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HAMMETT CORRELATIONS IN THE ¹H NMR SPECTRA OF SOME N-ARYLDIHALONICOTINAMIDES

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ABSTRACT

Excellent linear correlations of amide proton chemical shifts (δ_{NH}) (in DMSO- d_6) with Hammett substituent constants (σ) for a series of 4-substituted anilides of four dihalonicotinic acid systems were observed. Dihalonicotinilides with chlorine in the pyridine 2 - position exhibited a more positive slope in a Hammett plot of δ_{NH} vs. σ_R , where R is the substituent in the 4 position of the benzene ring. This observation is explained in terms of the inductive effect of chlorine which results in a slightly more acidic amide proton, which in turn causes an enhanced hydrogen bonding tendency to solvent. Four disubstituted anilides were also prepared, and the δ_{NH} of these derivatives correlated well with the additive value of the δ_p 's of the two substituents.

INTRODUCTION

The Hammett equation (Jaffe, 1953) has been used for many years to assess the electronic effects of substituents (R) through an aryl system on a reaction site (Y). Substituents located in the 2- position with respect to Y



are normally not studied to avoid any complication by steric effects. The equation normally takes the form:

$$\log k = \rho\sigma_R + \log k_0$$

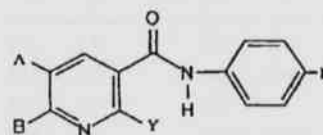
where k is the rate constant of the reaction being studied with different R substituents present, and k_0 is the corresponding rate constant of the unsubstituted compound (R = H). The substituent constant σ_R is a value determined from a standard reaction and is characteristic of the nature and position of the substituent. If the substituent is electron withdrawing σ_R has a value > 0, and a value < 0 indicates an electron donating substituent. The reaction constant ρ is characteristic of a given reaction and denotes the sensitivity of the reaction to substituent effects. It has a positive value if the reaction is enhanced by electron withdrawing substituents, and a negative value if the reaction is facilitated by electron releasing groups. Thus, insight into the polar nature of the transition state of the rate controlling step of a reaction may be obtained. A value for ρ may be determined graphically by plotting $\log k$ vs. the known value for σ_R and calculating the slope of the line.

There have been many successful as well as unsuccessful attempts to correlate properties other than reaction rates with the Hammett σ_R values (Exner, 1988). Properties such as ultraviolet and infrared absorption frequencies and intensities as well as biological activities have met with only limited success. However, correlations of ¹H NMR data with substituent constants have generally proved more rewarding (Ewing, 1978). Most relevant to this study is the reported correlation of substituent effects in a series of substituted acetanilides and phenylureas. (Giffney and O'Connor, 1975).

RESULTS AND DISCUSSION

We have reported previously the preparation and complete structural characterization of several N-(4-substituted phenyl)amides of 5-bromo-6-

chloro- and 5-bromo-2-chloronicotinic acid (Setliff and Caldwell, 1991) and of 2,6-dichloro- and 5,6-dichloronicotinic acid (Setliff and Soman, 1992). These compounds correspond to amide series IV, III, I and II as depicted in Figure 1. The R substituents are designated in Table I by letters. Having available such a closely related series of compounds we reasoned that there might be noticeable trends in their ¹H NMR spectra



Amide Series	A	B	Y	Correlation Equations	Correlation Coefficient (r ²)
I	H	Cl	Cl	$\delta_{\text{NH}} = 0.70\sigma_R + 10.71$	0.99
II	Cl	Cl	H	$\delta_{\text{NH}} = 0.57\sigma_R + 10.56$	0.99
III	Br	H	Cl	$\delta_{\text{NH}} = 0.69\sigma_R + 10.70$	0.99
IV	Br	Cl	H	$\delta_{\text{NH}} = 0.57\sigma_R + 10.54$	0.98

Figure 1. Dihalonicotinamide Systems and their Hammett ¹H NMR Correlation Equations.

