
Substituent Effects on the Electronic Structure and pK_a of Benzoic Acid

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ABSTRACT: The effects of substituents on the pK_a s of a set of 16 substituted benzoic acids have been examined using density functional theory [B3LYP/6-311G(*d, p*)] calculations. A variety of quantum chemical parameters were examined as indicators for the variations observed in the experimental pK_a s, including the Löwdin, Mulliken, AIM, and natural population analysis charges (Q_L , Q_M , Q_A , and Q_n) on atoms of the dissociating carboxylic acid group, the energy difference (ΔE_{prot}) between the carboxylic acid and its conjugate base, and the Wiberg bond index. Several of these calculated quantities yielded excellent correlations with the experimental pK_a : ΔH_{prot} , $r^2 = 0.958$; $Q_L(\text{H})$, $r^2 = 0.963$; $Q_n(\text{CO}_2\text{H})$, $r^2 = 0.969$; $Q_L(\text{CO}_2^-)$, $r^2 = 0.970$; and $Q_L(\text{CO}_2\text{H})$, $r^2 = 0.978$. The best correlation observed with the pK_a , as expected, was from the empirical Hammett constants designed for this purpose ($r^2 = 0.999$). © 2002 Wiley Periodicals, Inc. *Int J Quantum Chem* 90: 1396–1403, 2002

Key words: substituent effects; benzoic acids; acid dissociation constants (pK_a s); Hammett constants

Introduction

Substituent effects play a fundamental role in a variety of observed physical and chemical phenomena. For example, substituent effects influence the rates of nucleophilic substitutions and elimination reactions [1] and contribute to differences in thermal properties [2], nuclear magnetic resonance chemical shifts [3], positions of UV ab-

sorption bands [4], and the conformations of molecules. The nature and location of substituents also affect values of the acid-dissociation constants (pK_a s) [1]. Because the impact of substituents has implications in many areas of chemistry, it has long been a goal of chemists to understand how these substituents act at a molecular electronic level.

Since they were introduced in the 1930s, Hammett constants (σ) [5] have been the primary means for quantifying substituent effects. These empirical constants, which were derived from linear free-energy relationships, have been remarkably successful in their applications to a number of physi-

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cochemical phenomena. Although σ constants provide a valuable practical and heuristic tool, they cannot be expected to work in every case and sometimes yield little mechanistic insight. Recent efforts involving anilines [6–8] and phenols [8, 9] indicate that certain quantum chemical parameters might also serve as useful descriptors for understanding the physical and chemical effects of substituents.

Benzoic acid and its derivatives are chemically and biologically important molecules. Further, the σ constants were originally formulated from ratios of the acid-dissociation constants of substituted benzoic acids relative to the acid-dissociation constant of benzoic acid itself [5]. The present work examines the applicability of quantum chemical parameters as descriptors for substituent effects on the pK_a s of substituted benzoic acids.

Methods

To determine the lowest-energy conformations for each molecule, geometry optimizations were performed at the AM1 level for several starting geometries in which one or more torsional angles were systematically varied. When multiple low-energy geometries were found for a compound, HF/6-31G(*d*) single-point energy calculations were performed to determine the most stable conformer. The final geometry optimization for each of the compounds was conducted at the B3LYP/6-311G(*d, p*) level. Vibrational frequency analyses were performed at the B3LYP/6-311G(*d, p*) level to ensure that minimum energy geometries had been found. The wave functions for these equilibrium geometries were used to determine Mulliken, natural, AIM, and Löwdin charges, the Wiberg bond index, and ΔE_{prot} , the energy difference between the acid and its conjugate base relative to the energy difference between benzoate and benzoic acid.

The initial conformational analyses were performed with Spartan (v. 5.01) [10] software. Gaussian98 [11] was employed for the determination of the final equilibrium geometries and the calculation of nearly all of the quantum chemical descriptors. The AIMALL [12] suite of programs was used to calculate AIM charges from wave functions produced by Gaussian98. Löwdin charges were calculated with GAMESS-US [13]. It was necessary to exclude brominated compounds from the Löwdin study because the GAMESS-US 6-311G(*d, p*) basis set does not include bromine.

TABLE I
Hammett σ constants and experimental pK_a values for substituted benzoic acids.

