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A Novel Computational Approach to the Estimation of Steric Parameters Application to the Menschutkin Reaction

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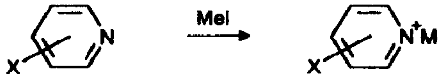
Abstract. A new purely computational approach to the estimation of steric parameters, suitable for use in QSAR studies, is described and tested by application to the Menschutkin reaction of substituted pyridines.

Quantitative structure activity relationships (QSAR)[1] for extensive sets of compounds can often be hampered by (i) the absence of tabulated substituent constants appropriate to the molecules under study, (ii) the lack of reported values for molecular properties, such as pK_a, (iii) the fact that not only the substituents, but also the backbone or the heterocyclic nucleus to which the substituents are attached, may differ between compounds in the dataset. In this context, using a *purely computational approach* to obtain QSAR parameters is very attractive, since it ensures that data can be obtained for *all* compounds, thereby avoiding the problems outlined above. A number of conventional measures of *electronic* effects, such as electron densities, orbital energies and orbital coefficients, are available in this way, so if *steric* parameters can also be obtained from parallel calculations, there is a clear advantage.

In this paper, we report just such a computational approach to the estimation of steric parameters. It was developed as part of our on-going study of the olfactory properties of aza-heterocycles having a bell-pepper odour and apparently similar compounds lacking that odour, which will be reported elsewhere. Here, we outline the approach and its validation, and show how we have tested it by applying the resulting parameters to a reliable dataset, that for the rates of the extensively-studied Menschutkin N-methylation of substituted pyridines.[2]



We use the AM1 semi-empirical MO method,[3] as implemented in MOPAC,[4] to calculate the proton affinities (A_p) and methyl ion affinities (A_{Me}), for reaction on the nitrogen atom, of an extensive series of substituted pyridines.[5] We then make the assumption that, in the absence of steric effects, *i.e.* for pyridines in which the 2- and 6-positions are unsubstituted, protonation and methylation will both depend on electronic effects in the same way and will show a linear correlation. In the case of 2-substituted pyridines, for which steric effects are important, they should have little or no effect on protonation, but a more pronounced effect on methylation. The data points for the latter should thus deviate from the correlation line obtained for unhindered pyridines and the deviation should be a quantitative measure of the steric hindrance around the nitrogen atom undergoing change.

This approach is parallel to that used by Gallo *et al.*[7] in deriving their S^0 values, in the sense that they considered an experimental Bronsted plot for methylation of unhindered pyridines and derived their steric factors from the deviation of hindered pyridines from that line. The present approach differs from theirs in two respects. Firstly it uses purely *calculated* rather than experimental data and secondly it uses a "Bronsted plot" involving the *thermodynamics* of methylation rather than the kinetics.

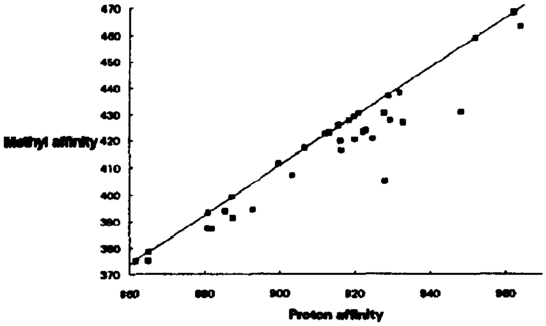


Figure. Correlation of proton affinity (A_p) and methyl ion affinity (A_{Me})/kJ mol^{-1}. The line is the best fit line through the points for the unhindered pyridines.

For a series of 15 substituted pyridines, lacking substituents at the 2-position (*i.e.* "unhindered") the calculated A_{Me} shows a linear correlation with A_p (in units of kJ mol^{-1}) according to equation 1 (see also Figure). The excellent correlation provides a first step in the validation of our approach.

$$A_{Me} = (0.933 \pm 0.004)\,A_p - (428.6 \pm 3.2) \qquad (1)$$
$$r = 0.999_5,\ n = 15,\ s = 0.368,\ F = 69{,}927$$

The slope of the correlation line is less than unity reflecting the fact that at least some of the charge on the nitrogen in the methylated pyridine will be delocalised on to the methyl group so that the electronic demands on the ring atoms and substituents will be less than for the protonated pyridine.

For 10 of our 3- and 4-substituted pyridines, gas phase basicities have been reported.[8] These experimental data show good correlation with our calculated proton affinities (r = 0.991), giving confidence in AM1 as a suitable level of calculation.

