J. Org. Chem. **2001,** *66,* 6919−6925

Comparison of Quantum Chemical Parameters and Hammett Constants in Correlating pK_a Values of Substituted Anilines

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Received March 5, 2001

Historically, Hammett constants have been extremely effective in describing the influence of substituents on chemical reactivity and other physical and chemical properties, whereas variables derived from quantum chemical calculations have generally been less effective. Taking the experimental pK_as of substituted anilines as a representative physicochemical property, five ab initio quantum chemical indices are compared for effectiveness as one-parameter regression descriptors for pK_a. All of the tested descriptors performed well for a set of 19 mono-, 13 di-, and 4 trisubstituted anilines, and two performed somewhat better than the traditional Hammett σ constants. Among the calculated quantities, the best representation of the aniline pK_as is produced by the minimum average local ionization energy on the molecular surface.

Introduction

Since their introduction in the 1930s,[1,2] Hammett constants (σ) have been the workhorse of organic chemists in relating the nature of substituents to their effects on chemical reactivity and other properties. These constants remain today an excellent guide in structure−property and structure−activity studies. In a recent review Hansch et al. observed: “Hammett constants have been astonishingly successful in correlating almost every kind of organic reaction in all sorts of solvents. Eventually one assumes that quantum chemical calculations will replace them, but this is not possible at present.” [3]

Indeed, σ constants have found use in predicting many types of chemical phenomena, including pK_as, reaction rates, and proton NMR shifts;[4−7] any reaction series exhibiting a linear free-energy relationship can be expected to correlate with σ constants.[2,6,8,9] However, despite their unusual success and far-reaching applicability, Hammett constants are empirical parameters and cannot be expected to work in all situations. For example, σ constants will fail to correlate reaction rates in situations where the substituent change results in a shift of the transition state position.[9] In cases such as this, a quantum chemical approach may be more desirable.[5,10,11] Our earlier work with substituted anilines demonstrated that certain quantum chemical parameters, namely the natural charge on the amino nitrogen atom Q_n,[12] the minimum electrostatic potential V_{min},[13] and the minimum local ionization energy on the molecular surface $\bar{I}_{S,min}$,[13] correlate well with the Hammett σ values. Accordingly, in the context of the comment by Hansch et al., we wished to test whether these and other computed quantities might now be comparable in effectiveness to Hammett constants.

The amino moiety is one of the most fundamental functional groups in organic chemistry, and its pK_a is an important and extensively studied property. (The pK_a refers to the conjugate acid, but it is used as a measure of the amine's basicity as pK_a + pK_b = pK_w, where K_w is the ionization constant of water.) The amino group K_a can vary over several orders of magnitude (ammonia, pK_a = 9.26; aniline, pK_a = 4.63) depending on its molecular environment.

Variations in pK_a are crucial to the action of enzymes[14] and important for RNA activity in protein synthesis.[15] While it is qualitatively understood how changes in the amino group's environment affect its alkaline nature, the ability to predict this property quantitatively in a wide variety of chemical systems is still actively pursued in our[12,13] and other research groups.[14,16−19]

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10.1021/jo010234g CCC: $20.00

Aniline, an important molecule in its own right, provides a good prototype for the study of substituent effects on the amino moiety. For example, substituents on the phenyl ring of aniline influence the amine pK_a depending on their positions and electron-donating or -withdrawing natures. Furthermore, aniline's relatively small size makes feasible accurate quantum mechanical study, which may allow the discovery of quantum chemical descriptors with accuracy comparable to, or better than, the empirical Hammett constants. In previous work, it was found in a series of monosubstituted anilines that Q_n, V_{min}, and $\bar{I}_{S,min}$ strongly correlated with the pK_a of the amine group.[12,13]

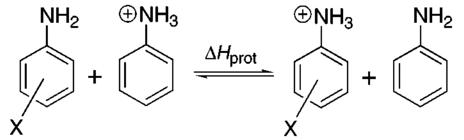
The intention of this work is to ascertain if, at least for the present system, descriptors derived from quantum mechanical calculations have caught up with or surpassed the Hammett parameters in their ability to correlate chemical phenomena. To do so, we extend our analyses described above to include more compounds and consider five different computed quantities, all of which are being used as measures of ability to attract a proton. These shall now be introduced.

