

## Hydrogen Bonding Parameters for QSAR: Comparison of Indicator Variables, Hydrogen Bond Counts, Molecular Orbital and Other Parameters

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Hydrogen bonding is an important property in drug and xenobiotic interaction with biota, and numerous attempts have been made to quantify it for use in quantitative structure–activity relationships. These attempts are reviewed, and their ability to model hydrogen bond donor ability examined by correlating them with the melting points of a series of anilines, known to be very dependent on hydrogen bonding. The best model was found to be a two-parameter model involving the charge on the hydrogen bonding hydrogen(s) and the energy of the lowest unoccupied molecular orbital. These parameters were further tested successfully by using them to replace other hydrogen bonding parameters in a series of QSAR correlations.

### 1. INTRODUCTION

Hydrogen bonding, although it is but a weak intermolecular force, is nonetheless an important factor in drug and xenobiotic activity. Many drug–receptor interactions involve hydrogen bonding, and aqueous solubility and partitioning are controlled in large part by it. Consequently, there have been a number of attempts over the years to devise hydrogen bonding parameters for use in QSAR (quantitative structure–activity relationship) studies.

The first such attempt was made by Seiler,<sup>1</sup> who used the difference between octanol–water and cyclohexane–water log *P* values (*P* = partition coefficient) to develop group contributions (*I<sub>H</sub>*) to hydrogen bonding; he reported *I<sub>H</sub>* values for 21 substituents.

A problem with this and most other substituent-based approaches is that the hydrogen bonding ability of a given substituent is not independent of the remainder of the molecule. Thus a whole-molecule approach is to be preferred, but this necessitates, in Seiler's method, knowledge of two experimentally measured log *P* values for each compound studied. This approach has been used by Young et al.,<sup>2</sup> who correlated blood–brain barrier penetration with the difference between octanol–water and cyclohexane–water log *P* values. A further drawback of the Seiler approach is that the difference between octanol–water and cyclohexane–water log *P* values must be a function of polarity as well as of hydrogen bonding, and hence *I<sub>H</sub>* values cannot be regarded as pure hydrogen bonding parameters.

Moriguchi<sup>3</sup> assumed that log *P* contained volume and polarity components and calculated the polarity component *E<sub>W</sub>* as the difference between the octanol–water log *P* value of a polar compound and that of a nonpolar compound with the same molecular volume. Although Moriguchi called *E<sub>W</sub>*

a polarity term, he showed that it correlated well with hydrogen bond strength. We now know that log *P* can be factored into volume, polarity, and hydrogen bonding terms,<sup>4</sup> so that *E<sub>W</sub>* must contain both polarity and hydrogen bonding components.

Fujita et al.<sup>5</sup> devised a hydrogen bonding indicator variable which simply took the value of unity if a molecule or substituent was capable of forming a hydrogen bond and of zero if it was incapable of doing so. This method can be adapted to distinguish between proton-donor and proton-acceptor ability, and the values for many substituents are listed by Hansch and Leo.<sup>6</sup> Because of its simplicity it has been to date the most widely used hydrogen bonding descriptor in QSAR studies. An example<sup>7</sup> of its use is shown in eq 1

$$\log \text{BR} = 0.0055\text{MR} - 0.37\text{HA} + 1.988 \quad (1)$$

$$n = 20 \quad r^2 = 0.709 \quad s = 0.36 \quad F = 20.7$$

where BR = inhibition of protozoan growth produced by pyridine derivatives, MR = molar refractivity, HA = indicator variable for hydrogen bond acceptor capability of the substituent(s), *n* = number of compounds, *r* = correlation coefficient of the regression, *s* = standard error of the estimate, and *F* = Fisher's statistic. The correlation with MR alone is *r*<sup>2</sup> = 0.626, so the HA term clearly gives a significant improvement.

