Correlation of Reaction Rates with a Substituent Constant Scale Derived from Calculated Electron Densities for a Computer Control Algorithm

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Synopsis. A new σ substituent scale based on electron density calculations by the AM1 quantum mechanical model has been established and used to correlate rates of *O*-methylation of substituted phenols, as part of a chemical artificial intelligence to control a fully automated apparatus for [^{11}C]-methyl iodide labeling.

One of the most versatile and commonly used methods for labeling biologically active compounds with the short half-life nuclide ^{11}C ($t_{1/2}$=20 min) for positron emission tomography (PET), is methylation by [^{11}C]-MeI. Although rapid methylation is readily accomplished at a variety of structural groups; e.g. –OH, –NH, and –SH, and many kinds of radiopharmaceuticals have been developed,[1] the optimum labeling conditions, of concentration and time, are a complex function of the reaction kinetics and the ^{11}C decay constant.[2] Thus the resulting yield–time curves generally show a steep rise followed by rapid tailing as the ^{11}C decays.

Methylation at phenolic oxygen (Scheme 1) with [^{11}C]methyl iodide has been used to label a number of important tracers[3—5] for PET studies. As part of the development of a fully automated [^{11}C]MeI labeling apparatus we investigated correlations of rates with substituent constants for a series of substituted phenols, in order to predict the optimum labeling conditions.

Experimental

N,*N*-Dimethylacetamide (DMAC), phenols, methoxybenzenes, and other reagents were purchased from Nacalai Tesque, Tokyo Kasei, and Aldrich Chemicals Inc. DMAC was dried over 4A molecular sieves before use.

A Typical Methylation. Methyl iodide (0.25 μmol) in DMAC (25 μL) was injected into a mixture of phenol (2.5 μmol) in DMAC (250 μL) and NaOH (aq) base (2 μL, 20 μmol) that was magnetically stirred in a 3 mL screw-capped vial with septum, maintained at 25±0.5°C. At an appropriate time the reaction was stopped by addition of sufficient hydrochloric acid (4 μL, 20 μmol) to neutralize the reaction mixture. The yield of methoxybenzene was measured by HPLC using reverse phase chromatography (C-18 capcell pak, SG120, 4.6×250 mm, Shiseido, Tokyo) with 65 : 35 methanol–phosphoric acid (0.01 M, M=mol dm^{-3}) as eluent.

Calculation of Rate Constants. The rate constants were calculated using the second-order bimolecular rate equation. The average value and standard deviation was obtained from at least 3 runs, quenched during the period when the reaction followed second-order kinetics.

$$\mathrm{ArOH} + [^{11}\mathrm{C}]\mathrm{MeI} \xrightarrow{\text{base}} \mathrm{ArO}[^{11}\mathrm{C}]\mathrm{Me} + \mathrm{HI}$$

Scheme 1.

AM1 Calculations. Electron densities on substituted phenolate anion oxygen atoms were calculated for optimized structures using the MOPAC V. 3.11 program, on a link to a CRAY X-MP/216 supercomputer.

Results and Discussion

We previously showed that rapid methylation of phenolic compounds was achieved in a DMAC–NaOH system at 25±0.5°C, using a large excess amount of base (80 times) and excess of substrate (10 times) to methyl iodide.[6] The measured rate constants of methylation for a series of mono- and multi-substituted phenols are summarized in Table 1. The Hammett type correlation of log k_X/k_H values with σ substituent constants was investigated and a good correlation with σ_m, σ_p^- or their summations was obtained (Fig. 1, ρ=−2.05, R^2=0.913, n=21). The reaction constant is double the value reported for the reaction of ethyl iodide with phenols in ethanol (ρ=−0.994; 42.5 °C),[7] reflecting the increased withdrawing ability of substituents and the increased charge developed on the oxygen reaction center when solvation of the transition state is decreased by using dipolar aprotic solvent. Although we were able

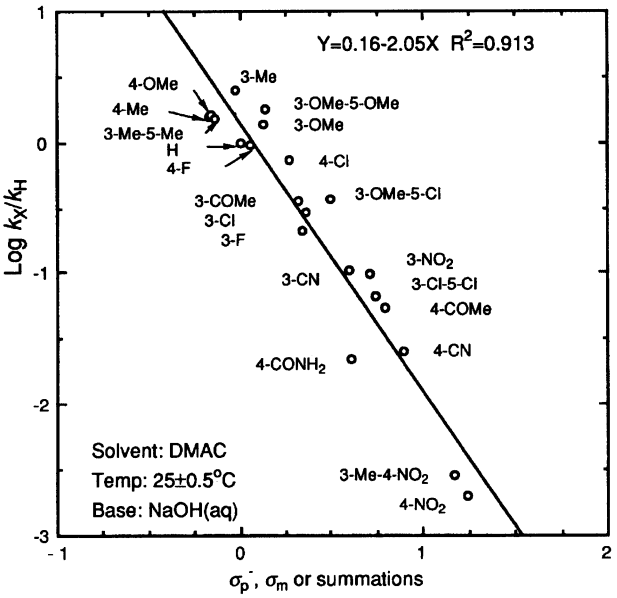

Fig. 1. Linear free energy relationship between log k_X/k_H and Hammett σ values for *O*-methylation of substituted phenols.