Natural Charge

Atomic charge is not physically observable, and its value depends on the scheme by which the electron density of a molecule is partitioned. Accordingly, different charge schemes vary in their usefulness. The natural charge is derived from natural population analysis (NPA), a prescription for transforming a wave function's delocalized molecular orbitals into localized, chemically intuitive orbitals using unitary transformations. This is done in a manner that preserves all information contained in the wave function.[20,21] NPA was proposed in an effort to overcome some of the problems associated with Mulliken's widely used procedure. We have demonstrated elsewhere the usefulness of the amino nitrogen natural charge Q_n as a structure–property parameter in a series of monosubstituted anilines.[12] In that study, Q_n was shown to correlate strongly with variations in several physical and chemical properties of the compounds, including the amino nitrogen–carbon bond length, the out-of-plane angle of the NH_2 group, the NH_2 inversion energy barrier, and the pK_a. It was also pointed out that other methods of population analysis, namely the Mulliken and electrostatic charges, performed quite poorly in this respect ($r^2 < 0.04$ in both cases). The shortcomings of the Mulliken charge, which stem from its equal apportionment of orbital overlap populations to the participating atoms, have been well documented.[21-23] Electrostatic charges are obtained from an iterative procedure in which a set of nuclei-centered point charges are chosen to reproduce the molecular electrostatic potential (MEP).[22,24] Since a small set of point charges cannot be expected to completely reflect the complexity of the MEP, which results from a combination of polarized electronic and electron lone-pair distributions, these charges offer only a crude representation of the electron population surrounding an atom, and their poor performance is not unexpected.

Relative Proton-Transfer Enthalpy

A measure of gas-phase basicity relative to aniline is given by the enthalpy change ΔH for the isodesmic reaction below, in which X represents either a single or several substituents. ΔH for the reaction in eq 1 is known as the relative proton-transfer enthalpy ΔH_{prot}.[25]



(1)

Since the sums of the zero-point energies and thermal corrections can be expected to be very similar for the reactants and products in eq 1, it should be acceptable to approximate ΔH_{prot} by the difference in the molecular energies, ΔE, as was done in this work. Furthermore, the isodesmic nature of the reaction suggests that electron correlation contributions will largely cancel,[26] justifying the use of Hartree–Fock energies.

Minimum Molecular Surface Local Ionization Energy

The ionization energy I of an atomic or molecular system is related to both its electronegativity (or chemical potential) and its polarizability.[27-30] Thus I is relevant to chemical reactivity in general, not just ionic or charge-transfer interactions. Since reactivity is site-specific rather than global, there has been introduced an average local ionization energy, $\bar{I}(\mathbf{r})$, defined within the framework of Hartree–Fock theory by eq 2:[31]

$$\bar{I}(\mathbf{r}) = \sum_i \frac{\rho_i(\mathbf{r})|\epsilon_i|}{\rho(\mathbf{r})} \qquad (2)$$

$\rho_i(\mathbf{r})$ is the electronic density of the ith atomic or molecular orbital at the point $\mathbf{r}$, ϵ_i is the orbital energy, and $\rho(\mathbf{r})$ is the total electronic density function. Since Koopmans' theorem[32] provides some justification for viewing

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the magnitudes of Hartree–Fock orbital energies as approximations to the electronic ionization energies,[33] $\bar{I}(\mathbf{r})$ is interpreted as the average energy needed to remove an electron from the point $\mathbf{r}$ in the space of an atom or molecule; $\bar{I}(\mathbf{r})$ focuses upon the point in space rather than upon a particular molecular orbital. Both $\bar{I}$ and $\bar{I}(\mathbf{r})$ have been shown to be related to the polarizabilities of atoms,[27,29] and it has been suggested that $\bar{I}(\mathbf{r})$ may be a measure of local polarizability in molecules.[29]

In applying $\bar{I}(\mathbf{r})$ to predicting and interpreting chemical behavior, it has been found useful to look at $\bar{I}_S(\mathbf{r})$, the pattern of $\bar{I}(\mathbf{r})$ on the molecular surface, as defined by the 0.001 au contour of $\rho(\mathbf{r})$.[34] The minima of $\bar{I}_S(\mathbf{r})$, denoted $\bar{I}_{S,min}$, indicate the points on the surface at which are found, on the average, the least tightly bound, most reactive electrons.

