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Background of the Hammett Equation As Observed for Isolated Molecules: Meta- and Para-Substituted Benzoic Acids

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Fundamental model compounds for the Hammett equation, meta- and para-substituted benzoic acids, were investigated by the density functional theory at the B3LYP/6-311+G(d,p) level. Energies of 25 acids and of their anions were calculated in all possible conformations and from them the energies of the assumed mixture of conformers. Relative acidities correlated with the experimental gas-phase acidities almost within the experimental uncertainty, much more precisely than in the case of previous calculations at lower levels. Dissection of the substituent effects into those operating in the acid molecule and in the anion was carried out by means of isodesmic reactions starting from monosubstituted benzenes. Both effects are cooperating in the resulting effect on the acidity; those in the acid molecule are smaller but not negligible. They are also responsible for some deviations from the Hammett equation (through-resonance of para donor substituents) and for the weaker resonance in the acid molecule in meta derivatives; in the anions the inductive and resonance effects are almost equal. On the other hand, the cooperation of effects in the acid and in the anion makes the relative acidity more sensitive to electron withdrawing and is probably one of the reasons why the Hammett equation is so generally valid.

Introduction

The main merit of the Hammett equation,

$$\log K_{i,X} - \log K_i^\circ = \rho_i \sigma_X \qquad (1)$$

is in its general validity within a given range for practically all substituents (subscript X), and for most reaction series well-defined (subscript *i*).[1] Successful applications are numberless and reported failings very scarce.[2] This broad success focused attention on the meta and para derivatives of benzene, particularly of benzoic acids as a reference standard. For this reason also quantum chemical calculations on these compounds were started early with different intentions. An important question was whether the linear form of eq 1 can be deduced even from low-level calculations. This was achieved[3] from the linear dependence of log $K_{i,X}$ calculated for two reaction series and for variable substituents X at the CNDO level; for para substituents even HMO was sufficient. It was suggested that empirical simplifications made in deriving eq 1 are similar in character as the simplifications involved in the low-level quantum chemical calculations. Similar conclusions would follow from earlier correlations of different quantum chemical indices in one reaction series.[4]

Most effort has been directed toward possible calculations of the substituent constants σ from quantum chemical indices. The most suitable reaction appears to be dissociation of substituted benzoic acids, which was also chosen[1] for the definition[5] of constants σ, primarily from the p*K* values in water.[5a] Most efficient and most straightforward was calculation of the relative acidity, i.e., of reaction energy of the isodesmic reaction, eq 2.

$$X{-}C_6H_4COOH + C_6H_5COO^- \rightleftharpoons X{-}C_6H_4COO^- + C_6H_5COOH \qquad (2)$$

These attempts were reasonably successful with AM1[6] or with an augmented STO-3G basis;[7] the real possibility of obtaining the σ constants by calculation was thus achieved. Less convincing results were based on charges[8] instead of on energies or using other model molecules than benzoic acids,[8c] sometimes even monosubstituted

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(1) (a) Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970; Chapters 11.9−11.16. (b) Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988; Chapter 2.3.

(2) For instance Waisser, K.; Palát, K., Jr.; Exner, O. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1295−1306 and the literature cited therein.

(3) Exner, O.; Ondrejičková, D.; Leška, J. *Org. Reactivity (Tartu)* **1979**, *16*, 285−295.

(4) (a) Koutecký, J.; Zahradník, R.; Čížek, J. *Trans. Faraday Soc.* **1961**, *57*, 169−182. (b) Kuthan, J.; Danihel, I.; Skála, V. *Collect. Czech. Chem. Commun.* **1978**, *43*, 447−462.

(5) (a) Shorter, J. *Pure Appl. Chem.* **1994**, *66*, 2451−2468. (b) Shorter, J. *Pure Appl. Chem.* **1997**, *69*, 2497−2510. (c) Hansch, C.; Leo, A.; Taft R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(6) Sotomatsu, T.; Murata, Y.; Fujita, T. *J. Comput. Chem.* **1989**, *10*, 94−98.

(7) Böhm, S.; Kuthan, J. *Int. J. Quantum Chem.* **1984**, *26*, 21−33.

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benzenes.[9,10] Most of these studies were carried out at lower computational levels: MNDO,[8a] AM1,[6,8b,c,9] augmented STO-3G,[7] and RHF/6-31G*(5D).[10]

In this paper, we focused attention on the energies of substituted benzoic acids and their anions. When applying the density functional theory (DFT) at the B3LYP/6-311+G(d,p) level, we hoped to obtain more accurate values than in previous work.[6−8] The main improvement should be dissection of the substituent effect into those operating in the neutral acid molecule and in its anion. This principle[11] has been applied by us systematically, e.g., to the steric effects in ortho-substituted benzoic acids,[12] anilines,[13] benzonitriles,[14] and pyridines,[15] to the inductive effect in various systems[16] and to resonance[17] and hyperconjugation.[18] Up to now, the acidity of benzoic acids has been treated as a property localized at the COOH group, while it is a difference of two effects which need not be proportional. In our case, the substituent effect in the acid molecule is represented by the isodesmic reaction, eq 3, and the effect in the anion by eq 4. These equations are not only isodesmic but also homodesmotic.[19]

$$X{-}C_6H_5 + C_6H_5COOH \rightleftharpoons X{-}C_6H_4COOH + C_6H_6 \quad (3)$$

$$X{-}C_6H_5 + C_6H_5COO^- \rightleftharpoons X{-}C_6H_4COO^- + C_6H_6 \quad (4)$$

The reaction enthalpies of eqs 3 and 4, denoted $\Delta_3H°$ and $\Delta_4H°$, respectively, are accessible experimentally: $\Delta_3H°$ from the enthalpies of formation $\Delta_fH°$(g) and $\Delta_4H°$ by combination with the gas-phase acidities $\Delta_2H°$(g), pertinent to eq 2. In this paper, we used DFT[20] and calculated the reaction energies Δ_3E and Δ_4E for substituted benzoic acids **1**−**25** with 12 common substituents X (Table 1) in the meta and para positions; Δ_2E was obtained as their difference.