Charton and Charton<sup>8</sup> modified the Fujita approach by using the number of hydrogen bonds that a molecule or substituent was capable of forming. Thus –NH<sub>2</sub> would score 2 as a proton-donor and 1 as a proton-acceptor, whilst –OH would score 1 as a proton-donor and 2 as a proton-acceptor, since there are two lone pairs of electrons on the oxygen atom.

Yang et al.<sup>9</sup> devised two hydrogen bonding parameters; HB<sub>1</sub> is very similar to the Charton and Charton parameter, save that –OH is regarded as accepting only one hydrogen

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bond, and certain groups (e.g.,  $\text{OCF}_3$ ) are treated as non-hydrogen bond acceptors. (Two other rules are that the carboxyl group is capable of accepting only two hydrogen bonds<sup>10</sup> and that amide nitrogen is incapable of accepting a hydrogen bond.<sup>11</sup> Of course the nitrogen atom of the nitro group cannot accept a hydrogen bond, since it does not possess a lone pair of electrons). For hydrogen bond donors, however, the values of  $\text{HB}_1$  are identical to the Charton and Charton parameter.  $\text{HB}_2$  is calculated by taking average enthalpy values for each type of hydrogen bond (e.g.,  $\text{OH}\cdots\text{O}$ ), multiplying by the number of such bonds and scaling by 0.1. For example,  $\text{HB}_2$  for  $-\text{OH}$  is calculated by taking  $\Delta H$  for  $\text{OH}\cdots\text{O}$  as  $6.05 \text{ kcal mol}^{-1}$ , multiplying by 2 (since the  $-\text{OH}$  group can act as both proton-donor and proton-acceptor) and scaling:  $\text{HB}_2 = 6.05 \times 2 \times 0.1 = 1.21$ . Yang et al.<sup>9</sup> reported  $\text{HB}_1$  and  $\text{HB}_2$  values for 144 substituents.

In recent years Kamlet and co-workers have developed their solvatochromic parameters, so-called because they were originally derived from spectroscopic data. These whole-molecule parameters comprise a volume term, a polarity/polarizability term, a hydrogen bond donor term  $\alpha$ , and a hydrogen bond acceptor term  $\beta$ . A combination of these terms can describe physico-chemical properties such as solubility<sup>12</sup> and biological effects such as toxicity.<sup>13</sup> They have, however, the disadvantage that they are experimentally derived. Methods have been proposed<sup>14,15</sup> for their calculation, but these are not very satisfactory at present. Abraham et al.<sup>16</sup> have used the solvatochromic approach to devise functional group hydrogen bonding parameters  $K_\alpha$  for proton-donor and  $K_\beta$  for proton-acceptor groups totaling 73 in all.

Wilson and Famini<sup>17</sup> and Dearden and Ghafourian<sup>18</sup> have used atomic charge on the hydrogen-bonding hydrogen atom ( $Q_H$ ) and the energy of the lowest unoccupied molecular orbital ( $E_{\text{LUMO}}$ ) to model hydrogen bond donor ability and the charge on the most negatively charged atom ( $Q_{\text{MN}}$ ) and the energy of the highest occupied molecular orbital ( $E_{\text{HOMO}}$ ) to model hydrogen bond acceptor ability.  $E_{\text{LUMO}}$  and  $E_{\text{HOMO}}$  represent the covalent contribution to hydrogen bonding.

Dearden et al.<sup>19</sup> have very recently used electron donor superdelocalizability ( $D_E$ ) and self-atom polarizability ( $P_E$ ) to model hydrogen bond donor ability. Raevsky et al.<sup>20</sup> have recently developed a multiplicative method (now available as the HYBOT software program) to obtain thermodynamic hydrogen bonding parameters.