A further satisfactory validation of equation 1, in a region of the figure not covered by the data for substituted pyridines, results if we calculate A_{Me} for ammonia and use the value to predict the corresponding A_p. A_{Me} is calculated from a combination of the AM1 value for $\Delta_f H^\circ(\mathrm{Me^+,g})$ with data for $\Delta_f H^\circ(\mathrm{NH_3,g})$[9] and $\Delta_f H^\circ(\mathrm{MeNH_3{}^+,g})$.[10] This leads to a prediction of A_p very close to the currently accepted value.[11]

For a series of 15 pyridines substituted in the 2-position (*i.e.* "hindered")[12] the points fall below the correlation line in the Figure. For these compounds, their A_{Me} is less than would be expected from their A_p, and the discrepancy is attributed to steric hindrance to methylation. The deviation from the line is divided by $2.3RT$ ($T = 298$ K) to convert it to dimensionless "log *k*" form, and the result is defined to be our steric factor ($\mathcal{S}$). Values are given in the Table, which correspond, at least qualitatively, with expectations. Quantitatively they agree with the Gallo S^o ($r = 0.944$)[5] and Taft E_s ($r = 0.933$)[13] better than those two do with one another ($r = 0.815$). The standard deviation of the estimate for the correlation line in the Figure establishes error limits on $\mathcal{S}$ of ± 0.06.

For a series of five 2-methylpyridines, with a second substituent elsewhere on the ring, having a range of A_p of over 80 kJ mol^{-1}, the mean $\mathcal{S}$ is -1.17 ± 0.07 ($n = 5$). While, strictly speaking, our $\mathcal{S}$ is a molecular property, rather than a substituent parameter, it is gratifying to find that the deviation of the points from the correlation line do not depend on where along that line they lie, and that the $\mathcal{S}$ value for a 2-methyl group does not depend on other substituents on the ring. The exception is 2,3-dimethylpyridine, for which $\mathcal{S} = -1.46$, lying more than 4σ outside the above range. This larger value is consistent with the expected buttressing effect in this molecule and gives promise that our approach can also deal with this phenomenon.[14]

Table. Calculated Steric Factors, $\mathcal{S}$, for 2-substituted pyridines

Pyridine	$\mathcal{S}$
2-*tert*-butylpyridine	− 5.58
2-dimethylaminopyridine	− 4.35
2-phenoxypyridine	− 3.49
2-benzylpyridine	− 2.56
2-*iso*-propylpyridine	− 2.32
2-phenylpyridine	− 1.84
2-acetylpyridine	− 1.77
2-hydroxymethylpyridine	− 1.71
2-ethylpyridine	− 1.56
2-formylpyridine	− 1.42
2-methylpyridine	− 1.10
2-bromopyridine	− 0.98
2-chloropyridine	− 0.65
2-cyanopyridine	− 0.59
2-aminopyridine	− 0.41

We have used our $\mathcal{S}$ parameter, together with the pK_a value taken as a measure of the electronic effect of a substituent to correlate the kinetic data reported by Gallo *et al.*,[7] which includes nine unhindered and eleven hindered pyridines. This gave Equation 2.

$$\log(k/k_H) = (0.65 \pm 0.07)\,\mathcal{S} + (0.43 \pm 0.05)\,pK_a - (2.26 \pm 0.26) \qquad (2)$$

$r = 0.942$, $n = 22$, $s = 0.48$ and $F = 74.55$

The quality of fit in equation 2 is very gratifying and confirms us in our belief that the approach will be of value in biochemical and medicinal QSAR studies. Replacement of the pK_a, an empirical quantity, by our calculated A_p, as an alternative measure of the electronic effect of the substituent, reduces the correlation coefficient only to 0.917. Replacement of our calculated δ by the empirical S^o improves the fit, as, indeed it must do, since these rate constants are the data which were used to define the latter parameter set. It is not surprising that the computational approach does not improve on the empirical parameters, but these results indicate that even a two parameter equation in which both parameters are obtained computationally holds promise in this context.

The coefficients in equation 2 can be interpreted in conventional mechanistic terms. The coefficient of the steric term shows that the methyl group experiences, in the transition state, 65% of the steric hindrance which it experiences in the methylpyridinium ion, and the value for the coefficient of the electronic term implies an effective charge of + 0.43 on the nitrogen atom in the transition state.

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