Results and Discussion

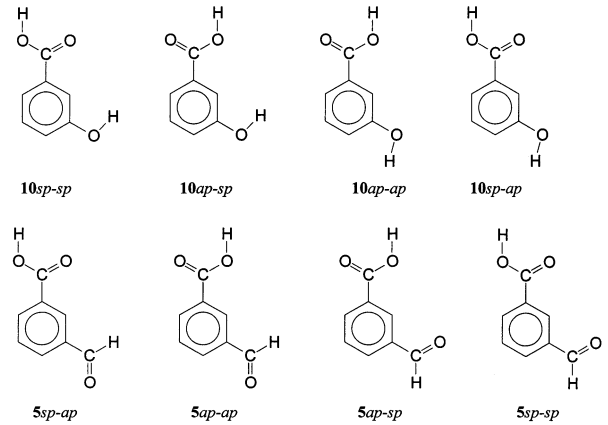
Conformation. We endeavored to calculate separately the energies of all possible conformations, although their effect on the final results was rather small. Axially unsymmetrical substituents were mostly coplanar with the benzene ring; in these cases, we calculated energies of all combinations of planar positions (see for instance the conformations of 3-hydroxybenzoic acid **10** or 3-formylbenzoic acid **5** in Scheme 1). All conformers are listed in Table S1 and all were used to calculate $\Delta_3E°$ and $\Delta_4E°$.

TABLE 1. Calculated Substituent Effects in Substituted Benzoic Acids[a]

no.	substituent	Δ_2E[b]	expl[c] $\Delta_2G°$	Δ_3E[b]	expl[b,d] $\Delta_3H°$	Δ_4E[b]	$\sigma_{m,p}$[e]
1	H	0	0	0	0	0	0
2	3-CH_3	3.39	2.9	−0.73	0.1	2.66	−0.06
3	3-CH_2Cl	−18.30	−13.3[f]	2.19	−2.4	−16.11	0.09
4	3-CF_3	−32.96	−30.5[f]	5.40		−27.56	0.44
5	3-CHO	−34.53		4.24		−30.29	
6	3-$COOCH_3$	−19.35		3.66		−15.69	0.33
7	3-CN	−43.76	−42.7	6.81		−36.95	0.62
8	3-NH_2	6.53	6.3	−1.04	7.6	5.49	0.00
9	3-NO_2	−48.04	−40.2	7.80		−40.24	0.73
10	3-OH	−8.69[g]	−5.4	0.51		−8.18	0.10
11	3-OCH_3	−3.15	−2.1	−0.53	0.0	−3.68	0.11
12	3-F	−18.58[g]	−15.9	3.73		−14.85	0.34
13	3-Cl	−22.85	−19.7	4.13	−18.5	−18.72	0.37
14	4-CH_3	5.51	4.6	−2.47		3.04	−0.16
15	4-CH_2Cl	−18.30	−15.4[f]	1.82		−16.48	0.12
16	4-CF_3	−35.95	−32.2[f]	6.01		−29.94	0.53
17	4-CHO	−36.17	−30.1[f]	6.17		−30.00	
18	4-$COOCH_3$	−22.75		4.33		−18.42	0.45
19	4-CN	−46.72	−45.6	6.58		−40.14	0.67
20	4-NH_2	18.52	9.6	−10.29	−5.5	8.23	−0.62
21	4-NO_2	−54.49	−49.0	8.61		−45.88	0.78
22	4-OH	4.40[h]	−17.2[h]	−5.43		−1.03	−0.36
23	4-OCH_3	8.57	2.9	−6.15	−5.8	2.42	−0.29
24	4-F	−13.60[g]	−12.1	0.02	0.5	−13.58	0.05
25	4-Cl	−19.73	−18.4	1.35	−16.2	−18.38	0.22

[a] Energies in kJ mol^{-1}, 298 K. [b] Subscript at Δ corresponds to the number of the isodesmic equation. [c] Reference 23. [d] Calculated as a sum of the enthalpies of formation taken for benzoic acids from a critical review (ref 31a), for monosubstituted benzenes from standard tables (ref 31b,c). [e] Values selected by Shorter from p*K* of benzoic acids in water (ref 5a) in the case of the substituent 4-CF_3 in aqueous ethanol (ref 5b). [f] Reference 24. [g] From the sum of electronic and thermal enthalpies, Δ*H*°(298), one obtains the values −8.28, −18.38, and −13.17 kJ mol^{-1} for the substituents 3-OH, 3-, and 4-F, respectively. [h] When 4-hydroxybenzoic acid is considered as a substituted phenol, its calculated Δ_5E according to eq 5 is −65.18, and its experimental $\Delta_5G°$ (ref 23) is −61.09 kJ mol^{-1}.