Murray and Politzer<sup>21</sup> and Ghafourian<sup>22</sup> have investigated the use of molecular electrostatic potential (MEP) to model hydrogen bonding ability. Ghafourian found that MEP was rather better than atomic charge in this respect, although more difficult to calculate. For example, for a series of 57 phenols, amines, amides, carboxylic acids, and alcohols, the correlations of Abraham's  $\Sigma\alpha_H$  values were with  $Q_H$  (Gasteiger method),  $r = 0.737$ ; with  $\text{MEP}^+$ ,  $r = 0.782$ . On the other hand when  $E_{\text{LUMO}}$  was included, the correlations were  $Q_H$  and  $E_{\text{LUMO}}$ ,  $r = 0.847$ ;  $\text{MEP}^+$  and  $E_{\text{LUMO}}$ ,  $r = 0.834$ .

We examined all the hydrogen bonding parameters involving hydrogen bond donation described above, with the exception of MEP, to see how well they performed. As a test set we took a set of substituted anilines for which Dearden<sup>23</sup> had developed a QSAR that related the melting points ( $T_m$ ) of the compounds to a number of parameters, of which hydrogen bond donor ability was the most important

$$T_m(\text{K}) = 437 + 169\alpha - 40.4\pi + 10.6\text{MR} - 63.6B_2 + 47.1I_4 - 19.4L \quad (2)$$

$$n = 42 \quad r^2 = 0.897 \quad s = 23.7 \quad F = 50.5$$

where  $\alpha$  = solvatochromic hydrogen bond donor parameter,  $\pi$  = Hansch hydrophobic substituent constant,<sup>6</sup>  $B_2$  = Sterimol second width parameter,<sup>6</sup>  $I_4$  = indicator variable for 4-substitution (important because symmetry improves crystal packing and thus raises melting point), and  $L$  = Sterimol length parameter.<sup>6</sup> The correlation with  $\alpha$  alone was

$$T_m = 218 + 277\alpha \quad (3)$$

$$n = 42 \quad r^2 = 0.671 \quad s = 39.5 \quad F = 81.4$$

Thus  $\alpha$ , modeling hydrogen bond donor ability, accounts for 67.1% of the variation of melting point in this series of anilines, which is why the series should prove a good test of hydrogen bond donor parameters. (In crystals of a pure compound, hydrogen bonding can occur only if the compound possesses a hydrogen bond donor group. Thus only hydrogen bond donor ability, and not hydrogen bond acceptor ability, is an important parameter.)

## 2. METHOD

Melting points were taken from the literature. For molecular orbital calculations, molecules were constructed and minimized in COSMIC or NEMESIS, and then the CNDO and AM1 Hamiltonians in MOPAC were used to calculate atomic charges and  $E_{\text{LUMO}}$ . Statistical analysis was carried out using the statistical software MINITAB 9.1.

## 3. RESULTS AND DISCUSSION

Dearden<sup>23</sup> examined 42 anilines in his QSAR study of melting point. Although the correlation he obtained was very good, we decided to remove those anilines capable of intramolecular hydrogen bonding, so as to make interpretation of the results clearer. This left 33 compounds, and their melting points and hydrogen bonding parameters calculated by the various methods are given in Table 1. The correlations obtained between melting point and each of the relevant parameters are shown in Table 2. All the parameters, with the exception of those of Seiler<sup>1</sup> and Moriguchi,<sup>3</sup> relate specifically to hydrogen bond donor ability.

It is surprising that the Seiler parameter<sup>1</sup> gives such a high correlation, since it reflects both hydrogen bond donor and acceptor ability, and also has a polarity component. Since, however, it requires experimental determination of partition coefficients, it cannot be recommended as a parameter.

