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Excellent correlation between substituent constants and pyridinium N-methyl chemical shifts

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Abstract

Substituents on the pyridinium ring of N-methylpyridinium derivatives, especially those on the 2- or 4-positions, have a large effect on the ^1H and ^{13}C NMR chemical shifts of the N-methyl group. Reasonable correlations between the chemical shift changes and the resonance substituent constants are observed. The dual substituent parameter approach provides an excellent correlation when a combination of polar and resonance substituent constants is employed.

The determination of the electronic effect that substituents have on reactions is very important in the elucidation of reaction mechanisms, especially the nature of the transition state.¹ The Hammett constants, σ_{meta} and σ_{para} , were first calculated from the comparison of ionization constants of substituted benzoic acids.² Two new types of σ constants, σ^+ and σ^- , were introduced for structures in which the substituent is able to come to direct resonance interaction with electron-deficient or electron-rich reaction sites, respectively.^{3,4} Later, the separation of polar and resonance parts of the substituent effect has led to the establishment of the polar substituent constant, σ_I , and four sets of resonance substituent constants, σ°_R , $\sigma_{R(\text{BA})}$, σ^-_R and σ^+_R .^{1,5} The four sets of resonance parameters are used for relatively unperturbed systems, substituted benzoic acids, electron-deficient and electron-rich benzene rings, respectively.^{1,5} In this report, we will describe the excellent correlation between the ^1H and ^{13}C NMR chemical shifts of substituted N-methylpyridinium and the substituent constants σ_I and σ^+_R using the dual substituent parameter approach (eq. 1).

$$\log(k/k_0) = \rho_I \sigma_I + \rho_R \sigma_R \quad (1)$$

We have recently examined the acidity of the α -CH group of 2-methoxy and 4-methoxypyridinium compounds through kinetic measurement of hydrogen-deuterium exchange.⁶ The $\text{p}K_{\text{a}}$ values of these two compounds in aqueous solution were found to be surprisingly high and a large solvent effect was observed for the hydrogen-deuterium exchange reactions. In our effort to investigate the effect of various substituents on the rate of hydrogen-deuterium exchange, we have found that these groups, and other π -electron donating groups, on the 2- or 4- positions have a large effect on the chemical shifts of the N-methyl group in pyridinium compounds. The upfield chemical shifts are a result of the lower charge density on

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the nitrogen atom due to the resonance structures as shown in If a good correlation were to be found between the chemical shift of the N-methyl group and the ability of substituents to donate electrons, it would be a valuable tool in the measurement of the resonance effects of substituents due to the ready availability of the N-methylpyridinium compounds. Therefore, we have prepared a series of substituted N-methylpyridinium molecules to investigate the relationship between the chemical shifts of the N-methyl group and the nature of the substituents.⁷ The ¹H and ¹³C NMR chemical shifts and the relevant substituent constants are listed in Table 1.

N-Methylpyridinium compounds substituted at the 2- or 4- positions were treated separately because the chemical shifts were quite different for the two sets of molecules. A better fit was found for 4-substituted pyridinium compounds. This result was reasonable considering the fact that the substituent constants were derived with *para*-substituted benzene derivatives. When $\Delta\delta$ (the differences between the substituted and parent pyridinium molecules) were plotted against resonance substituent constants alone, σ°_R , $\sigma_{R(BA)}$ and σ^+_R gave reasonable fits. The poor correlation with σ^-_R was fully expected because of the electron-deficient nature of the pyridinium ring.

One interesting observation is the relative electron-withdrawing ability of the cyano (–CN) and the ester group (–CO₂CH₃). The cyano group appears to be less electron-withdrawing than the ester group, based on the comparison of their resonance substituent constants. However, it is apparent from the reactivity of benzyl bromide derivatives in their oxidation to benzaldehyde derivatives that a *p*-CN substituent is more electron-withdrawing than a *p*-CO₂CH₃ group.⁸

One explanation is the strong polar effect associated with the cyano group, as evident from the larger σ_I value. When the dual substituent parameter approach was applied to the data, an excellent correlation ($R^2 = 0.99$) was observed between the chemical shift changes and the sum of polar and resonance effects ($\rho_I\sigma_I + \rho_R\sigma_R$) when σ^+_R was used as shown in Figure 2. The ratio of the coefficients ρ_I and σ_R (as indicated by $\lambda = \rho_R/\rho_I$) signified the larger contribution from the resonance effect. A good correlation ($R^2 = 0.96$) was also observed when $\sigma_{R(BA)}$ was employed.⁹ The better fit with σ^+_R is expected because of the electron deficient nature of the system studied here.