SCHEME 1. Conformers of 3-Hydroxybenzoic Acid 10 and 3-Formylbenzoic Acid 5 in the Sequence of Increasing Energy



(8) (a) Gilliom, R. D.; Beck, J.-P.; Purcell, W. P. *J. Comput. Chem.* **1985**, *6*, 437−440. (b) Kim, K. H.; Martin, Y. C. *J. Org. Chem.* **1991**, *56*, 2723−2729. (c) Ertl, P. *Quant. Struct.-Act. Relat.* **1997**, *16*, 377−382.
(9) Monaco, R. R.; Gardiner, W. C. *J. Phys. Org. Chem.* **1995**, *8*, 629−636.
(10) Krygowski, T. M.; Woźniak, K.; Bock, C. W.; George, P. *J. Chem. Research (S)* **1989**, 396−397.
(11) (a) Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1980**, *45*, 818−826. (b) Exner, O. *Org. Reactivity (Tartu)* **1995**, *29*, 1−6.
(12) (a) Exner, O. *J. Org. Chem.* **1988**, *53*, 1810−1812. (b) Decouzon, M.; Ertl, P.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Am. Chem. Soc.* **1993**, *115*, 12071−12078. (c) Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Böhm, S.; Jiménez, P.; Roux, M. V.; Exner, O. *New J. Chem.* **1997**, *21*, 561−573. (d) Fiedler, P.; Kulhánek, J.; Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Exner, O. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1433−1447. (e) Kulhánek, J.; Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Fiedler, P.; Jiménez, P.; Roux, M.-V.; Exner, O. *Eur. J. Org. Chem.* **1999**, *1589*, 9−1594.
(13) Böhm, S.; Decouzon, M.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Org. Chem.* **1994**, *59*, 8127−8131.
(14) Exner, O.; Böhm, S.; Decouzon, M.; Gal, J.-F.; Maria, P.-C. *J. Chem. Soc., Perkin Trans. 2* **2002**, 168−172.
(15) Roithová, J.; Exner, O. *J. Phys. Org. Chem.* **2001**, *14*, 752−758.
(16) Exner, O.; Nauš, P. *J. Phys. Org. Chem.* **2000**, *13*, 693−698.
(17) Exner, O.; Böhm, S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1994−1999.
(18) Exner, O.; Böhm, S. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1235−1240.
(19) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1222−1227.
(20) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

As usual, the population of conformers was estimated from the energy difference instead of the difference of Gibbs energy. From this population, the effective energies were calculated by the additivity principle. The difference against the minimum-energy conformer was usually small. It is negligible in the two limiting cases: when the energy difference is either low or high. As we pointed out,[21] the maximum correction possible in the case of two conformers is 0.63 kJ mol^{-1}; in the case of four conformers (unsymmetrical meta derivatives as **10**) it may be greater: the maximum value among our data was 1.15 kJ mol^{-1} (for 3-OCH_3). In the values of $\Delta_2E°$, the corrections still partly cancel. All values of $\Delta_2E°$, $\Delta_3E°$, and $\Delta_4E°$ in Table 1 relate to the assumed equilibrium of conformers.

Concerning the relative stability of conformations, some regularity can be observed. When a meta substituent bears a hydrogen atom, the *sp*-position toward the carbonyl oxygen is preferred, as observed with the substituents NH_2, CH_3, OH, CHO, and OCH_3 when oriented with H (or CH_3) toward =O (see the most stable forms of **5** and **10** in Scheme 1). When a meta substituent bears lone electron pairs, the reversed orientation, toward the OH group, is preferred. This is the case with substituents F, Cl, CN, and NO_2 and also with OH and OCH_3 when they are oriented with H or CH_3 opposite to the carboxyl (**10***ap*−*ap* more stable than **10***sp*−*ap*). Similarly, the substituents CHO and $COOCH_3$, when oriented with =O toward the carboxyl, prefer the orientation toward the OH group (**5***ap*−*sp* more stable than **5***sp*−*sp*). The conformations of para isomers are governed by the same rules, but the energy differences are smaller.[22]

Comparison with Experimental Results. For the main purpose of this work, comparison with the relative gas-phase acidities is most important, i.e., in terms of the isodesmic reaction, eq 2. The experimental gas-phase acidities of benzoic acids were obtained mostly by pulsed electron beam high-pressure mass spectrometry,[23] and several data also by Fourier transform ion cyclotron resonance.[24] Results of both methods are considered to be compatible.[25] A plot of the calculated Δ_2E vs the experimental Gibbs energies $\Delta_3G°$ (Figure 1) reveals first of all a great deviation of the substituent 4-OH. An evident explanation was already suggested[23] that it is the phenolic hydrogen which dissociates: 4-hydroxybenzoic acid **22** behaves as a substituted phenol and its relative acidity is expressed by an isodesmic reaction, eq 5.