The correlation with the most widely used indicator variable (Fujita et al.<sup>5</sup>) accounts for only about 56% of that with  $Q_H$  and  $E_{\text{LUMO}}$  but is nonetheless considerably better than the Charton and Charton<sup>8</sup> count of hydrogen bonds; a glance at Table 1 shows that this must mean that, in the crystal lattice, the  $\text{NH}_2$  group donates only one hydrogen bond. This led us to use the average charge on the two amino hydrogen atoms of  $\text{NH}_2$ , rather than their sum, in calculating  $Q_H$ ; the charges on the hydrogen atoms of

**Table 1.** Melting Points and Hydrogen Bonding Parameters for 33 Substituted Anilines

subst.	$T_m$ (K)	Seiler	Moriguchi	Fujita et al.	Charton & Charton	Yang et al.	Abraham et al. $K_a$	Kamlet $\alpha$	$Q_H$ (CNDO)	$Q_H$ (AM1)	$E_{LUMO}$ (AM1)	$D_E$	$P_E$	Raevsky $C_{HD}$
H	266.7	0	0	0	0	0	0	0.26	0.084	0.182	0.638	0.262	0.037	-2.08
2-Me	249.3	0	0	0	0	0	0	0.23	0.080	0.181	0.599	0.263	0.037	-1
2-Et	230	0	0	0	0	0	0	0.23	0.079	0.183	0.607	0.264	0.037	-1
3-Cl	262.7	0	0	0	0	0	0	0.33	0.085	0.188	0.262	0.254	0.037	-3.04
3-Br	291.5	0	0	0	0	0	0	0.33	0.075	0.187	0.163	0.254	0.037	-3.04
3-I	306	0	0	0	0	0	0	0.23	—	0.182	0.165	0.254	0.037	-3.04
3-Me	242.6	0	0	0	0	0	0	0.23	0.081	0.181	0.604	0.262	0.037	-2
3-Et	209	0	0	0	0	0	0	0.23	0.081	0.181	0.613	0.262	0.037	-2
3-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	312	0	0	0	0	0	0	0.24	0.081	0.181	0.409	0.262	0.037	-2
3-OMe	272	0	0	0	0	0	0	0.25	0.082	0.185	0.600	0.259	0.037	-2
3-OH	395	2.06	-0.89	1	1	0.61	2.1	0.86	0.218	0.408	0.542	0.514	0.063	-5.35
3-NH <sub>2</sub>	336.5	1.18	-1.7	1	2	0.26	0.6	0.52	0.165	0.367	0.746	0.526	0.074	-6.08
3-CN	326.5	0	0	0	0	0	0	0.38	0.084	0.190	-0.291	0.249	0.037	-3.5
3-COOH	447	2.87	-1.07	1	1	0.61	2	0.80	0.237	0.433	-0.375	0.500	0.064	-6.39
3-COOMe	312	0	0	0	0	0	0	0.30	0.081	0.187	-0.291	0.254	0.037	-3
3-NO <sub>2</sub>	387	0	0	0	0	0	0	0.40	0.089	0.198	-0.949	0.241	0.037	-3.56
4-F	272.2	0	0	0	0	0	0	0.28	0.081	0.185	0.287	0.255	0.037	-2.4
4-Cl	345.5	0	0	0	0	0	0	0.30	0.086	0.188	0.293	0.254	0.037	-2.4
4-Br	339.4	0	0	0	0	0	0	0.31	0.068	0.188	0.293	0.252	0.037	-2.24
4-I	340.5	0	0	0	0	0	0	0.31	—	0.192	0.221	0.252	0.037	-2.4
4-Me	316.7	0	0	0	0	0	0	0.23	0.079	0.181	0.620	0.263	0.037	-2
4-Et	268.1	0	0	0	0	0	0	0.23	0.079	0.181	0.622	0.263	0.037	-2
4-iPr	210	0	0	0	0	0	0	0.23	0.079	0.181	0.632	0.263	0.037	-2
4-tBu	290	0	0	0	0	0	0	0.23	0.078	0.181	0.651	0.263	0.037	-2.4
4-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	307.5	0	0	0	0	0	0	0.34	0.080	0.182	0.480	0.262	0.037	-2.4
4-OMe	330.2	0	0	0	0	0	0	0.23	0.081	0.176	0.518	0.263	0.038	-2.2
4-OEt	275.4	0	0	0	0	0	0	0.23	0.081	0.176	0.541	0.264	0.038	-2.2
4-OH	457	2.6	-0.89	1	1	0.61	2.1	0.86	0.213	0.391	0.439	0.521	0.064	-5.19
4-NH <sub>2</sub>	419	1.18	-1.7	1	2	0.26	0.6	0.52	0.160	0.347	0.643	0.534	0.075	-4.8
4-NHMe	309	0.61	-1.53	1	1	0.13	0.6	0.43	0.161	0.355	0.671	0.536	0.075	-3.6
4-CN	359	0	0	0	0	0	0	0.40	0.081	0.199	-0.194	0.246	0.037	-2.4
4-COOH	461.5	2.87	-1.07	1	1	0.61	2	0.80	0.239	0.447	-0.252	0.498	0.063	-5.29
4-NO <sub>2</sub>	421.5	0	0	0	0	0	0	0.42	0.089	0.216	-0.789	0.235	0.036	-3.64

