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Correlation of the Acidity of Substituted Phenols, Anilines, and Benzoic Acids Calculated by MNDO, AM1, and PM3 with Hammett-Type Substituent Constants

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Heats of formation and net atomic charges of some 120 structures involving substituted phenols, anilines, and benzoic acids and the corresponding anions were calculated by MNDO, AM1, and PM3 semiempirical methods. The gas phase acidities of substituted phenols and anilines and the net atomic charges on the anionic heteroatoms of the corresponding anions have been successfully correlated with σ^- constants. Moreover, good correlations with σ were found for the charges on the acidic hydrogens of substituted phenols and anilines. In contrast, the gas phase acidities of substituted benzoic acids and the charges on the anionic oxygens of the corresponding anions are better correlated with Taft σ° constants. Comparisons of these results with experimental data and *ab initio* theoretical calculations indicate that AM1 and PM3 methods are much better than MNDO in predicting the acidity of aromatic compounds.

INTRODUCTION

Linear free energy relationship studies have had a vast impact on the development of physical organic chemistry. The majority of these studies are for processes occurring in solution. However, such studies in the gas phase for ionic species, in particular, have become a very important field in recent years since they allow the investigation of intrinsic molecular properties of ionic species without the interference of solvent. This conclusion is also supported by the recent gas-phase acidity experiments, which indicate that a wide variety of carbanions are more stable than some other anions which are generally regarded as stable solution species.[1] For example, the benzyl anion was generated in the gas phase by proton transfer from toluene to methoxide ion even though in solution the pK_a of toluene is 15 pK_a units greater than that of methanol.[1b,c] This discrepancy between the reactivities in the gas and solution phases is an excellent indication that solvent participation may play a dominant role in determining solution properties and reactivities of anionic species.

Intrinsic gas phase acidities of anionic species can be determined by ion cyclotron resonance spectrometry (ICR),[2] high-pressure mass spectrometry,[3] and the flowing afterglow technique.[4] Although these experimental methods are of considerable interest and are stepping stones to the

understanding of the chemistry of anions, an important independent contribution to this field can be expected to be achieved from theoretical calculations.

Coincident with the continuing increase in the availability of sophisticated computers, quantum mechanical methods such as *ab initio* and semiempirical self-consistent field molecular orbital (SCF-MO) theories have become very important tools for the investigation of the structure and reactivity of neutral as well as ionic molecules.[5] The use of *ab initio* SCF-MO procedures is presently restricted to relatively small systems due to the large expenses related to the long times required for calculations. This has created a pressing need for a general procedure for studying the properties of large molecules. Recently, the use of the semiempirical methods such as MINDO/3,[6] MNDO,[7] and AM1[8] has become of serious interest. A number of systematic studies for neutral molecules,[9,10] excited states,[11] electron affinities and anions,[12] proton affinities,[13,14] cations,[15] and radical cations[16] have shown that these semiempirical methods may be as useful as the more expensive *ab initio* method.

There are a few reports in the literature on the interpretation of electronic effects of substituents in quantitative terms by MNDO, MINDO/3, and AM1 methods such as correlation analyses of Hammett constants with acidities of substituted benzoic acids[17,18] and proton affinities of monosubstituted pyridines.[19] These studies still remain insufficient and there is a need for a systematic study that involves a large number of

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systems calculated by a variety of different semiempirical methods. Thus, we sought to study the relationships between substituent constants (Hammett-type) and calculated properties of a variety of compounds by MNDO,[7] AM1,[8] and PM3[20] semiempirical methods. We have chosen here to report a study of the acidities of substituted phenols, anilines, and benzoic acids in the solution and gas phases. Our choice is justified by the fact that experimental data for these systems are available and hence comparisons may be made with the results of our study. Moreover, these systems are of considerable interest in the examination of the intrinsic substituent effects on the stabilities of anions.

METHODS

The MNDO, AM1 and PM3 calculations were done using MOPAC version 5.0 (QCPE No. 455)[21] running on a CRAY X-MP/28 computer in the Ohio Supercomputer Center. The starting geometries were obtained from the PCMODEL program.[22] The calculations were carried out by the standard MNDO,[7] AM1,[8] and PM3[20] programs based on the restricted Hartree–Fock (RHF) method. Geometries were optimized in internal coordinates and were terminated when Herberts test was satisfied in the Broyden-Fletcher-Goldfarb-Shanno method (BFGS). All optimizations were terminated when the change in energy on successive iterations was less than 0.00001 kcal/mole and the change in density matrix elements on two successive iterations was less than 0.001. In the AM1, MNDO, and PM3 calculations for neutral *meta*-substituted phenols, two conformations were considered: the one where the phenolic proton is coplanar to the benzene ring and *syn* to the substituent and the other where it is coplanar to the benzene ring and *anti* to the substituent. The starting geometries for the neutral *para*-substituted phenols were begun where the phenolic proton is coplanar to the benzene ring. In the case of the *meta*-hydroxy phenolate anion, two conformations were considered: the one where the hydroxy proton is *syn* to the anionic oxygen and the other where it is *anti*. In the AM1, MNDO, and PM3 calculations for the neutral *meta*- and *para*-substituted anilines, two conformations were considered: the one where the amine moiety is pyramidal and the other where it is planar. In all cases, it was found that the global minimum conformation is

with a pyramidal amino group. In the case of *meta*-substituted anilide anions, two conformations were also considered: one where the amino proton is *syn* to the substituent and the other where it is *anti*. In the MNDO and PM3 calculations for *meta*-substituted benzoic acids and benzoate anions, three conformations were considered: the first where the carboxyl group is perpendicular to the benzene ring, the second where it is coplanar to the benzene ring and *syn* to the substituent, and the third where it is coplanar to the benzene ring and *anti* to the substituent. In the cases of *para*-substituted benzoic acids and benzoate anions, two conformations were considered: the one where the carboxyl group is perpendicular to the benzene ring and the other where it is coplanar. All our calculations have been performed with full optimization of all geometrical variables (bond lengths, bond angles, and dihedral angles) without any symmetry constraint. For all the conformations considered, the one with the lowest energy was selected for the correlation analyses.