Table 1. Rates of Methylation, σ, Electron Densities, and $\sigma_{(ED)}$ Values for Substituted Phenols

Substituent, X, position					k_X	SD[a]	log k_X/k_H	σ[b]	ED[c]	$\sigma_{(ED)}$
2-	3-	4-	5-	6-	$dm^3\ mol^{-1}\ s^{-1}$					
—	—	—	—	—	10.6	1.9	0.000	0.00	6.5726	−0.035
—	—	Me	—	—	16.8	2.0	0.216	−0.17	6.5677	0.042
—	—	OMe	—	—	17.2	0.4	0.226	−0.16	6.5611	0.145
—	—	F	—	—	10.2	3.7	−0.001	0.05	6.5594	0.171
—	—	Cl	—	—	7.9	1.0	−0.111	0.27	6.5541	0.254
—	—	COMe	—	—	0.58	0.07	−1.246	0.79	6.5205	0.777
—	—	$CONH_2$	—	—	0.24	0.09	−1.629	0.61	6.5194	0.794
—	—	CN	—	—	0.27	0.03	−1.578	0.89	6.5202	0.782
—	—	NO_2	—	—	0.021	0.005	−2.687	1.24	6.4855	1.322
—	Me	—	—	—	26.4	2.2	0.412	−0.03	6.5724	−0.031
—	OMe	—	—	—	14.8	2.1	0.160	0.13	6.5614	0.140
—	F	—	—	—	2.2	0.5	−0.663	0.34	6.5557	0.229
—	Cl	—	—	—	3.1	0.2	−0.518	0.36	6.5533	0.266
—	COMe	—	—	—	3.8	0.2	−0.426	0.32	6.5550	0.240
—	CN	—	—	—	1.1	0.1	−0.956	0.60	6.5479	0.350
—	NO_2	—	—	—	1.0	0.2	−0.996	0.71	6.5387	0.494
—	Me	—	Me	—	16.2	1.0	0.200	−0.14	6.5721	−0.027
—	OMe	—	OMe	—	18.9	0.6	0.267	0.14	6.5558	0.227
—	OMe	—	Cl	—	3.9	0.3	−0.420	0.49	6.5433	0.422
—	Cl	—	Cl	—	0.70	0.03	−1.164	0.74	6.5361	0.534
—	Me	NO_2	—	—	0.031	0.004	−2.518	1.17	6.4868	1.302
Me	—	—	—	—	14.9	0.6	0.164		6.5656	0.075
OMe	—	—	—	—	3.3	0.4	−0.490		6.5531	0.269
F	—	—	—	—	4.1	0.1	−0.396		6.5415	0.450
Cl	—	—	—	—	2.5	0.1	−0.611		6.5390	0.489
COMe	—	—	—	—	0.14	0.01	−1.863		6.5123	0.905
$CONH_2$	—	—	—	—	0.24	0.02	−1.629		6.5567	0.213
CN	—	—	—	—	0.21	0.02	−1.687		6.5151	0.861
NO_2	—	—	—	—	0.012	0.0003	−2.930		6.4783	1.435
OMe	—	Me	—	—	6.8	0.2	−0.175		6.5487	0.338
Cl	—	Cl	—	—	0.65	0.05	−1.196		6.5224	0.748
OMe	—	COMe	—	—	0.28	0.03	−1.554		6.5026	1.056
OMe	—	NO_2	—	—	0.005	0.002	−3.356		6.4684	1.589
NO_2	—	NO_2	—	—	6.6×10^{-5}	0.8×10^{-5}	−5.189		6.4076	1.536
$CONH_2$	—	Cl	—	—	0.06	0.01	−2.231		6.5436	0.417
$CONH_2$	OH	Cl	—	Cl	0.007	0.002	−3.146		6.5133	0.889

a) Standard deviation. b) σ_m, σ_p^- or their summations from C. Hansch and A. Leo, Table of Parameter Values, Pomona College Medicinal Data Base, 1987. c) Electron density on phenolate ion oxygen by AM1 method.