Substituent	σ	pK_a
H (benzoic acid)	0	4.19
<i>m</i> -bromo	0.39	3.81
<i>m</i> -chloro	0.37	3.83
<i>m</i> -cyano	0.56	3.60
<i>m</i> -fluoro	0.34	3.87
<i>m</i> -hydroxy	0.12	4.08
<i>m</i> -methoxy	0.12	4.09
<i>m</i> -methyl	−0.07	4.27
<i>m</i> -nitro	0.71	3.49
<i>p</i> -bromo	0.23	3.97
<i>p</i> -chloro	0.23	3.98
<i>p</i> -cyano	0.66	3.55
<i>p</i> -fluoro	0.06	4.14
<i>p</i> -hydroxy	−0.37	3.57
<i>p</i> -methoxy	−0.27	3.47
<i>p</i> -methyl	−0.17	4.37
<i>p</i> -nitro	0.78	3.43

Hammett constants were taken from the compilation by Hansch et al. [14]. The values for experimental pK_a s were taken from Albert and Serjeant [15]. This compilation did not include pK_a values for *m*-amino and *p*-aminobenzoic acids, although experimental values for these compounds are reported elsewhere [16]. Because the latter pK_a values were from a separate source, the amino-substituted compounds were not included in the regression analyses. Instead, the regression equations have been used to predict the pK_a s for these amino compounds.

Results

HAMMETT CONSTANTS

The values for the σ constants employed here, as well as the experimental pK_a s, are given in Table I. The empirical Hammett σ constants, as expected, exhibited a strong correlation with the experimental pK_a values of this series of benzoic acids:

$$pK_a = -1.005(\pm 0.011)\sigma + 4.200(\pm 0.004)$$

$$n = 17, r^2 = 0.9985, s = 0.0126, F = 8788,$$

where n is the number of compounds, r is the correlation coefficient, s is the standard deviation, and F is the Fisher ratio. The regression is illus-

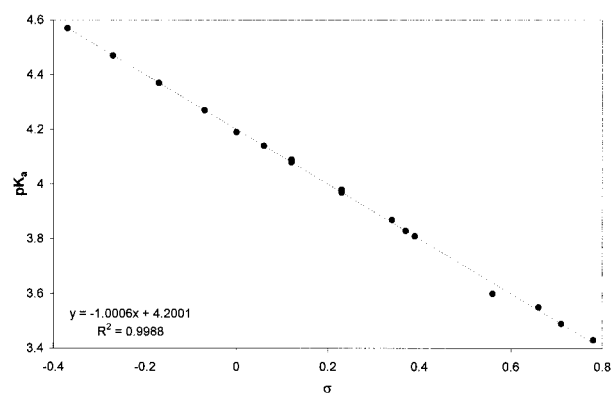


FIGURE 1. Correlation between Hammett constants and experimental pK_a .

trated in Figure 1. There were no outliers in this set. The *para* compounds ($r^2 = 0.9998$) showed a correlation that was only slightly better than the *meta* compounds ($r^2 = 0.9971$).

ATOMIC CHARGES

Although the atomic charge on an atom in a molecule is not a proper quantum chemical observable, the atomic charge concept has proven to be a valuable tool for the explanation of a variety of chemical phenomena. Several methods have been developed, both empirical and quantum mechanical, for the determination of atomic charge. The usefulness of the values obtained for these charges depends upon both the particular scheme employed for their calculation and the application under consideration [8].

Four separate types of charges have been included in the present study: Mulliken charges (Q_M) [17–20], Löwdin charges (Q_L) [21], natural population analysis charges (Q_N) [22], and AIM charges (Q_A) [23]. These charges were calculated for the acidic hydrogen (H) and the entire carboxylic acid group (COOH) for each of the neutral benzoic acid species. Charges on the oxygen (O^-) from which the proton was abstracted and the charge on the whole carboxylate group (COO^-) were determined for the corresponding conjugate bases. The results of these charge calculations are summarized in Tables II–V.

Mulliken Charges

The Mulliken charges performed well for this series of compounds (Table II), in contrast to their weak performance for a series of anilines studied earlier [7]. Among the Mulliken charges examined,

TABLE II
Calculated Mulliken charges for substituted benzoic acids.