RESULTS AND DISCUSSION

Correlation Analysis of Gas Phase Acidities of Phenol and Aniline Systems

The present study is based upon 88 substituted phenols and anilines and the corresponding anions. The selection of the derivatives is made on the basis of the diverse physicochemical properties of the substituent group and because of the availability of their gas phase experimental data.

The calculated properties of the substituted phenols and the corresponding anions are given in Tables I and II, whereas Tables III and IV list the properties of substituted anilines and of the corresponding anions. The properties shown in Tables I and III include MNDO, AM1, and PM3 calculated heats of formation of substituted phenols, $\Delta H_f^\circ X C_6H_4OH$, substituted anilines, $\Delta H_f^\circ X C_6H_4NH_2$, and the corresponding anions, $\Delta H_f^\circ X C_6H_4O^-$ and $\Delta H_f^\circ X C_6H_4NH^-$, respectively. Also included are the calculated energy differences for the isodesmic processes 1a and 1b, $\delta(\Delta H_f^\circ)_{1a}$ and $\delta(\Delta H_f^\circ)_{1b}$, respectively, as well as their experimental gas phase and STO-3G calculated energies, $(\delta\Delta G^\circ)_1$, and $\delta(\Delta E^\circ)_1$, respectively.[23] Tables II and IV list the calculated net atomic charges on the acidic hydrogens of substituted phenols (qH) and anilines (ΣqH) and on the an-
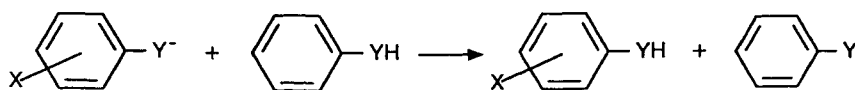
Process 1a; Y = O
Process 1b; Y = NH

Table I. Computed and experimental energies (kcal/mol) for process 1a.

Substituent X	MNDO			AM1			PM3			$(\delta\Delta G°)_{1a}$	$(\delta\Delta E°)_{1a}$	σ^-
	$\Delta H_f°$ XC_6H_4OH	$\Delta H_f°$ $XC_6H_4O^-$	$(\delta\Delta H_f°)_{1a}$	$\Delta H_f°$ XC_6H_4OH	$\Delta H_f°$ $XC_6H_4O^-$	$(\delta\Delta H_f°)_{1a}$	$\Delta H_f°$ XC_6H_4OH	$\Delta H_f°$ $XC_6H_4O^-$	$(\delta\Delta H_f°)_{1a}$			
p-Me	-34.48	-52.75	2.7	-29.77	-49.20	0.69	-30.89	-53.75	0.4	-1.3	-1.0	-0.15
p-NH₂	-25.80	-42.64	1.27	-22.93	-41.01	-0.66	-23.24	-45.58	-0.12	-4.2	-4.9	-0.15[d]
p-t-Bu	-32.45	-51.28	3.26	-40.51	-60.34	1.09	-44.68	-68.16	1.02	-	-	-0.14
p-OMe	-65.06	-86.16	5.53	-59.35	-81.17	3.08	-58.99	-84.10	2.65	-0.8	-3.0	-0.13
p-F	-72.85	-95.75	7.33	-67.03	-91.64	5.87	-64.97	-93.35	5.92	2.6	1.6	-0.02[d]
p-Br	-24.23	-48.95	9.15	-17.59	-45.55	9.22	-14.12	-44.33	7.75	-	-	0.25
p-COOEt	-109.76	-140.81	15.48	-104.60	-140.79	17.45	-107.30	-145.66	15.90	-	-	0.64
p-CF₃	-176.24	-210.86	19.05	-178.93	-213.86	16.19	-180.60	-219.09	16.03	-	11.5	0.65[d]
p-COOH	-115.82	-148.53	17.14	-112.90	-150.03	18.39	-111.92	-150.03	18.60	-	-	0.73[d]
p-CN	3.56	-28.04	16.03	8.83	-25.65	15.74	13.09	-25.78	16.41	17.7	21.4	0.88
p-CHO	-57.98	-88.95	15.40	-53.73	-87.76	15.29	-56.28	-92.61	13.87	-	13.8	1.04
p-NO₂	-11.15	-54.56	27.84	-19.54	-64.97	26.69	-31.69	-81.53	27.38	25.8	29.2	1.24
H	-26.66	-42.23	0	-22.23	-40.97	0	-21.64	-44.1	0	0	0	0
m-NH₂	-26.38	-43.28	1.33	-24.09	-42.74	-0.09	-24.13	-47.04	0.45	-0.9	-0.1	-0.16
m-Me	-34.18	-50.06	0.31	-29.80	-48.20	-0.34	-31.00	-53.13	-0.33	-0.4	-0.4	-0.07
m-OH	-74.94	-93.38	2.87	-66.79	-89.32	3.79	-67.26	-92.49	2.10	4.3	3.0	0.12
m-OMe	-65.79	-84.26	2.90	-60.41	-82.05	2.90	-60.08	-84.81	2.27	1.5	2.1	0.12
m-F	-73.15	-96.15	7.43	-67.48	-92.59	6.37	-65.42	-94.54	6.75	5.8	5.4	0.34
m-CHO	-56.99	-79.13	6.57	-52.77	-78.30	6.79	-55.55	-83.99	6.38	8.6	5.9	0.35
m-CF₃	-174.83	-203.57	13.17	-177.9	-208.55	11.91	-199.7	-213.65	11.68	9.7	8.4	0.43
m-CN	4.57	-21.03	10.03	9.73	-19.61	10.60	13.69	-20.26	11.56	14.3	14.5	0.56
m-NO₂	-11.38	-45.45	18.5	-17.91	-54.22	17.57	-29.88	-68.75	16.80	15.7	18.1	0.71

