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

Frank L. Setliff
University of Arkansas at Little Rock

John W. Hawley
University of Arkansas at Little Rock

Alan D. Toland
University of Arkansas at Little Rock

Follow this and additional works at: http://scholarworks.uark.edu/jaas

Part of the Organic Chemistry Commons

Recommended Citation

This article is available for use under the Creative Commons license: Attribution-NoDerivatives 4.0 International (CC BY-ND 4.0). Users are able to read, download, copy, print, distribute, search, link to the full texts of these articles, or use them for any other lawful purpose, without asking prior permission from the publisher or the author.
This Article is brought to you for free and open access by ScholarWorks@UARK. It has been accepted for inclusion in Journal of the Arkansas Academy of Science by an authorized editor of ScholarWorks@UARK. For more information, please contact scholar@uark.edu, ccmiddle@uark.edu.
Hamnett Correlations of Carbonyl $^{13}$C Chemical Shifts in a Series of N-(4-Substituted Phenyl)-6-Chloro-5-Fluoronicotinamides

Frank L. Setliff, John W. Hawley and Alan D. Toland
Department of Chemistry
University of Arkansas at Little Rock
Little Rock, AR 72204

Abstract

A series of nine N-(4-substituted phenyl)-6-chloro-5-fluoronicotinamides exhibited excellent correlations of their carbonyl $^{13}$C shifts ($\delta_{\text{CO}}$, ppm as measured in DMSO) with the standard Hammett substituent constants ($\sigma_R$) of the substituent in the 4-position. The linear relationship was defined by the equation $\delta_{\text{CO}} = 1.22 \sigma_R + 161.50$ 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 ($\delta_{\text{pH}}$) 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 ($\sigma_R$). 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 $\sigma_R$ values. In this paper we describe the results of $^{13}$C NMR studies which reveal very good correlation of the carbonyl chemical shift ($\delta_{\text{CO}}$, ppm) with the Hammett $\sigma_R$ 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 $\sigma_R$ values in benzylic and related systems. Specifically, in a study of ring substituted benzenamides (R-C$_6$H$_4$-CONH$_2$), attempts to correlate $\delta_{\text{CO}}$ with $\sigma_R$ 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 $\sigma_R$ 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-li (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 1450 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 AG-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$_4$
proton, being coupled to fluorine as well as H₂, appeared as a doublet of doublets [J = 8Hz(2Hz)] centered in the range of 8.41-8.46 ppm. The H₄ and H₅ 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, H₆ was exhibited as an ill-defined multiplet and H₅ 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 ¹³C spectra were also indicative of the respective structures of the amides, with the carbonyl carbon signal (δ₈) 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

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>R</th>
<th>M.p.(°C)</th>
<th>Yield (%)</th>
<th>σ_R</th>
<th>σ₈ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>OCH₃</td>
<td>198</td>
<td>67</td>
<td>-0.28</td>
<td>161.11</td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>203</td>
<td>80</td>
<td>-0.14</td>
<td>161.35</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>189</td>
<td>91</td>
<td>0.00</td>
<td>161.60</td>
</tr>
<tr>
<td>d</td>
<td>F</td>
<td>175</td>
<td>72</td>
<td>0.06</td>
<td>161.52</td>
</tr>
<tr>
<td>e</td>
<td>Br</td>
<td>197</td>
<td>48</td>
<td>0.22</td>
<td>161.72</td>
</tr>
<tr>
<td>f</td>
<td>COCH₃</td>
<td>260</td>
<td>67</td>
<td>0.47</td>
<td>162.09</td>
</tr>
<tr>
<td>g</td>
<td>CF₃</td>
<td>214</td>
<td>79</td>
<td>0.53</td>
<td>162.19</td>
</tr>
<tr>
<td>h</td>
<td>NO₂</td>
<td>207</td>
<td>85</td>
<td>0.81</td>
<td>162.45</td>
</tr>
<tr>
<td>i</td>
<td>4-Br,3-Me</td>
<td>215</td>
<td>98</td>
<td>0.22+(-0.06)</td>
<td>161.62</td>
</tr>
</tbody>
</table>

A plot of the carbonyl carbon shift (δ₈) 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:

δ₈ = 1.22σ_R + 161.50

A correlation coefficient of r² = 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-C₆H₄R 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.

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⁺Br and σ⁺Me when substituted into the correlation equation should generate a δ₈ 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 δ₈ correlations. Future work in the ¹³C area will include inductive effect sensitivity studies with N-(4-substituted phenyl)-2-halononicotinamides.

Acknowledgments.—The authors wish to thank the Agricultural Research Division of Rhone Poulenc, Inc. for partial support of this work and a National Science Foundation I.L.I grant for the purchase of the NMR spectrometer.
Literature Cited