**Table 2.** Correlation of Melting Points of 33 Anilines with Various Hydrogen Bonding Parameters

parameter	$r^2$	$s$
Seiler $I_H^1$	0.525	47.9
Moriguchi $E_W^3$	0.297	58.3
Fujita et al. <sup>5</sup>	0.412	53.3
Charton and Charton <sup>8</sup>	0.309	57.8
Yang et al. $HB_2^9$	0.509	48.7
Abraham et al. $K_a^{16}$	0.495	49.4
Kamlet whole-molecule $\alpha^a$	0.666	40.2
$Q_H$ (CNDO) <sup>22 b</sup>	0.519	49.7
$Q_H$ (AM1)	0.513	48.5
$E_{LUMO}$ (AM1)	0.282	58.9
$Q_H$ (AM1) & $E_{LUMO}$ (AM1)	0.739	36.1
$D_E$ & $P_E$	0.372	56.0
Raevsky $C_{HD}^c$	0.606	43.6

<sup>a</sup> Values kindly supplied by Dr. M. H. Abraham. <sup>b</sup> For 31 compounds, as CNDO not parametrized for iodine. <sup>c</sup> Values kindly supplied by Prof. O. A. Raevsky.

hydrogen bond-donating substituents were added to the amino hydrogen charge to give the total  $Q_H$ .

The CNDO and AM1 Hamiltonians give  $Q_H$  values that correlate with melting points to almost exactly the same extent. Ghafourian<sup>22</sup> has also found that the MNDO Hamiltonian gives  $Q_H$  values that model hydrogen bond donor ability very well but that the PM3 Hamiltonian gives rather poorer results. Thus the choice of Hamiltonian should be between CNDO, MNDO, and AM1.

It is disappointing that  $D_E$  and  $P_E$  together correlate so poorly. They correlate quite well with the Kamlet  $\alpha$  values ( $r^2 = 0.801$ ) and would have been expected to model melting

points better than they do. Further work is necessary to evaluate the usefulness of these parameters.

Raevsky's  $C_{HD}$  parameter gives a reasonably satisfactory correlation (some 82% of that of the best correlation). Further work is clearly necessary to check the validity of Raevsky's parameters, but given that they are readily obtained from a commercially available software package, they should prove valuable.