[a] Calculated from $\Delta H_f°(X\text{-}ROH) + \Delta H_f°(R\text{-}O^-) - \Delta H_f°(X\text{-}RO^-) - \Delta H_f°(R\text{-}OH)$. [b] Experimental and STO-3G data taken from ref. 23. [c] σ_p values are taken from ref. 24 and σ_m are taken as σ values from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958). [d] Taken from M. S. Tute, *Adv. Drug Res.*, **6**, 68 (1971).

Table II. Computed atomic charges for substituted phenols and phenoxide anions.

Substituent X	MNDO		AM1		PM3	
	qH XC_6H_4OH	qO⁻ $XC_6H_4O^-$	qH XC_6H_4OH	qO⁻ $XC_6H_4O^-$	qH XC_6H_4OH	qO⁻ $XC_6H_4O^-$
p-Me	0.1933	-0.5159	0.2168	-0.5268	0.1957	-0.5677
p-NH₂	0.1912	-0.5206	0.2144	-0.5292	0.1945	-0.5691
p-t-Bu	0.1930	-0.5133	0.2166	-0.5239	0.1958	-0.5644
p-OMe	0.1922	-0.5127	0.2160	-0.5186	0.1950	-0.5607
p-F	0.1951	-0.5120	0.2197	-0.5205	0.1983	-0.5599
p-Br	0.1968	-0.5035	0.2212	-0.5071	0.1988	-0.5511
p-COOEt	0.1994	-0.4856	0.2233	-0.4762	0.2010	-0.5178
p-CF3	0.2019	-0.4786	0.2249	-0.4896	0.2024	-0.5252
p-COOH	0.1994	-0.4796	0.2248	-0.4743	0.2017	-0.5146
p-CN	0.1991	-0.4810	0.2237	-0.4860	0.2014	-0.5201
p-CHO	0.1984	-0.4765	0.2226	-0.4790	0.1999	-0.5194
p-NO₂	0.2049	-0.4483	0.2288	-0.4541	0.2060	-0.4863
H	0.1925	-0.5330	0.2174	-0.5327	0.1964	-0.5726
m-NH₂	0.1937	-0.5239	0.2182	-0.5298	0.1970	-0.5686
m-Me	0.1924	-0.5280	0.2170	-0.5332	0.1961	-0.5727
m-OH	0.1953	-0.5170	0.2205	-0.5183	0.1989	-0.5602
m-OMe	0.1949	-0.5206	0.2199	-0.5236	0.1950	-0.5655
m-F	0.1971	-0.5120	0.2214	-0.5176	0.1995	-0.5557
m-CHO	0.1947	-0.5123	0.2193	-0.5155	0.1974	-0.5553
m-CF₃	0.1985	-0.5011	0.2229	-0.5070	0.2005	-0.5461
m-CN	0.1967	-0.5091	0.2220	-0.5119	0.2004	-0.5479
m-NO₂	0.2010	-0.4861	0.2253	-0.4939	0.2015	-0.5381

ionic heteroatoms of the corresponding anions, qO^- and qNH^-, respectively.

The results given in Tables I–IV were examined for linear relationships with both σ^{-24} and σ^{25} values. The σ^- values were used for correlation of calculated properties of the para substituted acids and σ for those of the *meta* derivatives (since σ^- values for *meta* substituents have not been measured). The correlation results were found to follow reasonably well the expression depicted in eq. (1), where ρ is the slope and C is the intercept.

$$Y = \rho_{calc}X + C \quad \text{(a) } Y = \delta\Delta H_f° \text{ or}$$
$$qY^-; X = \sigma^- \text{ (b) } Y = qH; X = \sigma \quad (1)$$

The regression outputs of the semiempirically calculated energy differences for the isodesmic processes 1a and 1b are shown as entries 1–6 and 7–12 in Table V, respectively. Entries 1–18 in Table VI list the values of the calculated net

atomic charges on the acidic hydrogens of substituted phenols (qH) and anilines (ΣqH) and those on the anionic heteroatoms of the corresponding anions (qO^- and qNH^-).

Examination of the results (Tables V and VI) reveals that, on the whole, there is a satisfactory correlation between the experimentally derived σ and σ^- constants and the calculated energy differences ($\delta\Delta H_f°$), as well as with the calculated atomic charges, qH, ΣqH, qO^-, and qNH^-. However, the correlation of the calculated MNDO properties were found to be significantly inferior to those of both the AM1 and PM3 methods. Although a good correlation was found for PM3 calculated net atomic charges, the predicted values are underestimated. Another significant result observed is the distinction between the calculated ρ values for the *meta* and *para* substituents. It was found that the acidity ρ values for *meta*-substituted phenols and anilines are higher than

Table III. Computed and experimental energies (kcal/mol) for process 1b.