In studies of monosubstituted benzene derivatives, we have found that the $\bar{I}_{S,min}$ correctly predict the ring-activating or -deactivating effects of substituents as well as their *ortho*/*para*- or *meta*-directing tendencies;[31,35] the $\bar{I}_{S,min}$ also correlate with the Hammett and Taft substituent constants.[31,35–37] In addition, we have been able to relate $\bar{I}_{S,min}$ to pK_a and to proton affinity for several types of compounds.[36–41]

Molecular Electrostatic Potential

The electrostatic potential $V(\mathbf{r})$ that is created in the space around a molecule by its nuclei and electrons is given by eq 3,

$$V(\mathbf{r}) = \sum_{A} \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')\,d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (3)$$

in which Z_A is the charge on nucleus A, located at R_A. The sign of $V(\mathbf{r})$ at any point depends on whether the effects of the nuclei or the electrons are dominant there. The electrostatic potential has long been applied to the interpretation of chemical reactivity;[42–50] for example, sites for electrophilic attack were identified and ranked by the locations and magnitudes of the most negative values (minima) of $V(\mathbf{r})$, while its overall pattern was used in analyzing biological recognition interactions. In recent years, it has been shown that the statistical characterization of the potentials on molecular surfaces can serve as the basis for correlating and predicting condensed phase macroscopic properties that depend on noncovalent interactions.[48,51–55] Both the overall (absolute) and the surface minima, V_{min} and $V_{S,min}$, have been found to correlate with hydrogen bond basicity and, to a lesser extent, with pK_a.[13,37,40,41,51,56–58]

Methods

Geometries for all the compounds were optimized at the Hartree–Fock (HF) level with 6-311G(d,p) basis sets using Spartan[59] and the Gaussian94[60] suite of programs. For molecules with multiple low-energy conformers, an initial grid search was performed at the AM1 level. The resulting conformers were more accurately ranked by single-point HF/6-31G(d) energy calculations, and an HF/6-311G(d,p) optimization was carried out for the most stable conformer. The optimized geometries were used to obtain the natural charges Q_n and relative proton-transfer enthalpies ΔH_{prot} at the HF/6-311G(d,p) level and the other properties ($\bar{I}_{S,min}$, V_{min}, and $V_{S,min}$) at the HF/STO-5G(d) level. It was verified that $\bar{I}_{S,min}$, V_{min}, and $V_{S,min}$ are in all instances associated with the amino group.

Hammett σ constants[61] and pK_a[62,63] values were taken from the literature. For molecules with multiple ionization constants, the pK_a associated with the amino group was chosen. In the case of multiply substituted anilines, additivity of the Hammett parameters was assumed and a total substituent constant σ was determined by summation: $\sigma = \Sigma_i\, \sigma_i$.

Results

Table 1 lists the calculated parameters, Q_n, ΔH_{prot}, $\bar{I}_{S,min}$, V_{min}, and $V_{S,min}$, as well as the Hammett σ and