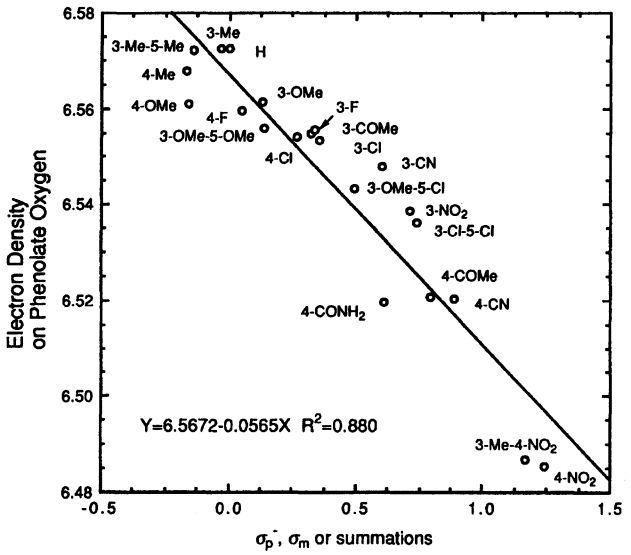

Fig. 2. Correlation between calculated electron density on phenolate oxygen atom and Hammett σ substituent constants.

to use this correlation to predict reaction rates for many 3- and 4-substituted phenols we found it necessary to search further for another correlation to predict rates for a wider range of compounds, including 2-substituted ones.

The AM1 quantum mechanical molecular model[8] was used to calculate the electron density (ED) on the phenolate anion oxygen atoms for substituted phenols (see Table 1) as it was expected that this would closely reflect the reactivity in our reaction system. The correlation equation (Fig. 2, $ED=6.5672-0.0565\sigma$) between the electron densities and the Hammett σ substituent constants for 3- and 4-substituted phenols was then used to put the electron densities on a σ scale, denoted as $\sigma_{(ED)}$ ($\sigma_{(ED)}=(ED-6.5672)/-0.0565$) in Table 1. This adjustment of the electron density scale allows the resulting correlations and reaction constant values to be easily understood in comparison to the established σ scales. Figure 3 shows a plot of the relative rates (log k_X/k_H values) for methylation against the $\sigma_{(ED)}$ values. It was found that two almost parallel correlation

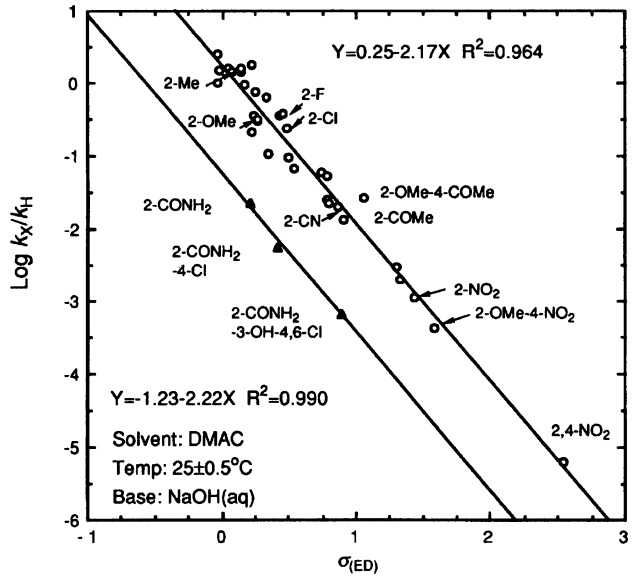

Fig. 3. Linear free energy relationship between log k_X/k_H and $\sigma_{(ED)}$ values for *O*-methylation of substituted phenols.

lines exist for methylation in the NaOH–DMAC system. The main correlation line is drawn through the log k_X/k_H values for all the substituted phenols except for three salicylamides ($\rho=-2.17$, $R^2=0.964$, $n=33$). The fact that several 2-substituted phenols could be included shows that the methylation is not significantly hindered sterically by one *ortho*-substituent.

The rate of methylation for 4-hydroxybenzamide fits on to the main correlation line but three 2-hydroxybenzamides (salicylamides) form a separate line ($\rho=-2.22$, $R^2=0.990$, $n=3$), showing that they are more slowly methylated than estimated by the main correlation. This is presumably due to the *ortho* nature of the $-CONH_2$ group in the salicylamides, which allows formation of an intramolecular H-bond between the amide group (N–H) and the reaction center ($-O^-$). As the steric effect of one *ortho*-substituent appears to be negligible under our reaction conditions, we suggest that the deviation is a result of the AM1 calculation failing to accurately allow for the transfer of electron density away from the oxygen reaction center through H-bonding.

By incorporating the above correlation equations into a computer control algorithm we have been able to predict optimum [^{11}C]MeI labeling conditions for a wide variety of phenolic compounds based upon the calculated electron densities for the phenolate anions.

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