Substituent X	MNDO			AMI			PM3				
	ΔH_f° $XC_6H_4NH_2$	ΔH°_f $XC_6H_4NH^-$	$(\delta\Delta H_f^\circ)'_b$	ΔH_f° $XC_6H_4NH_2$	ΔH_f° $XC_6H_4NH^-$	$(\delta\Delta H_f^\circ)'_b$	ΔH_f° $XC_6H_4NH_2$	ΔH_f° $XC_6H_4NH^-$	$(\delta\Delta H_f^\circ)'_b$	$(\delta\Delta G^\circ)'_b$	$(\delta\Delta E^\circ)'_b$
p-Me	13.86	3.03	2.87	12.95	10.91	0.90	12.04	4.62	0.43	-1.2	-1.0
p-NH₂	22.33	11.53	2.84	20.00	19.25	-0.39	19.67	12.79	-0.11	-	-4.8
p-t-Bu	15.80	4.38	3.46	2.16	-0.39	1.41	-0.64	-8.67	1.04	-	-
p-OMe	-17.71	-30.43	4.76	-16.55	-21.15	3.46	-16.15	-25.74	2.60	-0.9	-2.9
p-F	-24.67	-39.95	7.32	-24.59	-31.52	5.79	-22.27	-34.98	5.72	1.6	1.3
p-Br	24.08	6.72	9.40	24.66	14.08	9.44	28.71	14.07	7.65	-	-
p-COOEt	-65.48	-88.24	14.80	-69.88	-87.77	16.75	-65.66	-87.24	14.59	-	-
p-CF₃	-128.00	-155.59	19.63	-137.13	-154.79	16.52	-137.97	-160.99	16.03	11.5	10.7
p-COOH	-67.51	-91.08	15.61	-71.04	-90.10	17.92	-69.17	-92.11	15.95	-	-
p-CN	51.87	27.25	16.66	50.78	33.25	16.39	55.73	32.20	16.54	-	20.2
p-CHO	-9.87	-33.73	15.90	-11.79	-29.15	16.22	-13.54	-34.57	14.04	-	13.3
p-NO₂	36.96	0.04	28.96	21.56	-7.22	27.64	10.69	-24.09	27.79	-	27.7
H	21.73	13.77	0	20.51	19.37	0	21.31	14.32	0	0	0
m-NH₂	22.02	12.78	1.28	18.85	17.87	-0.16	18.95	11.50	0.46	-	-0.1
m-Me	14.20	5.86	0.38	13.03	12.07	-0.18	12.01	5.25	-0.23	-0.5	-0.3
m-OH	-26.38	-37.21	2.87	-24.04	-28.83	3.65	-24.13	-33.87	2.75	-	2.8
m-OMe	-17.17	-29.21	4.08	-17.48	-21.69	3.07	-16.81	-26.15	2.35	-	2.2
m-F	-24.78	-40.14	7.40	-24.99	-32.21	6.08	-22.57	-35.91	6.35	4.0	5.0
m-CHO	-9.27	-23.68	6.45	-10.24	-18.45	7.07	-12.70	-25.81	6.12	-	5.7
m-CF₃	-126.70	-147.90	13.24	-135.74	-148.73	11.85	-137.09	-155.36	11.28	8.0	7.6
m-CN	52.73	34.75	10.02	52.04	40.39	10.51	56.32	38.13	11.20	-	13.4
m-NO₂	36.64	12.53	16.15	24.02	5.20	17.68	12.55	10.57	16.08	-	16.9

° Calculated from $\delta\Delta H_f^\circ = \Delta H_f^\circ$ (RNH⁻) - ΔH_f° (RNH₂) + ΔH_f° (X-RNH₂) - ΔH_f° (X-RNH⁻). ᵇ Experimental and STO-3G data taken from ref. 23.

Table IV. Computed atomic charges for substituted anilines and anilide anions.

Substituent X	MNDO		AMI		PM3	
	ΣqH $XC_6H_4NH_2$	qNH^- $XC_6H_4NH^-$	ΣqH $XC_6H_4NH_2$	qNH^- $XC_6H_4NH^-$	ΣqH $XC_6H_4NH_2$	qNH^- $XC_6H_4NH^-$
p-Me	0.2287	-0.4417	0.3622	-0.4556	0.0584	-0.4560
p-NH₂	0.2209	-0.4410	0.3460	-0.4591	0.0549	-0.4590
p-t-Bu	0.2287	-0.4387	0.3620	-0.4527	0.0587	-0.4515
p-OMe	0.2300	-0.4391	0.3527	-0.4482	0.0565	-0.4460
p-F	0.2339	-0.4382	0.3690	-0.4503	0.0631	-0.4452
p-Br	0.2399	-0.4289	0.3827	-0.4358	0.0652	-0.4338
p-COOEt	0.2448	-0.3949	0.4018	-0.4003	0.0683	-0.3770
p-CF₃	0.2596	-0.4034	0.4054	-0.4167	0.0727	-0.3936
p-COOH	0.2444	-0.3957	0.4088	-0.3995	0.0709	-0.3749
p-CN	0.2493	-0.4058	0.3992	-0.4123	0.0703	-0.3856
p-CHO	0.2482	-0.3985	0.4017	-0.4028	0.0688	-0.3817
p-NO₂	0.2710	-0.3688	0.4357	-0.3775	0.0810	-0.332
H	0.2279	-0.4553	0.3650	-0.4630	0.0598	-0.4640
m-NH₂	0.2311	-0.4504	0.3660	-0.4602	0.0613	-0.4592
m-Me	0.2260	-0.4542	0.3624	-0.4623	0.0595	-0.4630
m-OH	0.2359	-0.4511	0.3764	-0.4561	0.0638	-0.4580
m-OMe	0.2333	-0.4448	0.3729	-0.4551	0.0618	-0.4542
m-F	0.2412	-0.4389	0.3824	-0.4475	0.0668	-0.4417
m-CHO	0.2347	-0.4398	0.3767	-0.4464	0.0652	-0.4413
m-CF₃	0.2432	-0.4299	0.3853	-0.4397	0.0692	-0.4297
m-CN	0.2382	-0.4362	0.3812	-0.4430	0.0683	-0.4301
m-NO₂	0.2532	-0.4200	0.3950	-0.4298	0.0722	-0.4196