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Table 1. Calculated and Experimental Parameters for Aniline Derivatives, with Experimental pK_as

substituent	Q_n	ΔH_{prot}[a]	$\Sigma_i\sigma_i$	$\bar{I}_{S,min}$[b]	V_{min}[a]	$V_{S,min}$[a]	pK_a
H (aniline)	−0.8139	0.00	0.00	13.33	−78.0	−40.5	4.58
m-amino	−0.8137	−2.32	−0.16	13.32	−78.0	−40.7	4.88
m-bromo	−0.8114	5.69	0.39	13.71	−70.6	−35.4	3.51
m-chloro	−0.8111	6.09	0.37	13.71	−70.8	−35.6	3.34
m-cyano	−0.8109	11.20	0.56	13.91	−66.7	−32.1	2.76
m-fluoro	−0.8116	6.03	0.34	13.67	−71.5	−36.4	3.59
m-hydroxy	−0.8129	2.08	0.12	13.52	−74.4	−39.2	4.17
m-methoxy	−0.8137	−0.37	0.12	13.41	−76.4	−39.5	4.20
m-methyl	−0.8140	−1.73	−0.07	13.31	−78.5	−41.0	4.69
m-nitro	−0.8108	12.37	0.71	14.01	−64.5	−30.6	2.50
p-amino	−0.8155	−7.55	−0.66	12.96	−85.3	−44.2	6.08
p-bromo	−0.8121	5.34	0.23	13.69	−70.8	−35.3	3.91
p-chloro	−0.8123	5.30	0.23	13.66	−71.5	−35.7	3.98
p-cyano	−0.8088	13.37	0.66	14.26	−59.4	−28.2	1.74
p-fluoro	−0.8140	3.03	0.06	13.35	−77.6	−39.3	4.65
p-hydroxy	−0.8148	−3.23	−0.37	13.08	−83.0	−42.8	5.50
p-methoxy	−0.8152	−4.90	−0.27	13.06	−83.4	−43.3	5.29
p-methyl	−0.8145	−2.78	−0.17	13.22	−80.4	−41.9	5.12
p-nitro	−0.8069	16.13	0.78	14.53	−54.2	−24.9	1.02
3,4-dimethyl	−0.8140	−4.21	−0.24	13.17	−81.0	−42.5	5.17
3-amino-4-hydroxy	−0.8143	−5.21	−0.53	13.27	−79.0	−41.0	5.70
3-bromo-4-methoxy	−0.8123	0.20	0.12	13.33	−73.0	−36.2	4.08
3-bromo-4-methyl	−0.8119	2.75	0.22	13.55	−73.7	−37.3	3.98
3-chloro-4-methyl	−0.8117	3.06	0.20	13.54	−74.0	−37.4	4.05
3-methyl-4-nitro	−0.8061	13.85	0.71	14.49	−55.0	−25.7	1.50
4-chloro-3-nitro	−0.8083	16.19	0.94	14.28	−59.3	−26.8	1.90
4-methyl-3-nitro	−0.8109	9.21	0.54	13.84	−67.8	−32.6	2.96
3,5-dibromo	−0.8085	10.70	0.78	14.03	−64.3	−31.2	2.34
3,5-dimethoxy	−0.8123	−2.49	0.24	13.42	−76.3	−40.2	3.82
3,5-dimethyl	−0.8140	−3.15	−0.14	13.24	−79.6	−41.8	4.91
3-chloro-5-methoxy	−0.8101	4.33	0.49	13.73	−70.5	−36.2	3.10
3-methoxy-5-nitro	−0.8093	10.49	0.83	14.03	−64.4	−31.4	2.11
3,5-dibromo-4-hydroxy	−0.8103	6.45	0.41	13.64	−72.0	−35.1	3.20
3,5-dibromo-4-methoxy	−0.8096	7.59	0.51	13.85	−67.6	−32.5	2.98
3,5-dibromo-4-methyl	−0.8089	7.78	0.61	13.87	−67.7	−33.2	2.87
3,5-dimethyl-4-nitro	−0.8077	10.19	0.64	14.23	−60.3	−28.9	2.59

[a] kcal/mol. [b] eV.

experimental pK_a values for each of the substituted anilines examined. A summary of the regression statistics, broken down into *para*-, *meta*-, and mono- and polysubstituted aniline subsets, can be found in Table 2. Aniline itself was included in each subset. As shown in Figure 1, the fits were good to excellent and contained only a few outliers.