Substituent	$Q_M(H)$	$Q_M(COOH)$	$Q_M(O^-)$	$Q_M(COO^-)$
H (benzoic acid)	0.2539	0.0071	-0.4909	-0.6485
<i>m</i> -bromo	0.2580	0.0398	-0.4808	-0.6169
<i>m</i> -chloro	0.2581	0.0396	-0.4820	-0.6206
<i>m</i> -cyano	0.2615	0.0502	-0.4777	-0.6117
<i>m</i> -fluoro	0.2570	0.0383	-0.4859	-0.6299
<i>m</i> -hydroxy	0.2540	0.0259	-0.4877	-0.6395
<i>m</i> -methoxy	0.2529	0.0215	-0.4880	-0.6364
<i>m</i> -methyl	0.2529	0.0190	-0.4909	-0.6461
<i>m</i> -nitro	0.2618	0.0583	-0.4740	-0.6029
<i>p</i> -bromo	0.2571	0.0321	-0.4856	-0.6297
<i>p</i> -chloro	0.2572	0.0185	-0.4862	-0.6304
<i>p</i> -cyano	0.2610	0.0341	-0.4797	-0.6145
<i>p</i> -fluoro	0.2560	0.0114	-0.4896	-0.6404
<i>p</i> -hydroxy	0.2523	-0.0074	-0.4921	-0.6520
<i>p</i> -methoxy	0.2514	0.0047	-0.4924	-0.6512
<i>p</i> -methyl	0.2525	0.0131	-0.4912	-0.6508
<i>p</i> -nitro	0.2619	0.0577	-0.4775	-0.6058
r^2	0.9216	0.8748	0.9152	0.9444

the charge on the entire carboxylate group correlated most favorably with the experimental pK_a s:

$$pK_a = -20.08(\pm 1.26)Q_M(COO^-) - 8.687(\pm 0.794)$$

$$n = 17, r^2 = 0.9444, s = 0.0828, F = 255.$$

TABLE III
Calculated Löwdin charges for substituted benzoic acids.

Substituent	$Q_L(H)$	$Q_L(COOH)$	$Q_L(O^-)$	$Q_L(COO^-)$
H (benzoic acid)	0.1135	-0.0533	-0.3699	-0.8018
<i>m</i> -chloro	0.1166	-0.0388	-0.3595	-0.7879
<i>m</i> -cyano	0.1187	-0.0328	-0.3561	-0.7825
<i>m</i> -fluoro	0.1158	-0.0385	-0.3621	-0.7901
<i>m</i> -hydroxy	0.1150	-0.0471	-0.3637	-0.7956
<i>m</i> -methoxy	0.1145	-0.0497	-0.3640	-0.7977
<i>m</i> -methyl	0.1136	-0.0549	-0.3696	-0.8021
<i>m</i> -nitro	0.1195	-0.0303	-0.3527	-0.7798
<i>p</i> -chloro	0.1156	-0.0459	-0.3645	-0.7907
<i>p</i> -cyano	0.1182	-0.0312	-0.3567	-0.7768
<i>p</i> -fluoro	0.1149	-0.0526	-0.3688	-0.7986
<i>p</i> -hydroxy	0.1127	-0.0667	-0.3726	-0.8076
<i>p</i> -methoxy	0.1123	-0.0688	-0.3729	-0.8076
<i>p</i> -methyl	0.1126	-0.0597	-0.3713	-0.8046
<i>p</i> -nitro	0.1191	-0.0254	-0.3540	-0.7719
r^2	0.9631	0.9776	0.9569	0.9698

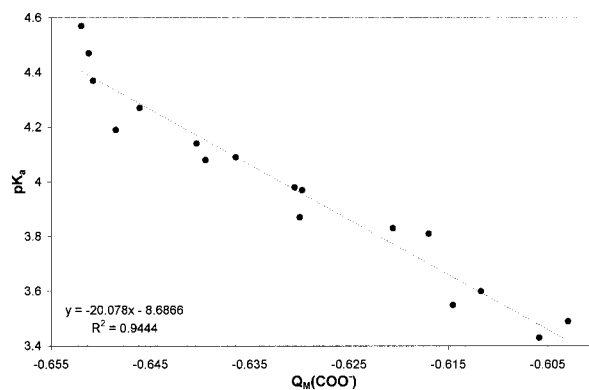
TABLE IV
 Calculated natural charges for substituted benzoic acids.