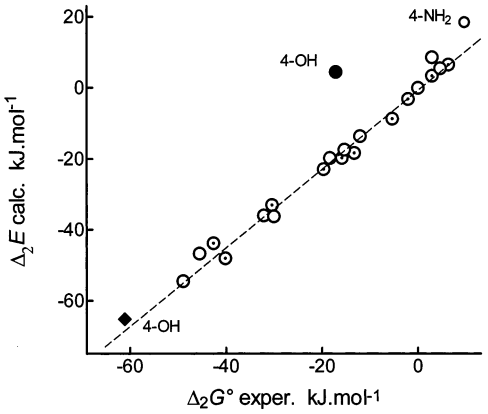


FIGURE 1. Calculated relative acidities Δ_2E of 3- and 4-substituted benzoic acids plotted vs the experimental gas-phase acidities, $\Delta_2G°$ (ref 23, 24): para derivatives, ○; meta derivatives, ⊙; points ● and ◆ correspond to the anion of 4-hydroxybenzoic acid calculated as 4-hydroxybenzoate or 4-carboxyphenolate (eq 5), respectively.

$$4\text{-}HOC_6H_4COOH + C_6H_5O^- \rightleftharpoons 4\text{-}^-OC_6H_4COOH + C_6H_5OH \quad (5)$$

This explanation was later questioned on the basis of MNDO and STO-3G calculations,[26] but it is now confirmed (in our opinion definitely) by our higher level calculations of the anions 4-$HOC_6H_4COO^-$ and 4-$^-OC_6H_4$-COOH (Table S1, footnote *c*).

Besides the compound **22**, some doubts could still arise about the NH_2 derivatives **8** and **20**, which can exist as zwitterions in solution. However, the zwitterions need not be taken into consideration in the case of isolated molecules: their calculated energies (Table S1) are raised by 250 or 280 kJ mol^{-1}, respectively.

The agreement of calculated Δ_5E and experimental $\Delta_5G°$ is apparently not very good (Table 1, footnote *h*), but one must take into account that these quantities are correlated with a slope slightly different from unity: Figure 1 gives a convincing picture. When the substituent 4-OH was eliminated, we obtained the correlation reported in Table 2, line 1. It may appear very good according to the correlation coefficient, but the standard deviation is still greater than the experimental uncertainty given,[23] 1.7 kJ mol^{-1}. We tested several possibilities how to improve the fit. When the substituent NH_2 is eliminated as an outlier (Table 2, line 1A), the improvement is statistically significant (at the level $\alpha = 0.01$) but not decisive. Further, we tried to improve the calculations. The sum of electronic and thermal enthalpies at 298 K, $\Delta H°(298)$, was calculated in two simple cases (substituents 3-F and 4-F) and in one case where the equilibrium of conformers was particularly complex (substituent 3-OH). The results (Table 1, footnote *g*) show that a significant improvement cannot be obtained in this way: the differences versus the values from ΔE are tenths of kJ mol^{-1}. Our previous experience with calculating this quantity was similar.[15,17,27] The last possible explanation—in our opinion rather probable—of the im-

(21) Exner, O.; Böhm, S. *Collect. Czech. Chem. Commun.* **2001**, *66*, 1623−1637.

(22) The regularities described must be understood as a kind of long-range interaction, although for instance an interaction between the H and =O atoms is very improbable when they are separated by an *o*-hydrogen. Evidently, the energy differences between these conformers are suitable quantities for pursuing such subtle effects: for the conformers of **5** and **10,** they account more than 3 kJ mol^{-1}. Even when hydrogen bonds are not possible, the polar character of interacting groups seems to be essential. Steric interaction of an alkyl group was observed at a similar distance only in the case of *tert*-butyl (ref 12e).

(23) McMahon, T. B.; Kebarle, P. *J. Am. Chem. Soc.* **1977**, *99*, 2222−2230.

(24) (a) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1−83. (b) Koppel, I. A.; Mishima, M.; Stock, L. M.; Taft, R. W.; Topsom, R. D. *J. Phys. Org. Chem.* **1993**, *6*, 685−689. (c) Decouzon, M.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Phys. Org. Chem.* **1994**, *7*, 615−624.

(25) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl 1.

(26) Böhm, S.; Kuthan, J. *Collect. Czech. Chem. Commun.* **1988**, *53*, 665−670.

(27) Böhm, S.; Exner, O. *New J. Chem.* **2001**, *25*, 250−254.

TABLE 2. Correlations of Calculated and Experimental Acidities of 3- and 4-Substituted Benzoic Acids

no.	response function	explanatory variables	b[a]	R[b]	SD,[b] kJ mol^{-1}	N[b]
1	Δ_2E, this work	$\Delta_2G°$(expl)[c]	1.13(3)	0.9911	2.89	21
1A	Δ_2E, this work	$\Delta_2G°$(expl)[c]	1.10(3)	0.9933	2.37	20[d]
2	Δ_2E, stat. corr.[e]	$\Delta_2G°$(expl)[c]	1.13(3)	0.9923	2.69	21
3	Δ_2E, single conf.[f]	$\Delta_2G°$(expl)[c]	1.14(3)	0.9916	2.80	21
4	Δ_2E, ref 7	$\Delta_2G°$(expl)[c]	0.88(5)	0.983	3.66	14
5	Δ_2E, ref 6	$\Delta_2G°$(expl)[c]	0.80(7)	0.949	5.59	16
6	$\Delta_2G°$(expl)[c]	$\sigma_{m,p}$ calcd, ref 8c	−49(5)	0.904	8.09	21
7	Δ_3E	Δ_4E	−0.191(12)	0.970	0.77	18[g]
8	Δ_3E meta	σ_I σ_R	12.0(13) 7.3(9)	0.971	0.77	13
9	Δ_3E para	σ_I σ_R	11.4(20) 20.5(14)	0.981	1.19	13
10	Δ_4E meta	σ_I σ_R	−59(7) −38(5)	0.970	3.94	13
11	Δ_4E para	σ_I σ_R	−63(7) −49(5)	0.977	4.10	13
12	Δ_2E para	Δ_2E meta	1.12(3)	0.9978	1.53	8[h]
13	Δ_3E para	Δ_3E meta	1.20(12)	0.972	0.96	8[h]
14	Δ_2E	$\sigma_{m,p}$	−71.1(34)	0.987	3.41	15[g]