Table 1. Substituent Constants and Amide Proton chemical Shifts (δ_{NH} ppm) for the four Dihalonicotinamide Series (Fig. 1)

Cpd.	R	σ_R	δ_{NH} Series I	δ_{NH} Series II	δ_{NH} Series III	δ_{NH} Series IV
a.	H	0.0	10.69	10.55	10.70	10.53
b.	OCH ₃	-0.28	10.53	10.43	10.56	10.41
c.	CH ₃	-0.14	10.59	10.48	10.60	10.45
d.	F	0.06	10.75	10.59	10.77	10.58
e.	Br	0.22	10.83	10.65	10.85	10.64
f.	COCH ₃	0.47	11.02	10.82	11.04	10.80
g.	CF ₃	0.53	11.06	10.86	-----	-----
h.	NO ₂	0.81	11.30	11.04	11.31	11.04
i.	OCH ₂ CH ₃	-0.26	-----	-----	10.55	10.40

which could be related to transmission of electronic effects through the benzene and/or pyridine ring. In this regard we were able to correlate the amide proton chemical shifts of the R-substituted N-aryldihalonicotinamides within all four dihaloamide series with the standard Hammett σ_R values. Chemical shift values (δ_{NH}) and σ_R values (Exner, 1988) are summarized in Table 1, and the excellent linear correlations are shown in Figures 2 and 3. Results of the linear regression analysis of these data are summarized in Figure 1 together with the correlation equation in slope intercept form. The slope of the line is interpreted as the Hammett ρ value.

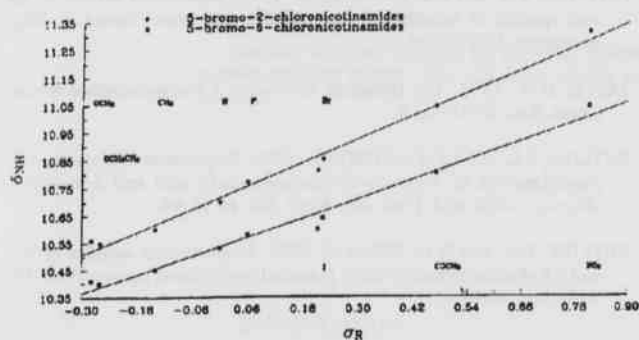


Figure 2. Hammett Plots of the 4-Substituted phenylbromo-chloronicotinamides.

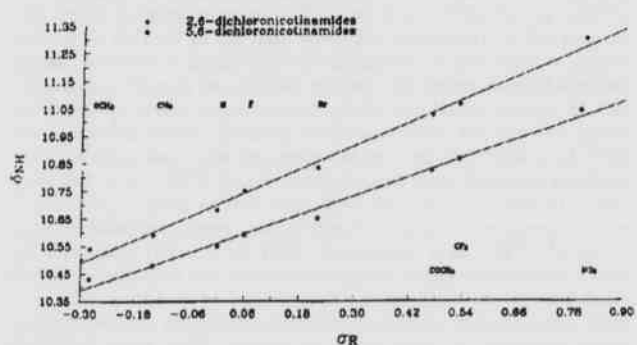


Figure 3. Hammett Plots of the 4-Substituted phenyldichloro-nicotinamides.

The positive ρ values in all four series indicate a sensitivity to electron withdrawing groups and that greater deshielding of the amide proton is occurring as the electron withdrawing power of the R substituent increases. Such deshielding is the result of the more efficient hydrogen bonding of the amide proton with the DMSO solvent as the proton is rendered more acidic by the transmission of electron density away from the amide nitrogen atom. For those electron withdrawing groups capable of withdrawing electron density by a resonance effect (CN and NO₂) the refined Hammett σ^+ values (Exner, 1988) which allow for "through conjugation" did not correlate at all. This suggests that the resonance effect is negligible and that the electron withdrawing process is chiefly one of simple induction.

A positional effect of the chlorine on the pyridine ring is noteworthy. With the chlorine in the pyridine 2-position (amide systems I and III) we note a larger ρ value than in amide systems II and IV where the chlorine is in the 6-position. The larger ρ value is attributed to the greater electron withdrawing inductive effect of the chlorine in the 2-position by virtue of its closer proximity to the amide nitrogen. This constant acidity enhancement throughout the series results in a greater hydrogen bonding

sensitivity to the transmission of electron density by R groups in the 4-position of the benzene ring. Thus, in the Hammett context, this greater sensitivity should predict a ρ value (slope) of greater magnitude.

In cases where there are more than one substituent on a benzene ring operating on a reaction center, the effects of the substituents may be generally shown to be additive (Exner, 1988). In order to test our model for additive substituent effects we prepared the N-(3-chloro-4-methoxyphenyl)dihalonicotinamides IIIj and IVj, and the N-(4-bromo-3-methylphenyl)-dihalonicotinamides IIIk and IVk. Their amide proton chemical shifts are listed in Table 2. If the substituent effects are additive, the algebraic sum of the two σ_R values when substituted in the correlation equation should yield a calculated δ_{NH} reasonably close to the observed chemical shift. The results are summarized in Table 2. Agreement of the calculated and observed δ_{NH} values are all within 0.08 ppm, which indicates acceptable additive predictability.