For the 2-substituted pyridinium compounds, the correlation was not as good when the chemical shift changes were plotted against the resonance substituent constants alone or a combination of polar and resonance substituent constants, $\rho_I\sigma_I + \rho_R\sigma_R$. This kind of poor correlation has been regularly observed with *ortho*-substituted benzene systems and was attributed to the proximity of the substituents to the reaction site and thus contributions from the proximity effect.⁵

For the 3-substituted pyridinium compounds, no good correlation was found between the $\Delta\delta$ and σ_{meta} or σ_I , although a reasonably good correlation has been reported between the ¹⁹F NMR chemical shifts of fluorobenzene derivatives and σ_I .¹⁰ When the dual substituent approach was employed using σ_I and σ°_R , a good correlation ($R^2 = 0.94$) was found for ¹³C but not ¹H NMR chemical shifts.

The coefficients ρ_I , ρ_R and λ are 1.37, 0.74, 0.54 for ¹³C NMR, respectively.¹¹ These numbers indicate the greater contribution from the polar effect, as expected. However, the contribution from resonance effect does play a role, presumably by reducing the overall charge of the pyridinium ring.

In summary, reasonable correlations between the ¹H and ¹³C NMR chemical shifts of the N-methyl group on pyridinium compounds and the resonance substituent constants has been observed. The best fit was found with 4-substituted pyridinium molecules. This could be a

useful way to assess the resonance electronic effects of various substituents. When both the polar substituent constant (σ_I) and the resonance substituent constants (σ^+_R) were considered, excellent correlations were observed. The results have further demonstrated the advantage of the dual substituent parameter approach.^{1,5}

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9. The dual substituent parameter approach using σ_R may underestimate the contribution from the polar effect in this case, as evident from the coefficients. The coefficients ρ_I , ρ_R and λ are 0.61, 4.12, 6.78 for ^{13}C NMR and 0.04, 0.54, 13.62 for ^1H NMR, respectively.
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11. When σ_R was used, a reasonable correlation was also found for ^{13}C NMR chemical shifts only ($R^2 = 0.92$). The coefficients ρ_I , ρ_R and λ are 1.37, 0.49, 0.36 for ^{13}C NMR, respectively.

Figure 1.
N-Methylpyridinium Derivatives and Representative Resonance Structures with Electron-Donating Groups

Figure 2. Correlation of ^{13}C (A) and ^1H (B) NMR chemical shifts of the N-methyl group in substituted N-methylpyridiniums with the polar and resonance substituent constants (σ_I and σ_R^+)

Table 1

Polar and Resonance Substituent Constants^a and Corresponding ¹H and ¹³C NMR chemical shifts of the N-methyl group in substituted pyridinium compounds

Substituent	σ_m	σ_I	σ°_R	$\sigma_{R(BA)}$	σ^+_R	δ (¹ H, ppm)	δ (¹³ C, ppm)
-H	0.00	0.00	0.00	0.00	0.00	4.426	51.043
-NH ₂	-.16	.12	-.48	-.82	-1.61	3.834 (2-) 4.243 (3-) 3.936 (4-)	44.055 (2-) 50.813 (3-) 47.552 (4-)
-NHAc	—	.26	-.25	-.36	-.86	4.243 (2-) 4.235 (4-)	47.079 (2-) 49.445 (4-)
-OCH ₃	.12	.27	-.34	-.61	-1.02	4.276 (2-) 4.390 (3-) 4.182 (4-)	44.153 (2-) 51.230 (3-) 49.071 (4-)
-CH ₃	-.07	-.04	-.11	-.11	-.25	4.258 (2-) 4.366 (3-) 4.330 (4-)	48.419 (2-) 50.747 (3-) 50.153 (4-)
-Cl	.37	.46	-.23	-.23	-.36	4.415 (2-) 4.431 (3-)	50.390 (2-) 51.357 (3-)
-Br	.39	.44	-.19	-.19	-.30	4.415 (3-)	51.204 (3-)
-CN	.56	.56	.13	.13	.13	4.636 (2-) 4.511 (3-) 4.521 (4-)	51.457 (2-) 51.982 (3-) 52.206 (4-)
-CO ₂ CH ₃	.37	.30 ^b	.14	.14	.14	4.486 (4-)	51.608 (4-)

Substituent	σ_m	σ_I	σ^+R	$\sigma_{R(BA)}$	σ^+R	δ (1H , ppm)	δ (^{13}C , ppm)
-COCH ₃	.38	.28	.16	.16	.16	4.517 (3-) 4.501 (4-)	51.478 (3-) 51.416 (4-)

^a Taken from references ¹ and ⁵.

^b Reported for -CO₂Et..