Substituent	$Q_n(\text{H})$	$Q_n(\text{COOH})$	$Q_n(\text{O}^-)$	$Q_n(\text{COO}^-)$
H (benzoic acid)	0.4808	0.0006	-0.7710	-0.7702
<i>m</i> -bromo	0.4836	0.0137	-0.7612	-0.7475
<i>m</i> -chloro	0.4837	0.0138	-0.7624	-0.7508
<i>m</i> -cyano	0.4859	0.0212	-0.7585	-0.7465
<i>m</i> -fluoro	0.4830	0.0104	-0.7662	-0.7603
<i>m</i> -hydroxy	0.4809	0.0015	-0.7654	-0.7673
<i>m</i> -methoxy	0.4802	-0.0012	-0.7662	-0.7680
<i>m</i> -methyl	0.4802	-0.0011	-0.7703	-0.7701
<i>m</i> -nitro	0.4861	0.0235	-0.7543	-0.7429
<i>p</i> -bromo	0.4828	0.0066	-0.7652	-0.7573
<i>p</i> -chloro	0.4828	0.0062	-0.7659	-0.7591
<i>p</i> -cyano	0.4853	0.0189	-0.7583	-0.7481
<i>p</i> -fluoro	0.4821	0.0007	-0.7698	-0.7658
<i>p</i> -hydroxy	0.4797	-0.0137	-0.7726	-0.7726
<i>p</i> -methoxy	0.4792	-0.0154	-0.7727	-0.7728
<i>p</i> -methyl	0.4799	-0.0052	-0.7715	-0.7710
<i>p</i> -nitro	0.4859	0.0233	-0.7558	-0.7452
r^2	0.9267	0.9689	0.9349	0.8958

The results (Fig. 2) demonstrate that benzoic acids substituted with electron-withdrawing groups (EWGs) have lower pK_a values than those with electron-donating groups (EDGs). EWGs increase

TABLE V
 Calculated AIM charges for substituted benzoic acids.

Substituent	$Q_A(\text{H})$	$Q_A(\text{COOH})$
H (benzoic acid)	0.5803	-0.1518
<i>m</i> -bromo	0.5840	-0.1189
<i>m</i> -chloro	0.5838	-0.1233
<i>m</i> -cyano	0.5865	-0.1090
<i>m</i> -fluoro	0.5830	-0.1279
<i>m</i> -hydroxy	0.5806	-0.1439
<i>m</i> -methoxy	0.5798	-0.1501
<i>m</i> -methyl	0.5796	-0.1571
<i>m</i> -nitro	0.5868	-0.1008
<i>p</i> -bromo	0.5843	-0.1316
<i>p</i> -chloro	0.5826	-0.1388
<i>p</i> -cyano	0.5859	-0.1216
<i>p</i> -fluoro	0.5818	-0.1422
<i>p</i> -hydroxy	0.5790	-0.1642
<i>p</i> -methoxy	0.5783	-0.1628
<i>p</i> -methyl	0.5792	-0.1501
<i>p</i> -nitro	0.5864	-0.1220
r^2	0.9134	0.8698


FIGURE 2. Correlation between pK_a and the Mulliken charge on the carboxylate group.

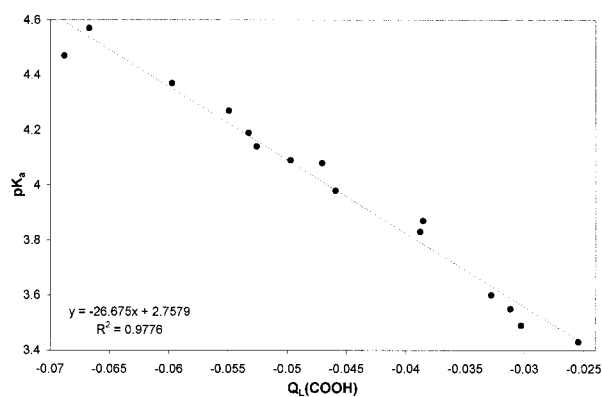
the delocalization of the negative charge that results from acid dissociation, thereby stabilizing the anionic conjugate base. EDGs decrease this delocalization, allowing less stabilization of the anionic species. The *para* compounds ($r^2 = 0.9538$) and *meta* compounds ($r^2 = 0.9562$) exhibited similar correlations for this set.

Löwdin Charges

The Löwdin charge on the carboxylic acid group proved to be an extremely effective quantum chemical parameter for the description of benzoic acid pK_a values (Figs. 3 and 4 and Table III). $Q_L(\text{COOH})$ correlated with pK_a almost as well as the Hammett σ constants:

$$pK_a = -26.68(\pm 1.12)Q_L(\text{COOH}) + 2.76(\pm 0.05)$$

$$n = 15, r^2 = 0.9776, s = 0.0560, F = 567.$$


FIGURE 3. Correlation between pK_a and the Löwdin charge on the carboxylic acid group.

