl	6.63	7.05	...	...
XXII (N—CH_3)	COC_6H_5	Cl	6.68	...	...	*(1)*
XXIII	$COCH_3$	H (~6.5)	~6.55	7.18	7.61	[c]
XXIV	$COCH_3$	Cl	6.54	7.13	7.60	(9)
XXV[d]	$COCH_3$	NO_2	6.80	8.03	8.64	(9)
XXVI	COC_6H_{11}	Cl	6.61	7.20	7.71	(2)

[a] Solvent was deuterated dimethylsulfoxide. [b] Aldrich Chemical. [c] Eastman Organic Chemical. [d] Solvent was a mixture of deuterated chloroform–dimethylsulfoxide.



Two compounds that have intermediate ΔH_α are compounds I and XXVII. These are compounds in which the *ortho* substituents are, respectively, a carboxyl and a tertiary alcohol. The ΔH_α for compound I is 1.62 ppm and approximately 1.6 ppm for compound XXVII. Compound XXVII



XXVII

has a doublet with J = 8.5 Hz centered at 8.23 δ. In

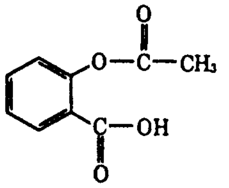
Table III. Chemical Shift Difference between Acylanilines and Anilines

Compounds	ΔH_α	ΔH_β	$\Delta H'_\alpha$
I vs. XVII	1.62	0.35	0.22
II vs. XVIII	2.18	. . .	. . .
III vs. XVIII	2.07	. . .	. . .
IV vs. XIX	1.95	. . .	. . .
V vs. XX	~2.08	. . .	. . .
VI vs. XXI	2.24	0.08	. . .
VII vs. XXI	2.16	0.07	. . .
VIII vs. XXI	2.34	0.05	. . .
IX vs. XXII	1.22	. . .	. . .
X vs. XXIV	2.15	0.38	0.30
XI vs. XXIV	2.14	0.36	0.25
XII vs. XXIII	~2.18	0.07	0.34
XIII vs. XXIV	2.16	0.39	0.27
XIV vs. XXV	2.17	0.43	0.16
XV vs. XXVI	2.16	0.27	0.15
XVI vs. XXVI	2.13	0.44	0.21

these cases a decrease in intramolecular H-bonding may be important.

In agreement with Zanger (*12*), the nature of the substituent on the acetyl group has only a minor effect. In going from hydrogen to bromine, compounds VI and VII, respectively, produced a change of 0.08 ppm. It was also found that, in a temperature range of 10–100°, no change occurred in the chemical shift of H_α.

Finally, several esters of *ortho*-substituted phenols were examined. The nmr of acetylsalicyclic acid, XXVIII, showed no absorption below 7.98 δ. Compound XXIX (*6*) had an nmr spectrum with no absorption below 7.83 δ. Both of these compounds are oxygen analogs of amides listed in Table I. The nmr spectra of the respective phenols showed only minor changes. Therefore, it would appear that the amide is necessary to cause the required planarity and electronegativity via its partial double bond to the carbonyl carbon. In addition, the orienting effect produced through intramolecular H-bonding by the amide hydrogen appears to increase the amount of deshielding.


XXVIII

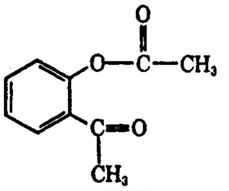

XXIX

Table IV. Physical Constants for New Compounds

Compound	Yield, %	Mp	Method[a, b]
XI	17.7	165°	B[c]
XII	100	95–96°	A
XIII	100	102–104°	A
XIV	68	145–146.5°	D
XXVII	8.6	116–118°	B[c]

[a] Compounds prepared by the method reported in Ref. *9*. [b] Analyses for C, H, Br, Cl, and N in agreement with theoretical values have been obtained and submitted for review. [c] *J. Org. Chem.*, **27**, 3781 (1962).

EXPERIMENTAL

The nmr spectra were obtained on a Varian Associates A-60A spectrometer operating at a frequency of 60 MHz. Samples were prepared in deuterated chloroform unless otherwise stated. Tetramethylsilane was incorporated in the solvent as an internal standard. The normal probe temperature was 35°. The compounds investigated were obtained either from commercial sources or by synthesis. The physical constants and method of preparation of previously unreported compounds are given in Table IV.

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