Although neither  $Q_H$ (AM1) nor (especially)  $E_{LUMO}$ (AM1) correlates well with melting point, it is pleasing that the combination of  $Q_H$  and  $E_{LUMO}$  does so very well. Indeed, the combination out-performs even Kamlet's  $\alpha$  values, long regarded as the standard in hydrogen bond parameters for QSAR. It should be noted that  $Q_H$ (AM1) and  $E_{LUMO}$ (AM1) are not themselves correlated ( $r^2 = 0.001$ ). When the nine anilines capable of intramolecular hydrogen bonding (2-F, 2-Cl, 2-Br, 2-I, 2-OMe, 2-NO<sub>2</sub>, 2-OH, 2-NH<sub>2</sub>, 2-COOH) were included, the correlation of melting point with  $Q_H$  and  $E_{LUMO}$  fell to  $r^2 = 0.522$ ,  $s = 48.2$ . However, the only 2-derivatives to have their melting points poorly predicted by  $Q_H$  and  $E_{LUMO}$  were 2-OH, 2-NH<sub>2</sub>, and 2-COOH, which suggests that intramolecular hydrogen bonding is weak, if present at all, in the others. Omitting the 2-OH, 2-NH<sub>2</sub>, and 2-COOH derivatives yielded a correlation comparable to that obtained with only 33 compounds ( $n = 39$ ,  $r^2 = 0.714$ ,  $s = 35.6$ ). It can thus be concluded that  $Q_H$ (AM1) and  $E_{LUMO}$ (AM1) can satisfactorily model intermolecular hydrogen bonding, in this series of compounds at least, save in those compounds in which the substituent is capable of donating an intramolecular hydrogen bond.



Hydrogen bonding is predominantly an electrostatic interaction, and we reasoned, as did also Wilson and Famini,<sup>17</sup> that atomic charge should be a valid measure of hydrogen bonding ability; the charge ( $Q_H$ ) on a hydrogen atom connected to an electronegative atom should indicate hydrogen bond donor ability, and the charge ( $Q_{MN}$ ) on an electronegative atom should indicate hydrogen bond acceptor ability. However, hydrogen bonding also has a covalent or charge-transfer component, which can be modeled by  $E_{LUMO}$  (for hydrogen bond donor ability) and  $E_{HOMO}$  (for hydrogen bond acceptor ability). Thus a combination of  $Q_H$  and  $E_{LUMO}$ , and  $Q_{MN}$  and  $E_{HOMO}$ , should model hydrogen bond donor and acceptor ability, respectively. We have therefore examined a number of published QSARs containing hydrogen bonding parameters to see how well atomic charge and orbital energy, and also MEP, performed in place of the published hydrogen bonding parameter(s).

Abraham et al.<sup>24</sup> developed a QSAR for upper respiratory tract irritation in mice by nonreactive chemicals

$$\log 1/C = -0.69 + 0.77\delta_2 + 2.81\pi^*_2 + 2.82V_X + 4.93\alpha^H_2 \quad (4)$$

$$n = 39 \quad r^2 = 0.970 \quad s = 0.14$$

where  $\delta_2$  = a polarizability term,  $\pi^*_2$  = a polarity term, and  $V_X$  = McGowan's characteristic molecular volume.

The correlation coefficient without the  $\alpha^H_2$  term included was  $r^2 = 0.850$ . We used both  $Q_H$  (MNDO) and MEP<sup>+</sup> (Gasteiger) to replace  $\alpha^H_2$  in this equation

$$\log 1/C = -0.70 + 0.91\delta_2 + 2.47\pi^*_2 + 2.74V_X + 13.1Q_H \quad (5)$$

$$n = 39 \quad r^2 = 0.968 \quad s = 0.14$$

$$\log 1/C = -0.59 + 1.23\delta_2 + 0.44\pi^*_2 + 2.74V_X + 0.0874MEP^+ \quad (6)$$

$$n = 39 \quad r^2 = 0.962 \quad s = 0.15$$

Kamlet et al.<sup>25</sup> correlated the Microtox toxicity of a range of chemicals with their solvatochromic parameters

$$\log EC_{50} = 7.61 - 4.11V/100 - 1.54\pi^* - 1.51\alpha_m + 3.94\beta \quad (7)$$

$$n = 38 \quad r^2 = 0.974 \quad s = 0.28$$

where  $V$  = solute molar volume.

The correlation without the  $\alpha_m$  and  $\beta$  terms included was  $r^2 = 0.767$ . We replaced their hydrogen bonding terms with CNDO-calculated parameters to obtain a comparable correlation

$$\log EC_{50} = 7.17 - 4.25V/100 - 1.16\pi^* - 8.87Q_H - 4.85Q_{MN} + 0.234E_{LUMO} \quad (8)$$

$$n = 38 \quad r^2 = 0.958 \quad s = 0.36$$

The  $E_{HOMO}$  term was not significant in this equation.