Hammett *σ* Constants

The traditional, empirical Hammett substituent parameter σ performed quite well in predicting pK_a for this set of anilines with

$$\mathrm{p}K_a = -3.03(\pm 0.13) \times \sigma + 4.46(\pm 0.06)$$

$$n = 36,\ r^2 = 0.940,\ s = 0.310,\ F = 530$$

Here, n is the number of compounds, r is the correlation coefficient, s is the standard deviation, and F is the Fisher ratio. There were three apparent outliers in this set, viz. *p*-nitroaniline, 3-methyl-4-nitroaniline, and *p*-cyanoaniline, which showed residuals greater than twice the standard deviation of the fit. Interestingly, a better relationship was obtained for the polysubstituted anilines than for the monosubstituted ones ($r^2 = 0.955$ vs $r^2 = 0.931$); among the latter, it was better for the *meta* than the *para* compounds ($r^2 = 0.989$ vs $r^2 = 0.938$).

These good results suggest that Hammett constant additivity is usually justifiable for these systems, sometimes even unexpectedly so. For example, the optimized geometry of 3-bromo-4-methoxyaniline shows the methoxy group to be rotated by about 78° compared to *p*-methoxyaniline, and this would be anticipated to affect its typically strong electron-donating character ($\sigma_p = -0.27$). Despite this steric interaction, however, σ predicts the pK_a of 3-bromo-4-methoxyaniline to within 0.02 pK_a units, well within the standard deviation of 0.31 pK_a units.

Natural Charge Q_n

For the 36 compounds studied, the amino nitrogen natural charge Q_n served as a good indicator of the aniline pK_a's:

$$\mathrm{p}K_a = -490(\pm 26) \times Q_n - 394(\pm 21)$$

$$n = 36,\ r^2 = 0.915,\ s = 0.368,\ F = 365$$

Only 3,5-dimethyl-4-nitroaniline and *m*-nitroaniline were outliers in this series. If just the monosubstituted anilines were considered, the relationship improved to $r^2 = 0.964$, but it was substantially better for the *para* derivatives than for the *meta* compounds ($r^2 = 0.984$ vs $r^2 = 0.896$).

Since the basicity of the amino nitrogen is commonly considered to be associated with its lone-pair electrons, we also investigated the correlation of the nitrogen lone-pair orbital occupancy (as given by natural population analysis) with the pK_a. Surprisingly, this correlation was relatively poor: $r^2 = 0.737$, $s = 0.646$, and $F = 95$.

Table 2. Regression Statistics (outliers inclusive) for pK_a versus Each of σ, Q_n, ΔH_{prot}, $\bar{I}_{S,min}$, V_{min}, and $V_{S,min}$