[a] Regression coefficient, standard deviation given in parentheses. [b] Correlation coefficient, standard deviation from the regression and number of items, respectively. [c] Experimental gas-phase acidities from refs 23, 24. [d] Substituent 4-NH_2 eliminated as outlier; see Figure 1. [e] Calculated with a correction of RT ln 2 for all meta derivatives; see Discussion. [f] Calculated only from the energies of the minimum-energy conformations. [g] Restricted to acceptor para substituents plus all meta substituents. [h] Only substituents without a lone electron pair in the α-position.

perfect fit to the experimental values could be that the experimental uncertainty was somewhat underestimated:[23] see particularly the reversed position of the substituents 3-CN and 4-CN as compared to 3-NO_2 and 4-NO_2 (Figure 1, on the left).[28]

While we are unable to improve further the agreement of our calculated acidities with experiment, we can prove that this agreement is much better than in previous attempts carried out at lower levels: STO-3G with diffusion functions on the oxygen atoms[7] (Table 2, line 4), AM1 with calculating all conformations[6] (Table 2, line 5), or AM1 based on calculating atomic charges[8c] (Table 2, line 6). We conclude that the theoretical model used by us is able to predict the experimental acidities with sufficient accuracy, in any case much better than the original cautious estimate of Becke himself[20] (10 kJ mol^{-1}). The improvement is obviously to be attributed to the principle of isodesmic reactions.[30]At the present state of development, calculations of energies are evidently more effective than correlations based on calculated atomic charges[8] or individual orbital energies, even when the latter may be eventually good, for instance with the 1s orbital energy on the hydroxyl oxygen.[7]

A much less efficient test is possible for the values of Δ_3E. They can be compared to the reaction enthalpies $\Delta_3H°(298)$ obtained by summing the experimental enthalpies of formation,[31] $\Delta_fH°(298)$. The resulting values (Table 1, column 6) show irregular differences and agree badly with the calculations. This confirms our recent opinion[21] that, at the present state of experimental technique and the level of calculation, the experimental enthalpies of formation are less reliable than the calculated energies, at least for simple compounds as dealt with here. Further conclusions of this paper will be based on the calculated energies $\Delta_2E - \Delta_4E$, while it is taken as proven that these agree with the experiments practically within their uncertainty.

The Entropy Problem. One source of differences between calculated energies and experimental ΔG could be still in the reaction entropy. We have always assumed[32] that the reaction entropy of an isodesmic reaction is negligible except its symmetry component, $S°_{sym}$, which deserves a detailed analysis. Eberson pointed out that the observed pK values of meta-substituted benzoic acids should be lowered by log 2 due to their lower symmetry, to get the true intrinsic ("chemical") values.[33] This view was not confirmed by comparison with 3,5-disubstituted acids in which the symmetry is restored.[34] According to our calculations, the meta-substituted benzoic acids are present as two conformers (Table S1) whose population can be taken as approximately equal with a sufficient approximation as assumed also in the Eberson theory.[33] However, we were unable to confirm this theory by comparison with experiments: When a correcting term of RT ln 2 is added to Δ_2E for all meta derivatives, the correlation with $\Delta_2G°$ is not significantly better (Table 2, line 2 as compared to line 1). Still more convincing is

(28) It was pointed out by a referee that agreement with experiment could be improved by using the data from the NIST Chemistry Webbook (www.webbook.nist.gov). On the contrary, we obtained a slightly worse agreement (R = 0.990, SD = 3.0 kJ mol^{-1}, N = 20). The NIST base is not quite dependable: some data cited from ref 23 do not agree, and some items from ref 24c are omitted. In our opinion, data from original sources are preferable, particularly when relative values are discussed. In a simultaneous study, ref 29, acidities of meta- and para-substituted benzoic acids were calculated at the MP2/6-311++G**//B3LYP/6-311+G* level. Agreement with experiment was insignificantly better (SD = 2.1 kJ mol^{-1}) for the substituents common with this work. Acidity of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids was recently calculated (Böhm, S.; Exner, O. *Chem. Eur. J.* **2002**, *8*, in press) using the same theoretical model as described here and agreed with experimental acidities with SD = 1.13 kJ mol^{-1}. The difference is most probably due to more precise experimental data determined only by Fourier transform ion cyclotron resonance.

(29) Wiberg, K. B. *J. Org. Chem.* **2002**, *67*, in press.

(30) In our opinion, ref 21, the principle of isodesmic reactions is more effective than a system using empirical contributions: Schmitz, L. R.; Chen, K.-H.; Labanowski, J.; Allinger, N. L. *J. Phys. Org. Chem.* **2001**, *14*, 90−96.