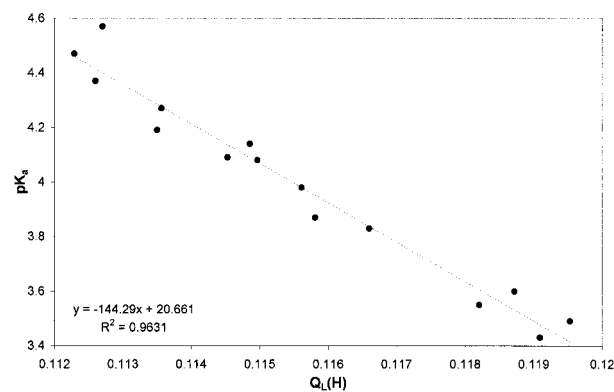


FIGURE 4. Correlation between pK_a and the Löwdin charge on the acidic hydrogen.

There were no apparent outliers in the set. The correlations resulting from the *para* group ($r^2 = 0.9863$) and the *meta* group ($r^2 = 0.9733$) were nearly identical.

There was also a strong correlation between the Löwdin charge on the acidic hydrogen and the pK_a :

$$pK_a = -144.3(\pm 7.8)Q_L(H) + 20.7(\pm 0.9)$$

$$n = 15, r^2 = 0.9631, s = 0.0719, F = 339.$$

More acidic hydrogens are in general involved in more highly polarized bonds. The charge on the hydrogen atom can serve as an indicator of the degree of this polarization. The plot of benzoic acid pK_a vs $Q_L(H)$ in Figure 4 shows that compounds with more positively charged hydrogens in the acid functional group have lower pK_a values.

Natural Population Analysis Charges

Of the four atom and group natural population analysis charges calculated, $Q_n(\text{COOH})$ showed the strongest correlation with pK_a (Table III). (This was also the case for the Löwdin charges.) In fact, the regression equation for $Q_n(\text{COOH})$ was nearly identical to that for $Q_L(\text{COOH})$:

$$pK_a = -27.94(\pm 1.29)Q_n(\text{COOH}) + 4.15(\pm 0.02)$$

$$n = 17, r^2 = 0.9689, s = 0.0620, F = 467.$$

This correlation is illustrated in Figure 5.

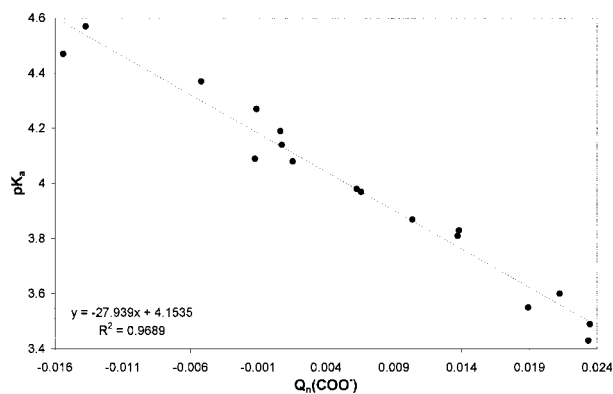


FIGURE 5. Correlation between pK_a and the natural charge on the carboxylate group.

AIM Charges

Due to difficulties in numerical integration, AIM charges could only be confidently determined for the acidic hydrogen atom and the entire carboxylic acid group (Table V). The regression (Fig. 6) for $Q_A(H)$ reaffirmed that hydrogens with a more positive charge are more acidic:

$$pK_a = -112.5(\pm 8.9)Q_A(H) + 69.5(\pm 5.2)$$

$$n = 17, r^2 = 0.9134, s = 0.1034, F = 158.$$

This correlation was not as strong as those obtained for other methods of charge determination. The values of $Q_A(\text{COOH})$ and pK_a were even less well correlated ($r^2 = 0.8698$).

RELATIVE PROTON TRANSFER ENERGIES

A measure of the acidity of the substituted benzoic acids relative to benzoic acid can be obtained

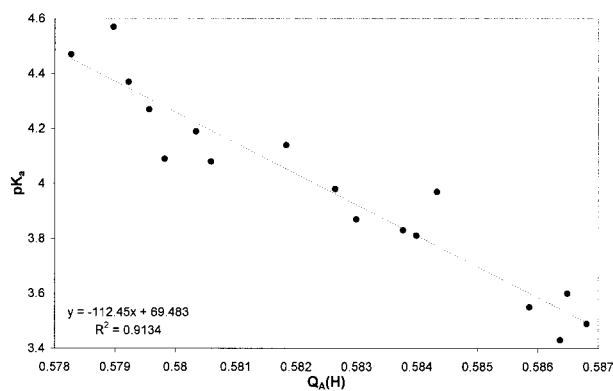
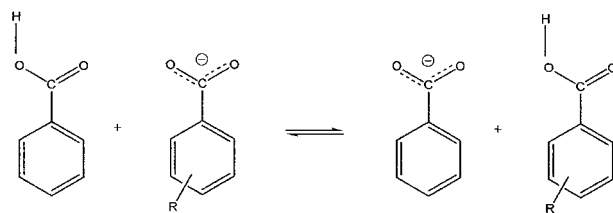


FIGURE 6. Correlation between pK_a and the AIM charge on the acidic proton.