those of the *para* derivatives. For example, the AM1 calculated ρ value for the acidities of *para*-substituted phenols is 16.62, whereas that of the *meta* substituents is 20.21 (entry 3 vs. 4 in Table V). This distinction may be rationalized as being due to stronger interactions of *para* substituents than those of *meta* substituents with O^- in phenoxide or NH^- in anilide. Also, it should be added that the correlation analysis for the acidities of the combined *para* and *meta* substituted phenols and anilines (where σ^- values were used for *para* substituents and σ values for *meta* substituents) were found to be nearly equal to those for the separated *meta* and *para* compounds. For example, the AM1 regression coefficient (r) for the acidities of the combined *para*

and *meta*-substituted phenols is 0.946, whereas for the separated *para*-phenols it is 0.950. These results suggest that the original σ_m constants may be used for correlation of *meta*-substituted anions.

Examination of Tables I–IV indicates a few systematic deviations which become pronounced and whose significance may be understood. For example, the usually stated explanation of the effect of substituents on the acidities of substituted phenols and anilines is fundamentally valid. Electron-donating groups (e.g., NH_2, CH_3) are acid weakening, whereas electron-withdrawing groups (e.g., NO_2, CN) are acid strengthening. This is not surprising since the interaction of O^- and ^-NH with the ring is through the π system.

Table V. Correlation of acidity constants calculated from the equation $\delta\Delta H_f^\circ = \rho_{calc}\sigma^- + C$.

Entry	Process	Substituent[a] Position	Method	ρ_{calc}	C	n[c]	r[d]
1	1a	para	MNDO	15.36 ± 1.79	5.06 ± 3.16	13	0.932
2	1a	meta	MNDO	20.10 ± 2.71	1.48 ± 2.30	10	0.964
3	1a	para	AM1	16.62 ± 1.64	3.73 ± 2.89	13	0.950
4	1a	meta	AM1	20.21 ± 1.97	1.10 ± 1.68	10	0.964
5	1a	para	PM3	16.25 ± 1.62	3.40 ± 2.85	13	0.949
6	1a	meta	PM3	19.63 ± 1.88	1.00 ± 1.60	10	0.965
7	1b	para	MNDO	15.49 ± 1.80	5.17 ± 3.17	13	0.933
8	1b	meta	MNDO	18.37 ± 2.37	1.78 ± 2.02	10	0.939
9	1b	para	AM1	16.92 ± 1.52	3.86 ± 2.68	13	0.958
10	1b	meta	AM1	20.20 ± 1.99	2.25 ± 1.70	10	0.963
11	1b	para	PM3	16.37 ± 1.58	3.31 ± 2.79	13	0.952
12	1b	meta	PM3	19.16 ± 1.81	1.04 ± 1.54	10	0.966
13[b]	3	p and m[b]	MNDO	10.57 ± 1.66	2.81 ± 2.34	16	0.862
14[b]	3	p and m[b]	PM3	10.99 ± 1.11	1.79 ± 1.56	16	0.936

[a] σ_p^- values were used for acidity correlation of para substituted acids and σ_m for those of the meta derivatives.
[b] Correlations were done with Taft constants (σ°). [c] Number of substituents correlated. [d] Value of correlation coefficient.

Table VI. Correlation of atomic charges on the acidic hydrogens of substituted phenols, anilines, and benzoic acids and on the anionic hetroatoms of the corresponding anions calculated from the equations $qH = \rho_{calc}\sigma + C$ and $qy^a = \rho_{calc}\sigma^- + C$, respectively.

Entry	System	Charge Atom	Substituent Position	Method	ρ_{calc}[b]	C[b]	n[c]	r[d]
1	phenol	qH	p and m	MNDO	0.87 ± 0.09	19.46 ± 0.16	22	0.898
2	phenol	qH	p and m	AM1	0.92 ± 0.08	21.88 ± 0.13	22	0.937
3	phenol	qH	p and m	PM3	0.71 ± 0.07	19.74 ± 0.12	22	0.915
4	phenoxide	qO⁻	para	MNDO	4.36 ± 0.41	-51.28 ± 7.29	13	0.954
5	phenoxide	qO⁻	meta	MNDO	4.19 ± 0.65	-52.39 ± 5.56	10	0.915
6	phenoxide	qO⁻	para	AM1	4.88 ± 0.45	-51.96 ± 7.96	13	0.956
7	phenoxide	qO⁻	meta	AM1	4.05 ± 0.54	-52.81 ± 4.64	10	0.935
8	phenoxide	qO⁻	para	PM3	5.27 ± 0.44	-56.03 ± 7.77	13	0.964
9	phenoxide	qO⁻	meta	PM3	3.99 ± 0.43	56.78 ± 3.63	10	0.957
10	aniline	ΣqH	p and m	MNDO	2.82 ± 0.36	23.33 ± 0.60	22	0.883
11	aniline	ΣqH	p and m	AM1	5.16 ± 0.59	37.04 ± 1.00	22	0.890
12	aniline	ΣqH	p and m	PM3	1.60 ± 0.13	5.16 ± 0.59	22	0.938
13	anilide	qNH⁻	para	MNDO	2.42 ± 0.37	23.21 ± 0.62	12	0.901
14	anilide	qNH⁻	meta	MNDO	2.47 ± 0.48	23.05 ± 0.41	10	0.875
15	anilide	qNH⁻	para	AM1	4.77 ± 0.47	36.74 ± 0.79	12	0.954
16	anilide	qNH⁻	meta	AM1	3.35 ± 0.45	36.82 ± 0.38	10	0.935
17	anilide	qNH⁻	para	PM3	1.33 ± 0.17	6.06 ± 0.28	12	0.928
18	anilide	qNH⁻	meta	PM3	1.43 ± 0.17	6.13 ± 0.14	10	0.947
19	benzoate	ΣqO⁻	p and m	MNDO	2.80 ± 0.30	-117.40 ± 0.43	16	0.926
20	benzoate	ΣqO⁻	p and m	PM3	3.11 ± 0.28	-123.29 ± 0.39	16	0.949