In the QSAR for inhibition of protozoan growth by pyridines<sup>7</sup> mentioned earlier (eq 1), MR and the indicator

variable HA were used as parameters. We found that simply replacing HA by  $Q_{MN}$ , without the need to include  $E_{HOMO}$ , gave a significant improvement

$$\log BR = 0.0055MR - 1.71Q_{MN} + 2.030 \quad (9)$$

$$n = 20 \quad r^2 = 0.753 \quad s = 0.34$$

The above examples show that calculated atomic charges and molecular orbital energies can model hydrogen bonding well and can successfully be used in QSAR correlations. It should be noted that these properties are conformation-dependent, and therefore it is essential that adequate energy minimization of molecular structures is carried out before such calculations are attempted.

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## REFERENCES AND NOTES

- (1) Seiler, P. Interconversion of Lipophilicities from Hydrocarbon/Water into the Octanol/Water System. *Eur. J. Med. Chem.* **1974**, *9*, 473–479.
- (2) Young, R. C.; Mitchell, R. C.; Brown, T. H.; Ganellin, C. R.; Griffiths, R.; Jones, M.; Rana, K. K.; Saunders, D.; Smith, I. R.; Sore, N. E.; Wilks, T. J. Development of a New Physicochemical Model for Brain Penetration and its Application to the Design of Centrally Acting H<sub>2</sub> Receptor Histamine Antagonists. *J. Med. Chem.* **1988**, *31*, 656–671.
- (3) Moriguchi, I. Quantitative Structure-Activity Studies I. Parameters Relating to Hydrophobicity. *Chem. Pharm. Bull.* **1975**, *23*, 247–257.
- (4) Leahy, D. E. Intrinsic Molecular Volume as a Measure of the Cavity Term in Linear Solvation Energy Relationships: Octanol-Water Partition Coefficients and Aqueous Solubilities. *J. Pharm. Sci.* **1986**, *75*, 629–636.
- (5) Fujita, T.; Nishioka, T.; Nakajima, M. Hydrogen-Bonding Parameter and its Significance in Quantitative Structure-Activity Studies. *J. Med. Chem.* **1977**, *20*, 1071–1081.
- (6) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley & Sons: New York, 1979.
- (7) Schultz, T. W.; Moulton, B. A. Structure-Activity Relationships of Selected Pyridines. I. Substituent Constant Analysis. *Ecotoxicol. Environ. Saf.* **1985**, *10*, 97–111.
- (8) Charton, M.; Charton, B. I. The Structural Dependence of Amino Acid Hydrophobicity Parameters. *J. Theoret. Biol.* **1982**, *99*, 629–644.
- (9) Yang, G.; Lien, E. J.; Guo, Z. Physical Factors Contributing to Hydrophobic Constant  $\pi$ . *Quant. Struct.-Act. Relat.* **1986**, *5*, 12–18.
- (10) Nagy, P. I.; Dunn, W. J.; Alagona, J.; Ghio, C. Theoretical Studies of the 2- and 4-Hydroxybenzoic Acids with Competing Hydrogen Bonds in the Gas Phase and in Aqueous Solution. *J. Phys. Chem.* **1993**, *97*, 4628–4642.
- (11) Gerothanassis, I. P.; Vakka, C. <sup>17</sup>O NMR Chemical Shifts as a Tool to Study Specific Hydration Sites of Amides and Peptides: Correlation with the IR Amide I Stretching Vibration. *J. Org. Chem.* **1994**, *59*, 2341–2348.
- (12) Kamlet, M. J.; Doherty, R. M.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. Linear Solvation Energy Relationships: 36. Molecular Properties Governing Solubilities of Organic Nonelectrolytes in Water. *J. Pharm. Sci.* **1986**, *75*, 338–349.
- (13) Kamlet, M. J.; Doherty, R. M.; Abraham, M. H.; Veith, G. D.; Abraham, D. J.; Taft, R. W. Solubility Properties in Polymers and Biological Media. 8. An Analysis of the Factors that Influence Toxicities of Organic Nonelectrolytes to the Golden Orfe Fish (*Leuciscus idus melanotus*). *Environ. Sci. Technol.* **1987**, *21*, 149–155.
- (14) Schüürmann, G. Quantitative Structure-Property Relationships for the Polarizability, Solvatochromic Parameters and Lipophilicity. *Quant. Struct.-Act. Relat.* **1990**, *9*, 326–333.
- (15) Hickey, J. P.; Passino-Reader, D. R. Linear Solvation Energy Relationships: "Rule of Thumb" for Estimation of Variable Values. *Environ. Sci. Technol.* **1991**, *25*, 1753–1760.
- (16) Abraham, M. H.; Duce, P. P.; Prior, D. V.; Barratt, D. G.; Morris, J. J.; Taylor, P. J. Hydrogen Bonding. Part 9. Solute Proton Donor and

