Hammett Correlations of Carbonyl 13C Chemical Shifts in a Series of N-(4-Substituted Phenyl)-6-Chloro-5-Fluoronicotinamides

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Abstract

A series of nine N-(4-substituted phenyl)-6-chloro-5- fluoronicotinamides exhibited excellent correlations of their carbonyl ^{13}C shifts (δ_{CO}, ppm as measured in DMSO) with the standard Hammett substituent constants (σ_R) of the substituent in the 4-position. The linear relationship was defined by the equation $\delta_{CO} = 1.22\,\sigma_R + 161.50$ with a correlation coefficient of 0.98. The transmission of electronic effects exerted by two substituent was shown to be additive.

Introduction

We have reported (Setliff et al., 1992) that the amide proton chemical shift (δ_{NH}) in several series of N-(4-substituted phenyl)- 2,5-, 2,6- and 5,6- dihalonicotinamides correlates extremely well with the standard Hammett substituent constants (σ_R). In more recent work (Persons et al., 1994) the correlation of the half-wave reduction potentials of these same compounds were also shown to correlate with the standard σ_R values. In this paper we describe the results of ^{13}C NMR studies which reveal very good correlation of the carbonyl chemical shift (δ_{CO}, ppm) with the Hammett σ_R values in a series of N-(4-substituted phenyl)-6-chloro-5-fluoronicotinamides. These compounds were also prepared as candidates for screening as potential agricultural agents.

^{13}C chemical shifts have been shown previously to correlate with Hammett substituent constants (Ewing, 1978), but the majority of the early reports dealt with correlations of a ring carbon resonance. Subsequently, work on exocyclic ^{13}C systems indicated that there was no correlation of standard σ_R values in benzylic and related systems. Specifically, in a study of ring substituted benzamides (R-C$_6$H$_4$-CONH$_2$), attempts to correlate δ_{CO} with σ_R led unexpectedly to a reverse substituent effect (Bromilow et al., 1981). This reverse effect was explained in terms of pi polarization utilizing a concept coined "molecular lines of force", and was defended by a correlation involving refined Hammett σ_R values in a dual substituent parameter equation (Craik et al., 1982). In view of the fact that such complicated substituent effects on the carbonyl electron density occur on the acid side of the amide linkage, we were interested in investigating the effects of aryl substituent groups when present on the nitrogen side of the amide function.

Materials and Methods

The nine N-(substituted phenyl)-6-chloro-5-fluoronicotinamides 1a-1i (Table 1) were prepared from 6-chloro-5-fluoronicotinic acid (Setliff and Rankin, 1972) by the general procedure described previously for the synthesis of analogous dihalonicotinamides (Setliff and Caldwell, 1991). All amides were recrystallized from aqueous ethanol, and melting points were taken on a Mel-Temp II apparatus. Infrared spectra were obtained in KBr disks using a Perkin Elmer 1430 instrument equipped with a Model 7300 data station. Elemental analyses were performed by Desert Analytics Inc., Tuscon, AZ. ^{13}C NMR spectra were acquired on a Bruker AC-F 200MHz superconducting FT spectrometer with DMSO-d$_6$ as solvent and tetramethylsilane as the internal standard. Sample concentrations were 20 mg/ml. The Hammett plot was produced by an Axum program available from Trimatrix, Inc., Seattle, WA.

Results and Discussion

Sharply melting samples of the nine amides 1a through 1i were obtained in adequate yields (Table 1). All compounds exhibited the expected infrared absorption bands for the secondary amide function. The NH stretch was of moderate intensity in the range 3230-3500 cm^{-1}, and the strong CO stretch was found in the range 1640-1680 cm^{-1}. Elemental analyses (C,H,N) were all within 0.4% of the theoretical values. The proton NMR spectra (DMSO-d$_6$) also supported the structures. The amide proton resonance, as in all analogous compounds studied, was the signal farthest downfield and occurred as a sharp singlet in the range 11.04-10.42 ppm. The H$_2$ proton (see structure in Table 1) in all cases appeared as a doublet (J = 2Hz) in the general range 8.86-8.82 ppm, while the H$_4$

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proton, being coupled to fluorine as well as H_2, appeared as a doublet of doublets [J = 8Hz(2Hz)] centered in the range of 8.41-8.46 ppm. The H_a and H_b protons on the benzene ring appeared as the characteristic AB doublets (J = 8Hz) except in compounds 1c and 1d. In the former, with a hydrogen in the 4-position, and in the latter, with a fluorine in the 4-position, H_a was exhibited as an ill-defined multiplet and H_b as a triplet (J = 8Hz). The methyl protons in 1a, 1b and if appeared as singlets with the respective chemical shifts of δ 3.75, 2.29, and 2.57 ppm. The ^{13}C spectra were also indicative of the respective structures of the amides, with the carbonyl carbon signal ($δ_{CO}$) being the farthest downfield. These chemical shifts are presented in Table 1. All other carbon signals were assigned, but for the sake of brevity will not be reported herein.

