



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-position, 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.

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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 and 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 Letter, 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 $\text{p}K_a$ 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- position 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 the nitrogen atom due to the resonance structures as shown in Figure 1.

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 ^{13}C NMR chemical shifts and the relevant substituent constants are listed out in Table 1.

N-Methylpyridinium compounds substituted at the 2- or 4-position 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 mole-

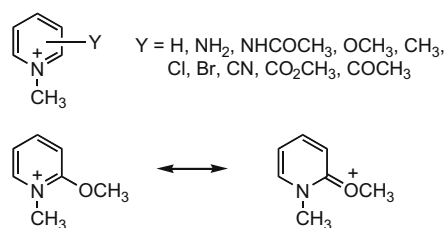


Figure 1. *N*-Methylpyridinium derivatives and representative resonance structures with electron-donating groups.

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Table 1Polar and resonance substituent constants^a and the 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-)	44.055 (2-) 50.813 (3-)
-NHAc	-	.26	-.25	-.36	-.86	3.936 (4-) 4.243 (2-)	47.552 (4-) 47.079 (2-)
-OCH ₃	.12	.27	-.34	-.61	-1.02	4.235 (4-) 4.276 (2-)	49.445 (4-) 44.153 (2-)
-CH ₃	-.07	-.04	-.11	-.11	-.25	4.390 (3-) 4.182 (4-)	51.230 (3-) 49.071 (4-)
-Cl	.37	.46	-.23	-.23	-.36	4.258 (2-) 4.366 (3-)	48.419 (2-) 50.747 (3-)
-Br	.39	.44	-.19	-.19	-.30	4.330 (4-) 4.415 (2-)	50.153 (4-) 50.390 (2-)
-CN	.56	.56	.13	.13	.13	4.431 (3-) 4.415 (3-)	51.357 (3-) 51.204 (3-)
-CO ₂ CH ₃	.37	.30 ^b	.14	.14	.14	4.636 (2-) 4.511 (3-)	51.457 (2-) 51.982 (3-)
-COCH ₃	.38	.28	.16	.16	.16	4.521 (4-) 4.486 (4-)	52.206 (4-) 51.608 (4-)
						4.517 (3-) 4.501 (4-)	51.478 (3-) 51.416 (4-)

^a Taken from Refs. 1 and 5.^b Reported for -CO₂Et.

cules) 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 ρ_R (as indicated by $\lambda = \rho_I/\rho_R$) 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 for ¹H NMR chemical shifts. The coefficients ρ_I , ρ_R and λ are 1.37, 0.74 and 0.54 for ¹³C NMR, respectively.¹¹ These numbers indicate the greater contribution from the polar effect, as expected. However, the con-

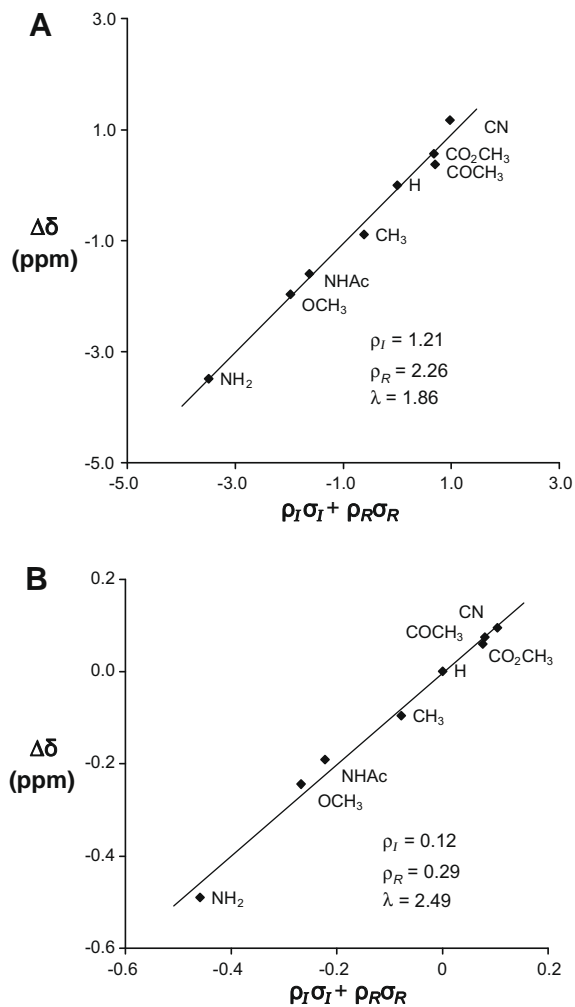


Figure 2. Correlation of ¹³C (A) and ¹H (B) NMR chemical shifts of the *N*-methyl group in substituted *N*-methylpyridiniums with the polar and resonance substituent constants (σ_I and σ_R^+).

tribution 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 ^{13}C NMR chemical shifts of the *N*-methyl group on pyridinium compounds and the resonance substituent constants have 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^\pm) 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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7. *Typical experimental procedures*: Pyridine (1 g) was dissolved in 5 mL anhydrous ethyl ether in a pressure tube. Methyl iodide (3 g) was added to the solution and the mixture was stirred overnight at room temperature. The resulting solid was filtered, washed with anhydrous ethyl ether, and dried to give *N*-methylpyridinium iodide as a white solid. In cases when the pyridine derivatives are not soluble enough in ether, ethyl acetate was used as the reaction solvent. All chemicals are commercially available and are used without further purification. NMR spectra were obtained with either QE 300 or Bruker 500 instruments. All chemical shifts are referenced to sodium 3-trimethylsilylpropionate at 0.00 ppm.
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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 and 6.78 for ^{13}C NMR and 0.04, 0.54 and 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 and 0.36 for ^{13}C NMR, respectively.