	slope	intercept	n	r^2	s	F
σ						
monosubstituted	−3.24 (0.21)	4.46 (0.09)	19	0.931	0.339	231
para-substituted	−3.53 (0.32)	4.36 (0.14)	10	0.938	0.404	122
meta-substituted	−2.78 (0.11)	4.51 (0.04)	10	0.989	0.085	733
polysubstituted	−2.88 (0.16)	4.45 (0.08)	18	0.955	0.251	337
all anilines	−3.03 (0.13)	4.46 (0.06)	36	0.940	0.310	530
Q_n						
monosubstituted	−571 (27)	−460 (22)	19	0.964	0.244	461
para-substituted	−565 (25)	−455 (21)	10	0.984	0.206	493
meta-substituted	−565 (68)	−455 (55)	10	0.896	0.262	69
polysubstituted	−464 (36)	−373 (30)	18	0.911	0.352	163
all anilines	−490 (26)	−394 (21)	36	0.915	0.368	365
ΔH_{prot}[a]						
monosubstituted	−0.190 (0.011)	4.61 (0.08)	19	0.946	0.301	297
para-substituted	−0.205 (0.015)	4.69 (0.12)	10	0.958	0.333	184
meta-substituted	−0.154 (0.009)	4.42 (0.06)	10	0.974	0.130	305
polysubstituted	−0.176 (0.014)	4.26 (0.11)	18	0.913	0.348	167
all anilines	−0.186 (0.009)	4.47 (0.07)	36	0.921	0.354	398
$\bar{I}_{S,min}$[b]						
monosubstituted	−3.13 (0.10)	46.4 (1.3)	19	0.984	0.164	1038
para-substituted	−3.08 (0.12)	45.8 (1.7)	10	0.988	0.182	633
meta-substituted	−3.21 (0.16)	47.5 (2.1)	10	0.981	0.111	420
polysubstituted	−2.94 (0.24)	43.8 (3.3)	18	0.903	0.367	148
all anilines	−3.02 (0.13)	44.9 (1.7)	36	0.949	0.285	633
V_{min}[a]						
monosubstituted	−0.157 (0.005)	−7.58 (0.38)	19	0.982	0.179	922
para-substituted	−0.155 (0.006)	−7.31 (0.47)	10	0.987	0.197	611
meta-substituted	−0.163 (0.009)	−8.10 (0.64)	10	0.978	0.130	347
polysubstituted	−0.149 (0.013)	−7.00 (0.90)	18	0.895	0.394	136
all anilines	−0.154 (0.006)	−7.38 (0.46)	36	0.945	0.301	580
$V_{S,min}$[a]						
monosubstituted	−0.241 (0.010)	−4.98 (0.39)	19	0.969	0.235	531
para-substituted	−0.245 (0.012)	−5.02 (0.46)	10	0.981	0.238	413
meta-substituted	−0.218 (0.012)	−4.25 (0.46)	10	0.975	0.138	306
polysubstituted	−0.217 (0.012)	−4.15 (0.70)	18	0.882	0.417	120
all anilines	−0.231 (0.011)	−4.63 (0.39)	36	0.931	0.336	458

[a] kcal/mol. [b] eV. Here, *n* is the number of compounds, *r* is the correlation coefficient, *s* is the standard deviation, and *F* is the Fisher ratio. Values in parentheses indicate the standard error. Note that aniline is a member of each subset.

Relative Proton-Transfer Enthalpy ΔH_{prot}

ΔH_{prot} was somewhat more effective than Q_n in relating changes in the pK_a:

$$pK_a = -0.186(\pm 0.009) \times \Delta H_{prot} + 4.47(\pm 0.07)$$

$$n = 36,\ r^2 = 0.921,\ s = 0.354,\ F = 398$$

3,5-Dimethoxyaniline and *p*-fluoroaniline were outliers. The results were again better when limited to the monosubstituted anilines ($r^2 = 0.946$), but now they were superior for the *meta* subset ($r^2 = 0.974$ vs $r^2 = 0.958$).

Solvent effects, which are not taken into account in calculating ΔH_{prot}, can cause complications. For instance, ΔH_{prot} indicates that *p*-methoxyaniline is a stronger base than *p*-hydroxyaniline in the gas phase, but experimental pK_a values show that the reverse holds in solution. Preliminary study suggests that for *p*-hydroxyaniline, a hydrogen bond between the hydroxyl hydrogen and a water molecule enhances the substituent's electron-donating character.[59] Such hydrogen bonding does not occur for *p*-methoxyaniline.

Minimum Molecular Surface Local Ionization Energies $\bar{I}_{S,min}$

For these 36 compounds, the minimum ionization energy $\bar{I}_{S,min}$ correlated very strongly with the experimental pK_a:

$$pK_a = -3.02(\pm 0.13) \times \bar{I}_{S,min} + 44.9(\pm 1.7)$$

$$n = 36,\ r^2 = 0.949,\ s = 0.285,\ F = 633$$

In this fit, 3-amino-4-hydroxyaniline and 3,5-dimethyl-4-nitroaniline are outliers. This parameter, $\bar{I}_{S,min}$, outperformed all others in this study for the entire database. For the monosubstituted anilines alone, the regression improves considerably, to $r^2 = 0.983$ and $F = 1010$.