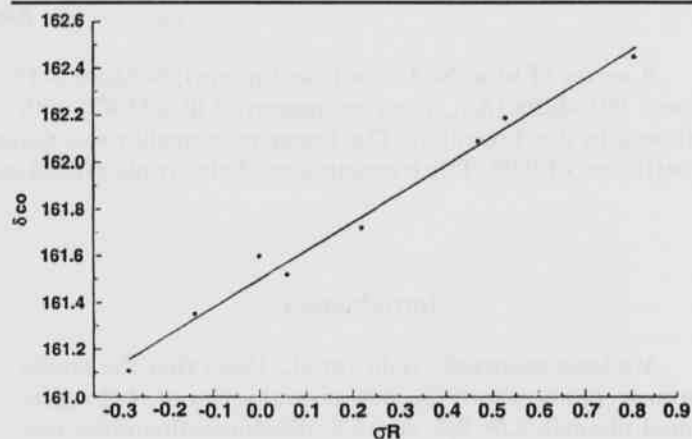Table 1. Data for the N-(4-substituted)-nicotinamides

Cpd.	R	M.p.(^{0}C)	Yld. (%)	$σ_R$	$σ_{CO}$(ppm)
a	OCH_3	198	67	-0.28	161.11
b	CH_3	203	80	-0.14	161.35
c	H	189	91	0.00	161.60
d	F	175	72	0.06	161.52
e	Br	197	48	0.22	161.72
f	$COCH_3$	260	67	0.47	162.09
g	CF_3	214	79	0.53	162.19
h	NO_2	207	85	0.81	162.45
i	4-Br,3-Me	215	98	0.22+(-0.06) = 0.16	161.62

A plot of the carbonyl carbon shift ($δ_{CO}$) for compounds 1a through 1h *vs.* the standard $σ_R$ value (Exner, 1988) of the substituent in the 4-position is shown in Fig. 1. The linear relationship is described by the equation:

$$δ_{CO} = 1.22 \, σ_R + 161.50$$

A correlation coefficient of r^2 = 0.98 indicates a good data fit. The positive slope of the correlation line demonstrates the sensitivity of the system to the removal of electron density from the carbonyl carbon. The downfield shifts observed in those compounds substituted with the electron withdrawing groups (more positive $σ_R$ values) is a

reflection of poor nitrogen lone pair resonance with carbonyl carbon. Therefore the resonance contributor $-)C=NH-C_6H_4-R$ is weak, resulting in a more electron deficient (and thus deshielded) carbon. In those instances where R is electron donating (negative $σ_R$) there is increased contribution by the resonance structure above, manifesting an upfield shift.

Fig. 1. Hammett Plot of Carbonyl Carbon Chemical Shifts $δ_{CO}$ vs Standard Hammett Substituent Constants $σ_R$.

In order to test for the additivity of two substituents, we prepared N-(4-bromo-3-methylphenyl)-6-chloro-5-fluoronicotinamide (1i) and examined its spectrum. If the substituent effects are in fact additive, the algebraic sum of $σ_{4-Br}$ and $σ_{3-Me}$ when substituted into the correlation equation should generate a $δ_{CO}$ which approximates the experimental chemical shift. The variance of this calculated chemical shift (161.69) from the experimental value (161.62) is only 0.04%. We therefore conclude that the transmission of electronic effects by two substituent on the aryl nitrogen side of the amide is additive. Interestingly, this was shown not to be the case on the aryl carbon side of the amide function (Bromilow et al., 1981).

Based on our previous work involving $δ_{NH}$ correlations which indicates that good Hammett relationships exist on the nitrogen side of the amide group regardless of the nature of the acid side of the amide linkage (Setliff et al., 1993), we assume the same to be the case of the $δ_{CO}$ correlations. Future work in the ^{13}C area will include inductive effect sensitivity studies with N-(4-substituted) phenyl)-2-halonicotinamides.

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