(31) (a) Pilcher G. In *The Chemistry of Functional Groups. Supplement B: The Chemistry of Acid Derivatives*; Patai, S., Ed.; Wiley: New York, 1992; Vol. 2; p 51−94. (b) Domalski, E. S.; Hearing, E. D. *J. Phys. Chem. Ref. Data* **1993**, *22*, 805−1159. (c) Bureš, M.; Holub, R.; Leitner, J.; Voňka, P. *Thermochemické veličiny organick'ych sloučenin (Thermochemical Quantities of Organic Compounds)*; Institute of Chemical Technology: Prague, 1987.

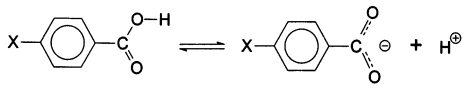
(32) Exner, O. *Prog. Phys. Org. Chem.* **1990**, *18*, 129−161.

(33) Eberson, L. In *The Chemistry of Carboxylic Acids Esters*; Patai S., Ed.; Interscience: London, 1969; p 211−293 (p 220).

(34) Kalfus, K.; Kroupa, J.; Večeřa, M.; Exner, O. *Collect. Czech. Chem. Commun.* **1975**, *40*, 3009−3019.

Figure 1, where no systematic deviations of meta substituents can be observed.

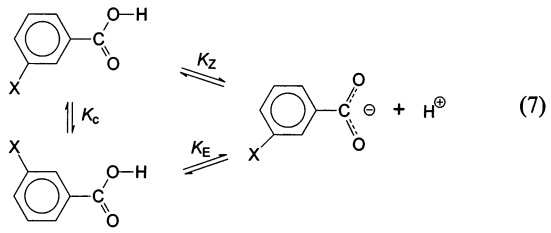
A more fundamental treatment of the problem appears necessary, either within the framework of the theory of external (σ_e) and internal (σ_i) symmetry numbers[35] or of statistical factors.[36] Application to para derivatives is unambiguous (eq 6).



σ_e	1	2	(6)
σ_i	2	2	

With $\sigma_e = 2$, entropy of the para-substituted anion is lowered by $-R$ ln 2 and the acid is weaker. The same result is obtained from the statistical factors:[36] When the reaction is followed from right to left, there are two possibilities of placing the proton; in the direction from left to right, there is only one possibility of its splitting.

Application to meta derivatives is less straightforward, since the two rotamers of the acid are no longer equivalent. Most correctly, the system is treated as an equilibrium of three compounds according to eq 7. Then the



(7)

apparent (also called "primitive") equilibrium constant K_{app} is defined when the two rotamers of the acid molecule are not distinguished. It is connected with the actual ("sophisticated") equilibrium constants of the two rotamers, K_E and K_Z, by eq 8, where $K_c = x/(1 - x)$ is the equilibrium constant of the conformational equilibrium. The acid molecule is represented more in the equilibrium and the acid is weaker. The decrease of $\Delta G°$, $\delta\Delta G°$, is expressed simply by eq 9, where $x \geq 0.5$ is the molar fraction of the more populated rotamer.

$$K_{app} = K_c K_E/(1 + K_c) = K_Z/(1 + K_c) \quad (8)$$

$$\delta\Delta G° = RT \ln x \quad (9)$$

When the two conformers are equally (or nearly equally) populated ($K_c \cong 1$, $x \cong 0.5$), the acid molecule is represented in equilibrium twice and its entropy is enhanced by R ln 2. In this case, there is no difference between meta and para isomers, in agreement with the experimental tests.[37] The heart of the problem is in eq 7, in which any internal symmetry number must not be applied: the two theories of symmetry numbers and of statistical factors must not be mixed.[38]

When the entropy $S°(298)$ is calculated by the standard Gaussian program,[39] the external symmetry numbers are included into the calculation only when the proper symmetry is input from the beginning; the internal symmetry number and the more or less free rotation are not taken into account. Most simply, the chemical entropy $S°_{chem}$ is calculated without any constraint (C_1 symmetry) and $S°_{sym}$ is determined separately. As an example, we obtained the reaction entropy $S°_{chem}(298)$ of eq 2 with X = 4-F or 3-*ap*-F as -0.1 or -0.3 J K^{-1} mol^{-1}, respectively. $\Delta_2 S°_{sym}$ is zero for 4-F and near to zero for 3-F when two conformers are taken into consideration. We conclude that the approximation[32] $\Delta S°_{chem} \cong 0$ is acceptable for isodesmic reactions;[40] in the particular case of meta- and para-substituted benzoic acid, even $\Delta S°_{sym}$ is near to zero when all its components are summed up.

Substituent Effects in the Acid Molecule and in the Anion. Separation of substituent effects was accomplished by eqs 3 and 4; their reaction energies $\Delta_3 E$ and $\Delta_4 E$ are given in Table 1, columns 5 and 7, respectively. The main question was how these two components contribute to the relative acidity $\Delta_2 E$; further it was of interest whether even $\Delta_3 E$ and $\Delta_4 E$ can be described in terms of common scales of substituent effects derived essentially from $\Delta_2 E$. Evidently, the energies of the anion $\Delta_4 E$ and of the acid molecule $\Delta_3 E$ are affected by substitution in an opposite sense; both contribute to the effect on the acidity and $\Delta_4 E$ is more important, say three times. This is a different picture than obtained previously with other models of substituent effects: In the cases of the inductive effect,[16,28] steric ortho effect,[12,14] or polarizability effect,[15] it was the energy of the ion which was determining the acidity or basicity. Effects in neutral species were either much smaller[14,28] or irregular[16] or sometimes of the same sign; in the last case, the effect on the acidity represented a small difference between two larger quantities.[12c,15] In our case, $\Delta_3 E$ and $\Delta_4 E$ are of importance and both affect the acidity in the same sense.