STRUCTURE 1.

by the examination of the energetics of the isodesmic reaction shown in Structure 1. The zero-point energies, thermal corrections, and entropies should be similar for the reactants and the products. Consequently, the difference in energies of the products and reactants provides a reasonable approximation to the enthalpy change ΔH_{prot} for the reaction and hence to the change in Gibbs energy of the reaction, ΔG_{prot} . Compounds involved in reactions for which ΔG_{prot} is negative should be less acidic than benzoic acid. The pK_a s for compounds taking part in reactions with a positive ΔG_{prot} should be lower than that of benzoic acid.

The ΔE_{prot} values obtained for reactions with each of the substituted benzoic acids (Table VI) support these assumptions. The values for ΔE_{prot} correlated well with experimental benzoic acid pK_a s (Fig. 7):

TABLE VI
Calculated relative proton transfer energies (Hartrees) for substituted benzoic acids.

Substituent	E (acid)	E (conjugate base)	ΔE
H (benzoic acid)	-420.9374	-420.3730	0.0000
<i>m</i> -bromo	-2994.4784	-2993.9243	0.0103
<i>m</i> -chloro	-880.5579	-880.0035	0.0100
<i>m</i> -cyano	-513.1991	-512.6518	0.0172
<i>m</i> -fluoro	-520.2003	-519.6424	0.0065
<i>m</i> -hydroxy	-496.1807	-495.6186	0.0023
<i>m</i> -methoxy	-535.4908	-534.9272	0.0009
<i>m</i> -methyl	-460.2652	-459.6998	-0.0009
<i>m</i> -nitro	-625.4882	-624.9418	0.0181
<i>p</i> -bromo	-2994.4791	-2993.9238	0.0091
<i>p</i> -chloro	-880.5609	-880.0032	0.0067
<i>p</i> -cyano	-513.2019	-512.6529	0.0155
<i>p</i> -fluoro	-520.2041	-519.6419	0.0022
<i>p</i> -hydroxy	-496.1850	-495.6155	-0.0050
<i>p</i> -methoxy	-535.4924	-534.9246	-0.0034
<i>p</i> -methyl	-460.2657	-459.6995	-0.0017
<i>p</i> -nitro	-625.4876	-624.9437	0.0206
r^2			0.9582

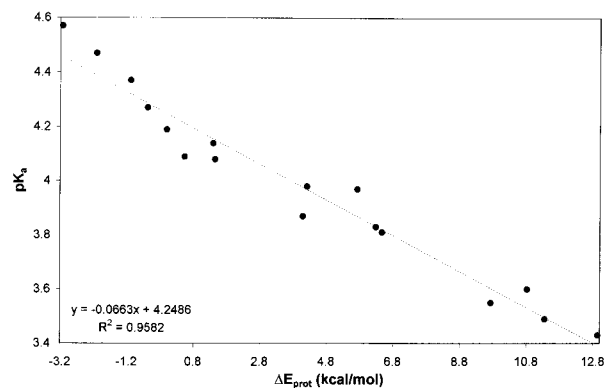


FIGURE 7. Plot of pK_a vs ΔE_{prot} . Energies of protonation are for the reaction substituted benzoate + benzoic acid \rightarrow substituted benzoic acid + benzoate.

$$pK_a = -0.066(\pm 0.004)\Delta E_{\text{prot}} + 4.249(\pm 0.023)$$

$$n = 17, r^2 = 0.9582, s = 0.0718, F = 344.$$

Obviously, the good agreement for these gas-phase calculations with the aqueous pK_a trends demonstrates that the solvation effects are moderately constant for these substituted benzoic acids.

BOND ORDER

Bond orders for the O—H bond in the carboxylic acid group have been calculated in the form of

TABLE VII
Calculated bond orders for substituted benzoic acids.