- Proton Acceptor Scales for Use in Drug Design. *J. Chem. Soc., Perkin Trans. II* **1989**, 1355–1375.
- (17) Wilson, L. Y.; Famini, G. R. Using Theoretical Descriptors in Quantitative Structure-Activity Relationships: Some Toxicological Indices. *J. Med. Chem.* **1991**, *34*, 1668–1674.
- (18) Dearden, J. C.; Ghafourian, T. Investigation of Calculated Hydrogen Bonding Parameters for QSAR. In *QSAR and Molecular Modelling: Concepts, Computational Tools and Biological Applications*; Sanz, F., Giraldo, J., Manaut, F., Eds.; Prous Science Publishers: Barcelona, 1995; pp 117–119.
- (19) Dearden, J. C.; Cronin, M. T. D.; Wee, D. Prediction of Hydrogen Bond Donor Ability Using New Quantum Chemical Parameters. *J. Pharm. Pharmacol.* **1997**, *49*, Suppl. 4, 110.
- (20) Raevsky, O. A.; Grigor'ev, V.; Mednikova, E. QSAR H-Bonding Descriptions. In *Trends in QSAR and Molecular Modelling* 92; Wermuth, C. G., Ed.; ESCOM: Leiden, 1993; pp 116–119.
- (21) Murray, J. S.; Politzer, P. Correlations between the Solvent Hydrogen-Bond-Donating Parameter  $\alpha$  and the Calculated Molecular Surface Electrostatic Potential. *J. Org. Chem.* **1991**, *56*, 6715–6717.
- (22) Ghafourian, T. Investigation of Calculated Hydrogen Bonding Parameters. Ph.D. Thesis, Liverpool John Moores University: Liverpool, U.K., 1996.
- (23) Dearden, J. C. The QSAR Prediction of Melting Point, a Property of Environmental Relevance. *Sci. Total Environ.* **1991**, *109/110*, 59–68.
- (24) Abraham, M. H.; Whiting, G. S.; Alarie, Y.; Morris, J. J.; Taylor, P. J.; Doherty, R. M.; Taft, R. W.; Nielsen, G. D. Hydrogen Bonding. 12. A New QSAR for Upper Respiratory Tract Irritation by Airborne Chemicals in Mice. *Quant. Struct.-Act. Relat.* **1990**, *9*, 6–10.
- (25) Kamlet, M. J.; Doherty, R. M.; Veith, G. D.; Taft, R. W.; Abraham, M. H. Solubility Properties in Polymers and Biological Media. 7. An Analysis of Toxicant Properties that Influence Inhibition of Bioluminescence in *Photobacterium phosphoreum* (the Microtox Test). *Environ. Sci. Technol.* **1986**, *20*, 690–695.

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