However, a detailed analysis reveals that $\Delta_3 E$ and $\Delta_4 E$ are not exactly proportional. According to the Hammett equation, they should depend on the constants σ, but the equation may be fulfilled poorly in reactions of uncharged particles.[2] Figure 2 reveals that $\Delta_4 E$ change regularly, roughly according to the constants σ_m and σ_p, but $\Delta_3 E$ are less regular. For meta substituents and para acceptor substituents, they are inversely proportional to $\Delta_4 E$ and reduced to one-fifth (Table 2, line 7). Donor substituents in the para position show characteristic deviations: their stabilizing effect in the acid molecule is stronger. It has

(35) Benson, S. W. *J. Am. Chem. Soc.* **1958**, *80*, 5151−5154.

(36) (a) Bishop D. M.; Laidler K. *J. Trans. Faraday Soc.* **1970**, *66*, 1685−1687. (b) Exner, O. *Chem. Listy* **1993**, *87*, 473−483.

(37) Previously the problem was treated in a less rigorous way (ref 12b) based on the formula for mixing entropy; for $K_c \approx 1$, the results are equal. Also the reference to hindered rotation (ref 34) was misleading in this context: the rotation is hindered slightly and practically to the same degree in the two isomers.

(38) It was pointed out that application of symmetry numbers in agreement with facts could be sometimes very difficult (ref 36b).

(39) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzales, C.; Pople, J. A. *Gaussian 94*, revision C.3; Gaussian, Inc.: Pittsburgh, PA, 1995.

(40) In the case of simpler molecules, not in isodesmic reactions, it was found recently that the entropy of ionization must not be approximated only by its symmetry component: Gal, J.-F.; Maria, P.-C., Raczyńska, E. D. *J. Mass Spectrom.* **2001**, *36*, 699−716.

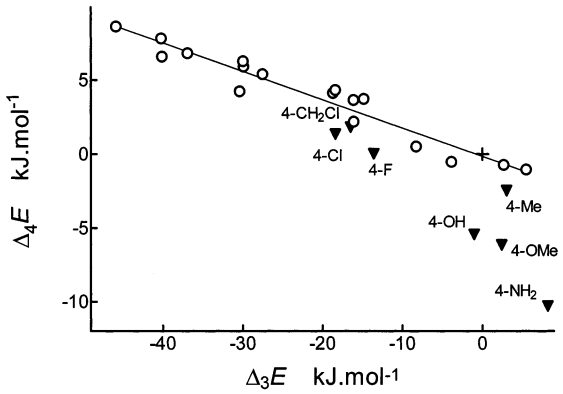
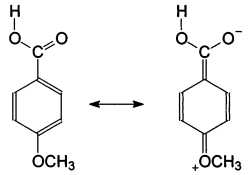


FIGURE 2. Plot of calculated substituent effects in substituted benzoic acids, Δ_3E, vs the substituent effects in their anions, Δ_4E: acceptor substituents in the para position and all meta substituents, ○; donor substituents in the para position, ▼; unsubstituted benzoic acid, +. The regression line belongs to the first group.

been known for a long time that the Hammett equation is slightly unsymmetrical with respect to acceptors and donors. The effects of the latter are overestimated as explained by the term through-resonance in the acid molecule;[23,41] for example, with 4-methoxybenzoic acid **23** it is expressed by the formulas **23a** ↔ **23b**. To remedy this defect, constants denoted $\sigma_p°$ were advanced[41] not including the through-resonance.



23a **23b**

Once Δ_3E and Δ_4E have been separated, they can be analyzed separately in terms of inductive and resonance effects (dual substituent parameter treatment[24a,42]) according to eq 10.

$$\Delta_{3(4)}E = \rho_I\sigma_I + \rho_R\sigma_R + \epsilon \qquad (10)$$

The correlations in Table 2, lines 8−11, are not very close but allow us to conclude that resonance is more important in Δ_3E than in Δ_4E, and of course also in para derivatives more than in meta. With para substituents $\rho_I \cong \rho_R$ for Δ_4E (Table 2, line 11), while for Δ_3E ρ_R is greater (line 9) due to the resonance as in **23a** ↔ **23b**. With meta substituents, the effect on Δ_4E is little changed (line 10 as compared to line 11), but for Δ_3E ρ_R is strongly reduced (line 8). The observed effect on the acidity is given by the difference $\Delta_4E - \Delta_3E$. By subtracting the pertinent ρ values, we obtain similar conclusions as known from solution chemistry: inductive effect and resonance are equal in the para position (by definition), while in the meta position resonance is reduced to about one-half. We may now add that this is caused essentially by the effects in the acid molecule.

Additional evidence of resonance can be obtained also from the bond lengths C1−C(O) (Table S1). The value of 1.486 Å in benzoic acid is reduced in para derivatives with donor substituents, up to 1.474 Å in **20**. It is slightly lengthened by para acceptor substituents (up to 1.492 Å), remarkably also in all meta derivatives with substituents of either type.[43] Similarly as in Figure 2, the resonance effect of donors is stronger and of graduated intensity, while the effect of acceptors is weaker and uniform.[44] In the anions, the bond length C_{ar}–C(O) is longer (1.554 Å in the benzoate anion), showing virtually no conjugation of the COO^- group with the benzene ring. Also the substituent effects are much smaller.