Table 2. Additive Substituent Effects. Comparison of Observed δ_{NH} (ppm) to Calculated Values.

Cpd.	R substituents	σ_R (additive)	δ_{NH} series III		δ_{NH} series IV	
			obs.	calc.	obs.	calc.
j.	3-Cl, 4-OCH ₃	.09	10.72	10.76	10.52	10.59
k.	4-Br, 3-CH ₃	.16	10.70	10.81	10.55	10.63

MATERIALS AND METHODS

All ¹H NMR spectra were determined on a Bruker 200 MHz FTACF superconductivity spectrometer equipped with ASPECT 3000 computer control. Extremely sharp melting crystalline samples of all compounds were used in the ¹H NMR analyses, and were dissolved in analytical grade DMSO-d₆ containing 1% tetramethylsilane. Sample concentrations were 20 mg per ml of solvent.

Hammett plots were done on a Zenith 248 computer using an Axum least squares linear fit program available from Trimetrix, Inc. Seattle Washington.

The N-(disubstituted phenyl) dihalonicotinamides were prepared from the dihalonicotinic acids via their respective dihalonicotinyl chlorides and the appropriately disubstituted anilines by general procedures already described (Setliff and Caldwell, 1991). Their structures were confirmed by elemental analysis (Desert Analytics Tucson, Arizona) as well as by infrared and ¹H NMR spectroscopy. Experimental data are summarized below. All compounds were recrystallized from aqueous ethanol, and all ¹H NMR proton signals were observed in the correct area ratios.

N-(3-Chloro-4-methoxyphenyl)-5-bromo-2-chloronicotinamide (IIIj).- obtained in 95% yield, m.p. 158°C. IR: ν 3299(NH), 1648(C=O)cm⁻¹. ¹H NMR: δ 10.72 (s) amide H, 8.71 (d) pyridine H4, (d) pyridine H6, 7.85 (d) benzene H2; 7.53 (d of d) benzene H6; 7.17 (d) benzene H5, 3.85 (s) OCH₃. Anal. calc'd for C₁₃H₉N₂O₂BrCl₂(%): C, 41.52; H, 2.41; N, 7.45. Found: C, 41.58; H, 2.31; N, 7.29.

N-(3-Chloro-4-methoxyphenyl)-5-bromo-6-chloronicotinamide (IVj).- obtained in 82% yield, m.p. 218°C. IR: ν 3277 (NH), 1643 (C=O) cm⁻¹. ¹H NMR: δ 10.52, (s) amide H; 8.91 (d) pyridine H₂, 8.71 d (pyridine H₄), 7.90 (d) benzene H₂; 7.64 (d of d) benzene H₆; 7.2 (d) benzene H₅, 3.85(s), OCH₃. Anal. Calc'd for: C₁₃H₉N₂O₂BrCl₂(%): C, 41.52; H, 2.41; N, 7.45. Found: C, 41.72; H, 2.28; N, 7.41.

N-(4-Bromo-3-methylphenyl)-5-bromo-2-chloronicotinamide (IIIk).- obtained in 82% yield, m.p. 182°C. IR: ν 3252 (NH), 1664 (C=O) cm⁻¹. ¹H NMR: δ 10.78(s) amide H, 8.72 (d) pyridine H₄, 8.46 (d) pyridine (H₆), 7.70 (benzene H₂), 7.6 (d) benzene H₅, 7.45 (d of d) benzene H₆, 2.35 (s) CH₃. Anal. Calc'd for C₁₃H₉N₂OBr₂Cl(%): C, 38.60; H, 2.24; N, 6.93. Found: C, 38.42; H, 2.21; N, 6.86.

N-(4-Bromo-3-methylphenyl)-5-bromo-6-chloronicotinamide (IVk) obtained in 60% yield, m.p. 192°C. IR: ν 3277 (NH), 1643 (C=O)cm⁻¹. ¹H NMR: δ 10.55 (s) amide H, 8.90 (d) pyridine H₂, 8.70 (d) pyridine H₄, 7.74 (s,b) benzene H₂, 7.55 (m) benzene H₅ and H₆, 2.34 (s) CH₃. Anal. Calc'd for C₁₃H₉N₂OBr₂Cl(%): C, 38.60; H, 2.24; N, 6.93. Found: C, 38.58; H, 2.22; N, 6.70.

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