Pergamon

Tetrahedron Letters, Vol. 37, No. 26, pp. 4617-4620, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00891-X

A Novel Computational Approach to the Estimation of Steric Parameters
III. Extension to Aliphatic Amines and Application to the Adrenergic Blocking Activity of β-Haloalkylamines

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Abstract. We have extended our new purely computational approach to the estimation of steric parameters, ẟ, intended for QSAR studies, to the consideration of aliphatic amines and correlated kinetic data for the Menschutkin reaction of 26 amines with six alkyl iodides in LFERs. We have also used our calculated steric factors in QSARs to correlate the adrenergic blocking activity of β-haloalkylamines

We have recently reported[1,2] a novel approach to the estimation of steric parameters which is *purely computational*. Our initial illustration[1] showed satisfactory correlation between our steric factors and the rates of the Menschutkin N-methylation reaction[3] of substituted pyridines. Subsequently,[2] we showed that our approach had a distinct advantage over conventional transferable substituent parameters in that kinetic data for the Menschutkin reaction of a set of hindered substrates which included 2- and 4-substituted thiazoles as well as 2-substituted pyridines gave a *single* linear free energy relationship (LFER), which required only two parameters, the pK_a of the heterocyclic base and our computed steric factor ẟ,

Our approach utilised the AM1[4] method to calculate the proton affinity (A_p) and methyl cation affinity (A_{Me}) for reaction at the nitrogen atom of series of compounds in which the nitrogen atom was unhindered, *e.g.* pyridines in which the 2- and 6-positions are unsubstituted. We anticipated that, for such compounds, steric effects around the nitrogen atom should be absent, and that both protonation and methylation should depend on electronic effects in the same way. We found a linear correlation between A_p and A_{Me} for fifteen 3- and 4-substituted pyridines, with a correlation coefficient of 0.99993. In the case of hindered 2-substituted pyridines, the points were displaced from this correlation line because steric effects were expected to have little or no effect on protonation, but a more pronounced effect on methylation. The extent of displacement, suitably scaled by $2.3RT$ (T = 298 K), was taken as a quantitative measure of the steric effect for each compound considered.[1]

In extending this approach to aliphatic amines, a key problem was that it was not possible to define an unhindered series of real molecules to develop the essential correlation of A_p and A_{Me}, as had been done for the heterocyclic amines. Instead, we resorted to an artifice using the "sparkles" facility within MOPAC.[5] A pair of charges was placed on the 3-fold axis to polarise an ammonia molecule, as shown in the Figure, for both the neutral molecule, and after protonation and methylation, leading to values for A_p and A_{Me} for a perturbed ammonia molecule.[6] By variation of r_1 from 1 to 11 Å, and r_2 from 7 to 17 Å, A_p could be varied from 885 to 992 kJ mol^{-1}, leading to the correlation shown in equation 1.

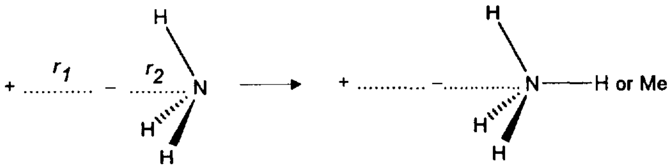


Figure. The use of sparkles to polarise ammonia.

$$A_{Me} = (0.971 \pm 0.001)\,A_p - (446.78 \pm 0.54) \qquad (1)$$
$$r = 0.99998,\ n = 121,\ s = 0.155,\ F = 2.75\times10^6$$

An extensive set of kinetic data has been reported by Popov *et al.*[7,8,9] for the alkylation of up to 26 aliphatic amines ($R_1R_2R_3N$) with each of 6 alkyl iodides (RI) in acetonitrile at 25 °C. For these amines, the nucleophilic nitrogen atom is hindered and, when we applied our method,[1,2] the calculated A_{Me} was found to be less than that estimated from the calculated A_p and equation 1. The discrepancy led to the steric factors ẟ, given in Table 1.

Table 1. Steric factors (ẟ) for selected aliphatic amines

Primary amines		**Secondary amines**				**Tertiary amines**	
R_1	**ẟ**	**R_1, R_2**	**ẟ**	**R_1, R_2**	**ẟ**	**R_1, R_2, R_3**	**ẟ**
Me	−1.70	Me, Me	−3.37	Et, *i*-Pr	−5.81	Me, Me, Me	−5.07
Et	−1.84	Me, Et	−4.18	*i*-Bu, *i*-Bu	−5.48	Me, Me, *n*-Bu	−6.31
n-Bu	−1.90	Me, *i*-Bu	−4.80	*i*-Bu, *i*-Pr	−6.00	Me, Me, *n*-Hex	−6.28
i-Bu	−1.93	Me, *i*-Pr	−5.07	*i*-Pr, *i*-Pr	−7.29	Me, Me, $PhCH_2$	−6.68
i-Pr	−2.60	Et, Et	−4.95	*n*-Bu, *n*-Bu	−5.24	Me, Et, Et	−7.38
t-Bu	−3.74	Et, *i*-Bu	−5.17	– $(CH_2)_5$ –	−3.45	Et, Et, Et	−8.52
c-Hex	−2.69					Me, – $(CH_2)_5$ –	−6.78