[a] y is O⁻ or NH⁻. [b] The real numbers are 100 times smaller. [c] See Table V, note C. [d] See Table V, note d.

Thus, interactions which tend to enhance π donation to the ring are likely to be favorable and vice versa. This conclusion is also confirmed by the net atomic charges listed in Tables II and IV which show that π donation by O⁻ in phenoxide and HN⁻ in anilide increases considerably with nitro or cyano substituents, in particular at the *para* positions. For example, the charge on the oxygen of p-nitrophenolate is −0.4541 calculated by the AM1 method, whereas that of phenolate anion is −0.5327 (Table II).

The results listed in Table VI (entries 1–18) show that the electronic charges on the acidic hydrogens and on the anionic heteroatoms are a good index for the electronic effect of substitu-ents on aqueous and gas phase acidities of phenol and aniline systems. Moreover, the comparison of the energy differences ($\delta\Delta H_f^\circ$) for processes 1a and 1b (Tables I and III) with those obtained for processes 2a and 2b indicates well the decomposition of the substituent effect into the effect on the neutral molecule and the appropriate anionic species. Interaction energies ($\delta\Delta H_f^\circ$) over 25 kcal/mol are obtained for electron-withdrawing substituents in phenoxide and anilide systems (see $\delta\Delta H_f^\circ$ of p-NO₂ substituents, Tables I and III), whereas for the neutral (processes 2a and 2b) the values are generally under 6 kcal/mol.[26] These results indicate quite clearly that such interactions in substituted phenoxide
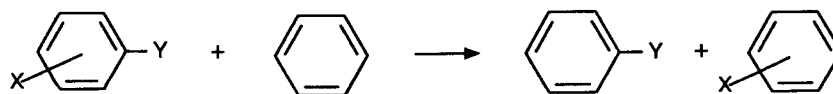
Process 2a; Y = OH
Process 2b; Y = NH₂

and anilide anions are dominant. In other words, p-NO_2 and p-CN substituted phenols are strong acids because the corresponding anions are relatively stable.
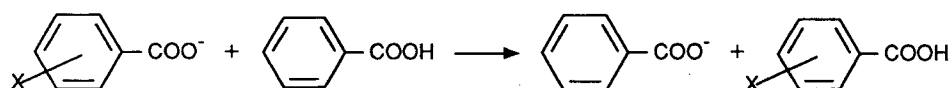
In order to establish further credence to the reliability of this computational study, the calculated differential energies for processes 1a and 1b were compared with gas phase experimental values and STO-3G calculated values.[23] The comparison of the results (entries 1–12 in Table VII) shows a good agreement among the semiempirical, experimental, and *ab initio* methods. However, the quality of the MNDO correlation coefficient is found to be much poorer than those of AM1 and PM3. Also, it should be added that ρ values obtained from correlations of experimental and semiempirical data (see entries 1–3 and 7–9 in Table VII) are close to unity. This indicates that variations in the free energy difference for gas phase acidity are strongly dependent on the enthalpy changes. This is in accordance with recent studies which indicate that entropy changes in gas phase dissociation reactions are small.[3b]

Comparison of interaction energies ($\delta \Delta H_f^\circ$) in phenoxides with those of anilides shows them to be almost identical (see entries 1–6 vs. 7–12 in Table V). Based on the relative π electron donation powers of NH^- and O^- groups, it might have been expected that a NH^- group would interact more strongly with a series of substituents than an O^- group, and hence to lead to larger interaction energies. It seems that the reason for this unexpected result stems from a large negative charge associated with O^- and NH^- in the gas phase. This constitutes a sufficiently large perturbation to these groups so as to reduce significantly any intrinsic differences between them.[23]

It is noteworthy that the difference between the gas phase calculated ρ values for the acidity of phenols and anilines (16 to 20 in the phenol system) and the solution acidity values (ρ = 2 to 5 in the phenol system) is likely the result of solvent participation.