Substituent	Wiberg bond index
H (benzoic acid)	0.7476
<i>m</i> -bromo	0.7452
<i>m</i> -chloro	0.7452
<i>m</i> -cyano	0.7433
<i>m</i> -fluoro	0.7459
<i>m</i> -hydroxy	0.7476
<i>m</i> -methoxy	0.7481
<i>m</i> -methyl	0.7482
<i>m</i> -nitro	0.7432
<i>p</i> -bromo	0.7460
<i>p</i> -chloro	0.7460
<i>p</i> -cyano	0.7438
<i>p</i> -fluoro	0.7467
<i>p</i> -hydroxy	0.7487
<i>p</i> -methoxy	0.7491
<i>p</i> -methyl	0.7484
<i>p</i> -nitro	0.7433
r^2	0.9353

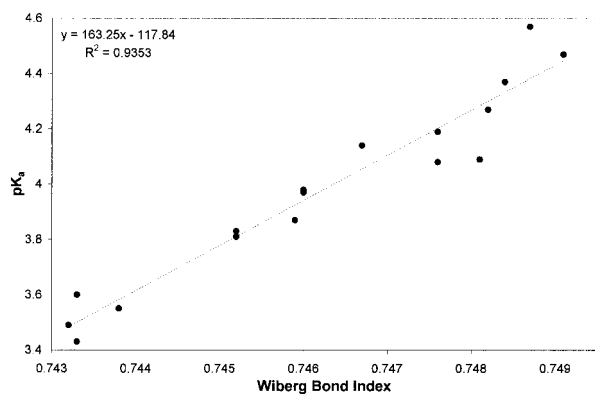


FIGURE 8. Correlation between pK_a and the O—H Wiberg bond index.

Wiberg bond indices for each of the benzoic acid species (Table VII). A positive correlation was obtained between bond order and pK_a :

$$pK_a = 163.2(\pm 11.1)BI - 117.8(\pm 8.3)$$

$$n = 17, r^2 = 0.9353, s = 0.0893, F = 217.$$

The relationship between bond order and pK_a is illustrated in Figure 8. Bond orders are a measure of the strength of a chemical bond. The results show that the acid-dissociation constants for benzoic acids are proportional to the strength of the bond between hydrogen and oxygen in the carboxylic acid group. Note that small differences in the bond index correspond to fairly substantial changes in the pK_a .

TABLE VIII
Experimental and predicted pK_a values for amino-substituted benzoic acids.

Parameter	<i>m</i> -amino		<i>p</i> -amino	
	Value	pK_a	Value	pK_a
Experiment	—	4.78	—	4.874
σ	-0.16	4.36	-0.66	4.86
$Q_M(\text{COO}^-)$	-0.6472	4.76	-0.6593	5.01
$Q_L(\text{COOH})$	-0.7994	4.10	-0.8119	4.82
$Q_n(\text{COOH})$	-0.7709	4.22	-0.7771	4.92
ΔE_{prot} (kcal/mol)	-1.9573	4.38	-4.8061	4.57
Wiberg				
bond index	0.7490	4.43	0.7505	4.68
Average of QM parameters	—	4.38	—	4.80

TABLE IX
Correlations among selected parameters.

	pK_a	σ	$Q_n(\text{H})$	$Q_n(\text{COOH})$	$Q_M(\text{H})$	$Q_M(\text{COOH})$	$Q_L(\text{H})$	$Q_L(\text{COOH})$	$Q_A(\text{H})$	$Q_A(\text{COOH})$	BI	ΔE_{prot}
pK_a	1.0000											
σ	-0.9994	1.0000										
$Q_n(\text{H})$	-0.9626	0.9583	1.0000									
$Q_n(\text{COOH})$	-0.9843	0.9812	0.9661	1.0000								
$Q_M(\text{H})$	-0.9600	0.9561	0.9991	0.9616	1.0000							
$Q_M(\text{COOH})$	-0.9353	0.9327	0.8848	0.9350	0.8738	1.0000						
$Q_L(\text{H})$	-0.9814	0.9784	0.9801	0.9699	0.9777	0.9236	1.0000					
$Q_L(\text{COOH})$	-0.9887	0.9890	0.9402	0.9862	0.9381	0.9354	0.9630	1.0000				
$Q_A(\text{H})$	-0.9557	0.9514	0.9905	0.9596	0.9905	0.8885	0.9842	0.9471	1.0000			
$Q_A(\text{COOH})$	-0.9326	0.9266	0.9505	0.9506	0.9395	0.9226	0.9533	0.9225	0.9534	1.0000		
BI	0.9671	-0.9625	-0.9996	-0.9717	-0.9983	-0.8905	-0.9816	-0.9459	-0.9903	-0.9525	1.0000	
ΔE_{prot}	-0.9789	0.9757	0.9831	0.9679	0.9825	0.9270	0.9858	0.9575	0.9815	0.9362	-0.9852	1.0000