We consider first data for the *secondary* amines, for which any electronic factor should be constant, if, as is generally accepted,[10] all alkyl groups have the same inductive effect. The data were fitted to equations of the form of (2) and the results of the regression are given in Table 2. In order to correlate the complete data set which also included *primary* and *tertiary* amines, we needed to include an additional term in the LFER to code for electronic effects (eq. 3). Our best results came from the use of n_H, the number of hydrogen atoms attached to the nitrogen atom in the amine. In effect, this is a scale of polar substituent constants in which the value for the methyl group is 0.00, as for the Taft scale,[11] all alkyl groups are taken to be the same as methyl, as concluded by Charton,[10] and the value for the hydrogen atom is set arbitrarily at 1.00. The data were fitted to equation 3 and the results are given in Table 2.[12] Markedly inferior correlations were obtained when n_H in equation 3 was replaced by the pK_a of the amine[13] or by the sum of the Taft σ^*[14] values for the groups attached to the nitrogen atom.

Table 2. Regression data for analysis using equations 2 and 3.

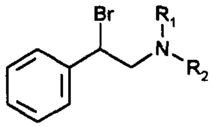
RI	*A*	*B*	*C*	n	r	s	F
Secondary amines only (equation 2)							
MeI	0.55±0.04		1.49±0.21	12	0.975	0.14	191
EtI	0.77±0.05		0.85±0.24	12	0.982	0.17	269
n-PrI	0.83±0.06		0.56±0.31	7	0.986	0.21	178
i-AmI	0.88±0.09		−0.18±0.40	4	0.990	0.17	94
i-BuI	0.77±0.03		−1.03±0.14	4	0.999	0.07	859
i-PrI	1.08±0.07		0.32±0.36	11	0.982	0.25	247
All amines (equation 3)							
MeI	0.41±0.04	−1.31±0.11	2.00±0.23	25	0.936	0.20	78
EtI	0.60±0.05	−1.48±0.13	1.32±0.37	25	0.932	0.25	73
n-PrI	0.67±0.06	−1.51±0.14	1.10±0.39	20	0.946	0.26	73
i-AmI	0.65±0.12	−1.34±0.23	0.33±0.71	10	0.914	0.31	18
i-BuI	0.63±0.05	−1.49±0.12	−0.26±0.35	11	0.978	0.20	89
i-PrI	0.93±0.07	−1.75±0.18	1.19±0.49	18	0.963	0.32	95

$$\log(k_{\mathrm{RI}}) = A\,\text{ẟ} + C \qquad (2)$$

$$\log(k_{\mathrm{RI}}) = A\,\text{ẟ} + B\,n_{\mathrm{H}} + C \qquad (3)$$

For the secondary amines, the fits to equation 2 are impressive, showing that, when electronic effects can be ignored, ẟ is an excellent indicator of the steric environment around the nitrogen atom. The somewhat poorer fits to equation 3, when all classes of amines are included, can thus be attributed to the difficulty of finding a satisfactory parameter to code for electronic effects[13,14] rather than to any deficiency in the ẟ parameter. The coefficients *A*, the steric sensitivity parameter, shows the expected dependence on the electrophile. For both parts of Table 2, the *A*-values for the primary iodides are equal within the error limits, and there is an increase in the order methyl iodide < primary iodides < *i*-propyl iodide. This is also consistent with Popov's analysis[7] which used experimentally-derived steric parameters, E_N.

The approach, now widened in scope, promises to be useful in biochemical and medicinal QSAR studies. As an illustration of this, we have applied the method to examine data for the adrenergic blocking activity of β-haloalkylamines.[15] We considered only those compounds for which R_1 and R_2 varied, and in which the aromatic ring was unsubstituted, and calculated ẟ values as above. We used n_H as the electronic parameter, as discussed above, and introduced a hydrophobicity term, $\Sigma\pi = \pi(R_1) + \pi(R_2)$. Correlation coefficients of 0.95 for antagonist activity against adrenaline and 0.97 for antagonist activity against noradrenaline, both in the cat, were obtained. These are comparable to those reported by Hansch using corrected Taft E_s parameters, Taft σ^* and n_H in the regression.[16] This gives confidence that these computationally-derived steric parameters will be valuable in QSAR studies.



Acknowledgements. This research was supported by RAM Research Ltd.; we are grateful to Ernest Polak for his interest and support of this work and to Andrew (Jack) Smith for helpful discussions.

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12. The only data excluded were the rate constants for dimethylbenzylamine, for which the experimental values were consistently a factor of about three slower than those predicted by the regression on the other points. This is consistent with the known electron-withdrawing effect of the benzyl group[10] and indicates that, for this substrate, n_H is not an appropriate measure of the electronic effect of the benzyl group.
13. It is known that aqueous pK_a values of aliphatic amines do not show a simple dependence on electronic effects. See, for example, Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1972**, *94*, 4726-4728.
14. The values of σ^* for alkyl groups have been criticised by Charton[10] on the grounds that they code for steric effects. Not surprisingly, there was a good correlation between $\Sigma\sigma^*$ and our s values ($r = 0.96$) and this led to a colinearity problem when data were fitted to equation 3, modified in this way.
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(*Received in UK* 17 *April* 1996; *accepted* 10 *May* 1996)