Gas Phase Acidities of Substituted Benzoic Acids

Recently, some theoretical analyses of electron effects on the acidities of benzoic acids have been made. Bohm and Kuthan computed properties of some benzoic acids using the STO-3G basis set of diffuse functions for all oxygen atomic centers of the probe groups ($COOH$ and $CO\overline{O}$).[27] They found a good correlation of the gas phase acidities of substituted benzoic acids with the energy differences for isodesmic process 3.[27] Gilliom and co-workers studied the acidities of benzoic acid systems by the MNDO semiempirical method.[17] They found a reasonable correlation of σ° constants with both the net charge on the anionic oxygen of benzoate anion and the reciprocal of the energy of the HOMO. However, their attempts to find correlations with the energy differences for process 3 ($\delta \Delta H_f^\circ$) failed.[17] The recent study of Sotomatsu and co-workers shows that good correlation of σ could be obtained with AM1 calculated net atomic charges of the acid moiety of substituted benzoic acids. However, their attempts to correlate 6 constants with either the energy differences for process 3 and E (HOMO) for the anions or the neutral acids failed to give any notable correlations.[18]

Process 3

Table VII. Correlation of isodesmic energy differences ($\delta \Delta H_f^\circ$) for processes 1a, 1b, and 3 calculated by MNDO, AM1, and PM3 with those of experimental ($\delta \Delta G^\circ$) and *ab initio* ($\delta \Delta E^\circ$) methods as obtained from the equation $\delta \Delta H_f^\circ = \rho_{calc} \delta \Delta G^\circ (\delta \Delta E^\circ) + C$.

Entry	Process	Method	Data for Comparison	ρ_{calc}	C	n*	r*
1	1a	MNDO	$(\delta\Delta G^\circ)_{1a}$	1.02 ± 0.10	-1.93 ± 3.04	16	0.938
2	1a	AM1	$(\delta\Delta G^\circ)_{1a}$	1.05 ± 0.07	-1.01 ± 2.18	16	0.969
3	1a	PM3	$(\delta\Delta G^\circ)_{1a}$	1.04 ± 0.07	-1.04 ± 2.03	16	0.972
4	1a	MNDO	$(\delta\Delta E^\circ)_{1a}$	1.08 ± 0.12	-2.65 ± 3.85	18	0.917
5	1a	AM1	$(\delta\Delta E^\circ)_{1a}$	1.12 ± 0.09	-1.80 ± 2.97	18	0.954
6	1a	PM3	$(\delta\Delta E^\circ)_{1a}$	1.14 ± 0.08	-1.87 ± 2.69	18	0.960
7	1b	MNDO	$(\delta\Delta G^\circ)_{1b}$	1.35 ± 0.18	3.14 ± 2.27	8	0.949
8	1b	AM1	$(\delta\Delta G^\circ)_{1b}$	1.23 ± 0.14	2.10 ± 1.70	8	0.965
9	1b	PM3	$(\delta\Delta G^\circ)_{1b}$	1.22 ± 0.12	1.84 ± 1.47	8	0.973
10	1b	MNDO	$(\delta\Delta E^\circ)_{1b}$	0.81 ± 0.09	3.71 ± 3.26	18	0.914
11	1b	AM1	$(\delta\Delta E^\circ)_{1b}$	0.85 ± 0.07	2.67 ± 2.54	18	0.950
12	1b	PM3	$(\delta\Delta E^\circ)_{1b}$	0.85 ± 0.06	2.20 ± 2.25	18	0.961
13	3	MNDO	$(\delta\Delta G^\circ)_{3}$	0.95 ± 0.14	-1.30 ± 2.39	15	0.877
14	3	PM3	$(\delta\Delta G^\circ)_{3}$	1.07 ± 0.09	-0.91 ± 1.53	15	0.951

* See Table V, note c. ᵇ See Table V, note d.

Table VIII. Computed properties for substituted benzoic acids and benzoate anions.

Substituent X	MNDO					PM3						
	$\Delta H_f^°$ XC₆H₄COOH	$\Delta H_f^°$ XC₆H₄COO⁻	$(\delta\Delta H_f^°)^3$	qH	ΣqO^-	$\Delta H_f^°$ XC₆H₄COOH	$\Delta H_f^°$ XC₆H₄COO⁻	$(\delta\Delta H_f^°)^3$	qH	ΣqO^-	$(\delta\Delta G^°)^b$	$\sigma^{°c}$
p-NH₂	-67.51	-81.5	-0.31	0.2011	-1.1793	-69.17	-91.5	-1.17	0.1964	-1.2380	-2.3	-0.38
p-OMe	-104.2	-123.0	4.49	0.2022	-1.1738	-103.4	-127.9	0.95	0.1960	-1.2381	-0.7	-0.16
m-NH₂	-66.9	-81.9	0.59	0.2137	-1.1770	-68.1	-91.8	0.21	0.2263	-1.2351	-1.5	-0.14
p-OH	-115.9	-130.4	0.20	0.2133	-1.1800	-110.6	-135.4	1.30	0.1974	-1.2382	-4.1	-0.13
p-Me	-72.4	-90.2	3.51	0.2023	-1.1769	-74.6	-98.8	0.68	0.1976	-1.2369	-1.1	-0.12
H	-67.6	-81.9	0	0.2143	-1.1804	-66.2	-89.7	0	0.2279	-1.2371	0	0
m-OH	-115.1	-131.3	1.85	0.2148	-1.1748	-109.3	-136.4	3.56	0.1961	-1.2321	1.3	0.04
m-OMe	-106.1	-120.9	0.43	0.2145	-1.1738	-103.7	-127.3	0.10	0.2271	-1.2303	0.5	0.06
p-F	-110.3	-132.1	7.45	0.2020	-1.1703	-107.9	-136.7	5.24	0.1974	-1.2286	2.9	0.17
p-Cl	-71.4	-94.1	8.28	0.2036	-1.1655	-71.2	-99.2	4.51	0.1978	-1.2274	4.4	0.27
m-F	-113.1	-132.0	4.59	0.2172	-1.1667	-108.8	-136.4	4.05	0.2295	-1.2242	3.8	0.35
m-Cl	-74.5	-93.6	4.72	0.2168	-1.1645	-72.3	-99.0	3.12	0.2291	-1.2252	4.7	0.37
m-CN	-35.9	-56.8	6.57	0.2180	-1.1621	-30.0	-61.0	7.44	0.2322	-1.2169	10.2	0.62
p-CN	-32.4	-57.7	10.85	0.2039	-1.1592	-28.3	-61.4	9.62	0.1984	-1.2150	10.9	0.69
m-NO₂	-49.2	-76.6	13.04	0.2211	-1.1469	-73.4	-107.9	10.96	0.2345	-1.2061	9.6	0.70
p-NO₂	-51.0	-77.5	12.12	0.2208	-1.1449	-72.9	-109.3	12.88	0.2333	-1.9993	11.7	0.82