AMINO-SUBSTITUTED COMPOUNDS

As noted earlier, experimental pK_a values for *m*-amino and *p*-aminobenzoic acid were not included in the source [15] employed for the pK_a s of the other compounds, and as a precaution these compounds were not included in the regression analyses. Regression equations from several of the quantum chemical parameters described above have been used to predict the pK_a s of the amino-substituted compounds (Table VIII).

The average value for the pK_a of *m*-aminobenzoic, as predicted by the quantum chemical parameters, was 4.38. Further, the pK_a value for *m*-aminobenzoic acid as predicted by the Hammett constant is 4.36, essentially identical to the value predicted by the quantum models. The Handbook of Chemistry and Physics [16] lists an experimental value of 4.78 for the *m*-aminobenzoic acid. Models can sometimes call attention to the presence of questionable or erroneous reported experimental values [24], and we suggest that the reported pK_a value for *m*-aminobenzoic acid warrants reexamination.

In contrast, the quantum chemical parameters (on average) predict the pK_a of *p*-aminobenzoic acid to be 4.80. This is consistent with the reported experimental value of 4.874 [16]. The Hammett constant for *p*-aminobenzoic acid predicts its pK_a to be 4.86.

The correlations among selected parameters and the pK_a are shown in Table IX.

Conclusions

This study of benzoic acids, along with previous studies of anilines [6, 7] and phenols [9], demonstrates that quantum chemical parameters can be used successfully to account for substituent effects. In addition to their ability to quantitatively relate the electronic properties of substituents to their physicochemical effects, an attractive feature of quantum chemical parameters is that they are both flexible and interpretable. Such models can also call attention to questionable experimental values reported in the literature, and encourage a reexamination of the experiments in such cases.

References

- Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Collins: New York, 1987.

- Wesolowski, M.; Konarski, T. *J Therm Anal Calor* 1999, 55, 995–1002.
- Caiser, C. R.; Basso, E. A.; Rittner, R. *Magnet Reson Chem* 2001, 39, 643–644.
- Ohshita, J.; Hiroyuki, K.; Takata, A.; Toshiyuki, I.; Kunai, A.; Ohta, N.; Komaguchi, K.; Shiotani, M.; Adachi, A.; Sakamaki, K.; Okita, K. *Organometallics* 2001, 20, 4800–4805.
- Hammett, L. P. *J Am Chem Soc* 1937, 59, 96–103.
- Gross, K. C.; Seybold, P. G.; Peralta-Inga, Z.; Politzer, P. *J Org Chem* 2001, 66, 6919–6925.
- Gross, K. C.; Seybold, P. G. *Int J Quantum Chem* 2000, 80, 1107–1115.
- Gross, K. C.; Seybold, P. G.; Hadad, C. M. *Int J Quantum Chem*, 2002, 90, 445–458.
- Gross, K. C.; Seybold, P. G. *Int J Quantum Chem* 2001, 85, 569–579.
- Spartan 5.1. Wavefunction Inc.; Irvine, CA.
- Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian98*, Revision A.9; Gaussian Inc.; Pittsburgh, PA, 1998.
- Keith, T. AIMALL; Yale University: New Haven, CT.
- Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J Comput Chem* 1993, 14, 1347–1363.
- Hansch, C.; Leo, A.; Taft, R. W. *Chem Rev* 1991, 91, 165–195.
- Albert, A.; Serjeant, E. P. *Ionization Constants of Acids and Bases*; Meuthen: London, 1962.
- CRC Handbook of Chemistry and Physics, 77th ed. Lide, D. R., editor, CRC Press: New York, 1996.
- Mulliken, R. S. *J Chem Phys* 1955, 23, 1833–1840.
- Mulliken, R. S. *J Chem Phys* 1955, 23, 1841–1846.
- Mulliken, R. S. *J Chem Phys* 1955, 23, 2338–2342.
- Mulliken, R. S. *J Chem Phys* 1955, 23, 2343–2346.
- Löwdin, P.-O. *Adv Quantum Chem* 1970, 5, 185–199.
- Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J Chem Phys* 1985, 83, 735–746.
- Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: Oxford, UK, 1999.
- Gauch, H. G. *Am Sci* 1993, 81, 468–478.