Molecular Electrostatic Potential Minima V_{min} and $V_{S,min}$

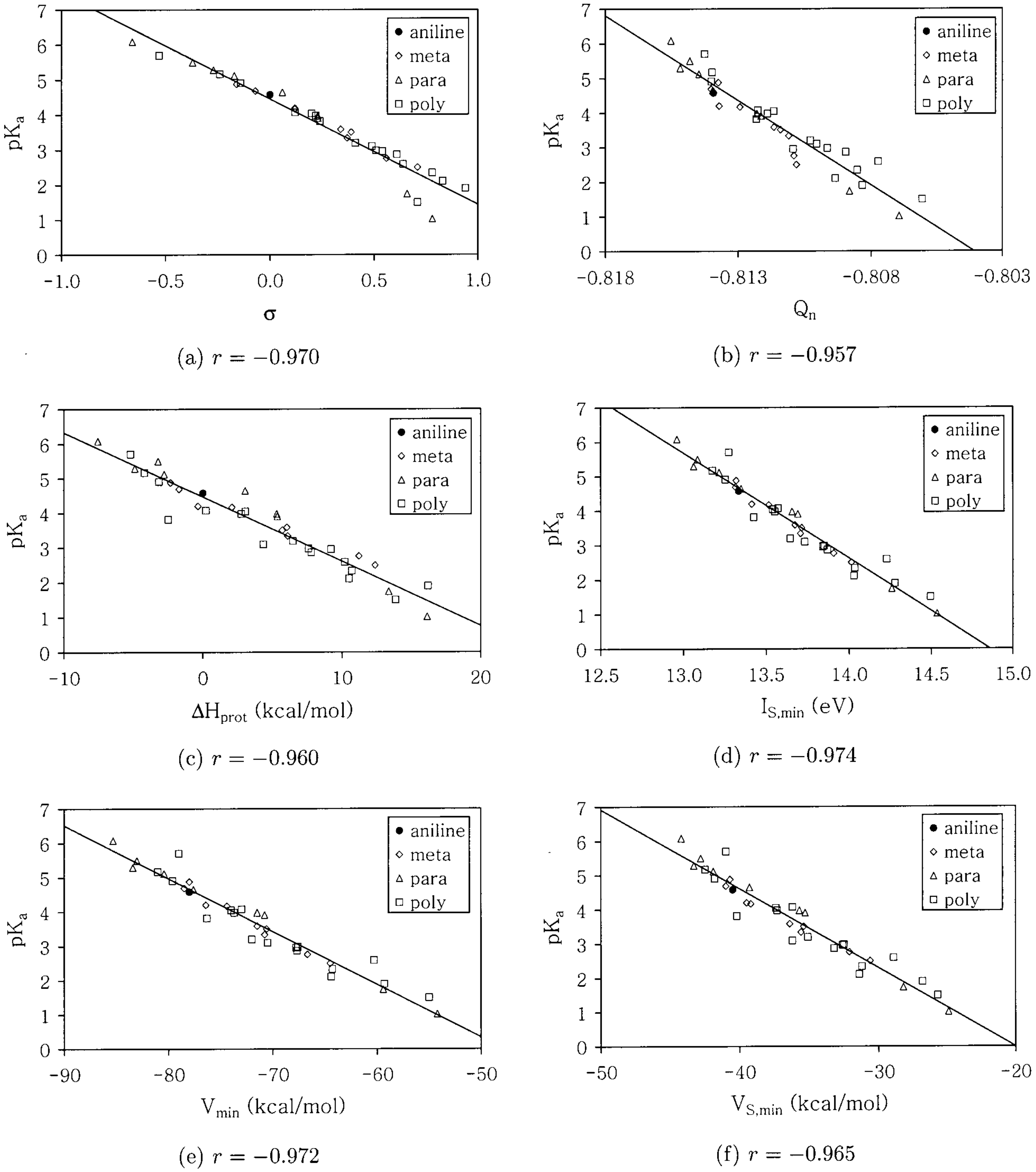
The overall minimum of the molecular electrostatic potential, V_{min}, is second only to $\bar{I}_{S,min}$ as an indicator of pK_a for these compounds:

$$pK_a = -0.154(\pm 0.006) \times V_{min} - 7.37(\pm 0.46)$$

$$n = 36,\ r^2 = 0.945,\ s = 0.300,\ F = 585$$

The outliers are 3-amino-4-hydroxyaniline, 3,5-dimethoxyaniline, and 3,5-dibromo-4-hydroxyaniline. The surface minimum, $V_{S,min}$, is somewhat less effective:

$$pK_a = -0.232(\pm 0.011) \times V_{S,min} - 4.65(\pm 0.39)$$



(a) $r = -0.970$ (b) $r = -0.957$

(c) $r = -0.960$ (d) $r = -0.974$

(e) $r = -0.972$ (f) $r = -0.965$

Figure 1. Plots of pK_a versus each of (a) σ, (b) Q_n, (c) ΔH_{prot}, (d) $\bar{I}_{S,\min}$, (e) $V_{\min}$ and (f) $V_{S,\min}$ below which is their (unsquared) correlation coefficient.

$$n = 36,\ r^2 = 0.932,\ s = 0.334,\ F = 466$$

3-Amino-4-hydroxyaniline and 3,5-dimethoxyaniline are again outliers, as is 3-chloro-5-methoxyaniline. For both $V_{\min}$ and $V_{S,\min}$, a better relationship is obtained for the monosubstituted anilines than for the polysubstituted compounds (Table 2).

Conclusions

As expected, the Hammett σ parameters perform well in their ability to estimate pK_a values for monosubstituted anilines. Surprisingly, they perform even better in predicting pK_a values for multiply substituted anilines than for the singly substituted compounds. This is surprising since steric and electronic interactions between the substituents might be expected to reduce the effectiveness of the inflexible σ constants in modeling the molecular changes. The five calculated quantities Q_n, ΔH_{prot}, $\bar{I}_{S,\min}$, $V_{\min}$, and $V_{S,\min}$ are generally comparable to σ in their ability to estimate pK_a, although not as good when aniline is multiply substituted; of the five, $\bar{I}_{S,\min}$ is somewhat superior to the others.

Earlier, we argued that pK_a should be expressed in terms of both $\bar{I}_{S,\min}$ and $V_{\min}$ or $V_{S,\min}$;[27,38] the minimum local ionization energy and the minimum electrostatic potential were considered to complement each other, V_{min} or $V_{\mathrm{S,min}}$ being related to the initial attraction that brings the proton into the vicinity of the amino group, and $\bar{I}_{\mathrm{S,min}}$ to the subsequent charge sharing or charge transfer. We continue to believe that this view is valid. In the present study, however, such a double-parameter treatment is not necessary; for these aniline derivatives, $\bar{I}_{\mathrm{S,min}}$ itself correlates very well with both V_{min} and $V_{\mathrm{S,min}}$ ($r^2 > 0.98$), so that inclusion of either of the latter would be superfluous (as we verified). It should be stressed, however, that a close linear relationship between $\bar{I}_{\mathrm{S,min}}$ and V_{min} or $V_{\mathrm{S,min}}$ is not typical; see, for example, Brinck et al.[38]

We conclude that parameters derived from quantum chemical calculations have reached a stage at which they can make useful contributions to the analysis of pK_a and other properties. Further support for this view is found in a study of monosubstituted phenols, where we demonstrate that the natural charge, highest-occupied molecular-orbital energy, and proton-transfer energy outperform σ as pK_a regression variables.[64] (It is assumed that $\bar{I}_{\mathrm{S,min}}$, V_{min}, and $V_{\mathrm{S,min}}$ will also strongly correlate with the phenol pK_as, although this study has not been completed.) We would argue that the quantum chemical parameters described here and elsewhere[64] provide a more flexible approach and offer a more fundamental understanding of the factors underlying the observed property variations than do empirical methodologies, such as the use of Hammett constants.

Supporting Information Available: Cartesian coordinates and energies for the molecules studied are available free of charge via the Internet at http://pubs.acs.org.

JO010234G

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