* Calculated from $\delta\Delta H_f^° = \Delta H_f^°$ (RCOO⁻) $-\Delta H_f^°$ (RCOOH) $+ \Delta H_f^°$ (X-RCOOH) $-\Delta H_f^°$ (X-RCOO⁻). ᵇ Experimental data taken from ref. 3b.
ᶜ Taken from ref. 28.

Continuing our investigation to find a semiempirical method which might be practically equal to *ab initio* methods in predicting gas phase acidities, we also studied the acidities of some substituted benzoic acids by using the PM3 and MNDO methods with full optimization. Our choice to reinvestigate the MNDO study was based on the fact that optimization constraints used in the MNDO study by Gilliom[17] could affect the accuracy of the calculations.

The results of this study are summarized in Table VIII which lists the heats of formation of benzoic acids, $\Delta H_f^° XC_6H_4COOH$, and of the corresponding anions, $\Delta H_f^° XC_6H_4COO^-$, the calculated energy differences for process 3 ($\delta \Delta H_f^°$) and the gas phase experimental energies ($\delta \Delta G^°)_3$ as well as the net atomic charges on the acidic hydrogens of benzoic acids and the total charges on the anionic oxygens ($\Sigma q O^-$) of the corresponding anions.

The results given in Table VIII were examined for linear relationships with σ and with $\sigma^°$.[28] The correlation results are summarized in Tables V (entries 13, 14), VI (entries 19, 20), and VII (entries 13, 14). Unexpectedly, correlation using Taft sigma constants ($\sigma^°$) were found to be superior to those obtained using the original sigma values (σ). For example, the r coefficient for the correlation of PM3 calculated energy differences ($\delta \Delta H_f^°)_3$ with $\sigma^°$ is 0.925, whereas that with σ is only 0.864. This distinction may be understood on the basis of the decreased importance of charge-separated resonance structures in the gas phase relative to those in solution.[3b] Moreover, the results depicted in Tables V and VI (the last two entries in each) indicate that correlations of PM3 calculated properties (Σq^- and ($\delta \Delta H_f^°)_3$) with $\sigma^°$ have much better quality than those of MNDO.[29] Similarly, correlation of PM3 calculated energy differences ($\delta \Delta H_f^°$) with gas phase experimental energies ($\delta \Delta G^°)^{3b}$ for process 3 were found to be much better than those derived from the MNDO method.[30] Also, it should be added, that the ρ values obtained from these correlations are close to unity.[31] This indicates that acidity of benzoic acids is controlled by enthalpy changes and that the entropy changes are almost negligible, similar to that observed in phenol and aniline systems. Attempts to correlate MNDO and PM3 calculated net atomic charges on the hydrogens of benzoic acids (qH) with either $\sigma^°$ or σ failed (r squared values obtained from the regression outputs are less than 0.3).

It is also interesting to note that the differences between the ρ_{calc} values for acidities of benzoic acids (ca. 10) and the ρ values obtained from solution (ca. 1) likely stem from solvent participation in the dissociation reactions in solvent.

Comparison between the calculated ρ values of the acidities of phenols and anilines on the one hand, and that of benzoic acids, on the other (entries 1–12 vs. 13, 14 in Table V), indicates that the intrinsic substituent effects in the first two systems are higher than those of the latter. The greater power of the substituents on the phenols and anilines to affect acidity might be connected with the fact that in the phenolate and anilide anions there is a more effective resonance interaction with the ring than for the benzoate.[3b]

CONCLUSIONS

The following salient points emerge from this work: (1) The semiempirical methods, in particular, AM1 and PM3, are as good as the much more expensive *ab initio* method for accommodating quantitatively the intrinsic effects of substituents on the acidity of a variety of systems.[32] (2) The AM1 and PM3 methods are much better than the MNDO method in predicting energies and charges for anionic species. (3) The three semiempirical methods used in this study can also be used for distinguishing solvation effects of a wide variety

of aromatic systems which are difficult to deal with by the *ab initio* method.

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29. Our MNDO-calculated energy differences $(\delta \Delta H_f^\circ)_3$ were found to correlate much better with σ° than did those of Gilliom (reference 17).
30. The p-OH derivative was excluded from the correlation analysis, because this compound seems to ionize at the phenolic group in the gas phase.[3b]
31. A similar result was found from correlation of gas phase experimental data and STO-3G calculated data; see reference 27.
32. One referee noted that it has been shown [J. M. L. Martin, J. P. François, and R. Gijbels, *J. Comp. Chem.*, **10**, 346 (1989)] "that basis sets of at least double zeta quality are required for a good quantitative description of proton affinities, which is then markedly superior to that obtained with semiempirical methods, albeit at an increased computational cost." We thank the referee for pointing this out.