The Meta/Para Relationship. The linear relationship between substituent effects in the meta and para positions was found for substituents without lone electron pairs in the α-position[44] (CH_2X, CN, NO_2, SO_2X, with some approximation also COX). It was explained by a suggestion that these substituents are negligibly conjugated. The slope $\lambda = 1.14$ reveals a stronger substituent effect in the para position. Its interpretation is controversial and has been much discussed;[44b] a possible explanation uses the term π-inductive effect. Originally, the relationship was formulated[44] for log K or log k; if it is written for $\Delta G°$, it takes the form of eq 11.

$$\Delta G°_{para} - \Delta G°_{H} = \lambda(\Delta G°_{meta} - \Delta G°_{H}) \qquad (11)$$

This equation was heavily criticized,[42a,44b] but it was confirmed[24c] on the gas-phase acidities and basicities of 26 pairs of compounds with the substituents CN, NO_2, CF_3, SO_2CH_3, SO_2F, CH_2Cl, $COCH_3$, and $COOCH_3$. However, λ in the gas phase is only 1.06 but still significantly different from unity,[24c] at variance with the common literature.[42b] We can test eq 11 on the calculated energies. Figure 3 reveals a very good correlation, including even the substituents CHO and $COOCH_3$. The slope $\lambda = 1.12$ is greater than unity without any doubt (Table 2, line 12). In our opinion, the best explanation remains that the common acceptor substituents are negligibly conjugated, although some related experimental facts need particular explanation.[44c] There is only some uncertainty as to which substituents belong into this category. It seems that, in the isolated molecules and in the gas phase,[24c] even the carbonyl substituents are conjugated negligibly, in water perhaps more. The meta/para relationship is observable even for the energies Δ_3E of benzoic acids (Figure 4), although these values are much smaller. This confirms that Δ_3E of acceptors behave regularly, and all deviations arise from the donors. In these meta/para plots, with separate Δ_3E and Δ_4E, the difference between conjugated and nonconjugated substituents is better evident than in the plot of the acidities Δ_2E.[29]

(41) (a) Hoefnagel, A. J.; Wepster, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 5357−5366. (b) Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1198−1205. (c) ref 1b, Chapter 4.1.

(42) (a) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1−80. (b) ref 1b, Chapter 6.1.

(43) Through-resonance in some other molecules has been doubted and replaced by a picture in which only the donor is conjugated, the acceptor acts merely by its inductive effect: Krygowski, T. M. *Prog. Phys. Org. Chem.* **1990**, *17*, 239−291; see also ref 44c. This reasoning need not apply to the resonance in **23**.

(44) (a) Exner, O. *Collect. Czech. Chem. Commun.* **1966**, *31*, 65−89. (b) ref 24c and references therein. (c) Exner, O.; Krygowski, T. M. *Chem. Soc. Rev.* **1996**, *25*, 71−75.

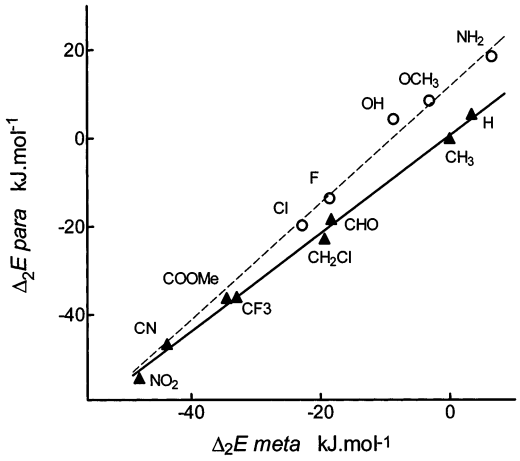


FIGURE 3. The meta/para plot of calculated acidities of substituted benzoic acids: substituents without a lone electron pair in the α-position, ▲; substituents with a lone electron pair, ○.

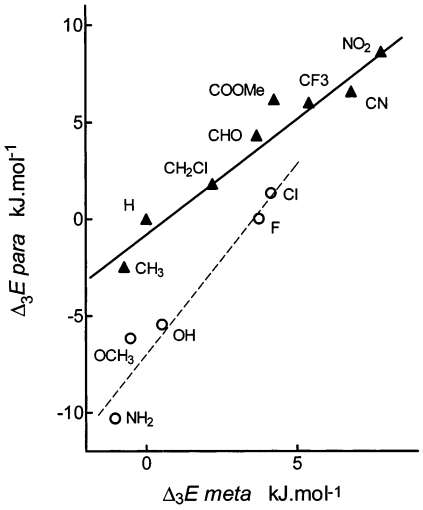


FIGURE 4. The meta/para plot of calculated energies Δ_3E of substituted benzoic acids: substituents without a lone electron pair in the α-position, ▲, substituents with a lone electron pair, ○.

Recently Pytela worked out the alternative interpretation of substituent effect (AISE),[45] which can be graphically represented[45b] as a more elaborated meta/para relationship. Substituents are divided into three classes of which not only the acceptors (class III: CN, NO_2, CHO, $COOCH_3$) but also donors (class II: OH, OCH_3, NH_2, F, Cl) and neutral substituents (class I: H, CH_3, C_6H_5, CH_2Cl, even CF_3) are situated each on a separate line. The graph consists of three straight lines intersecting at one point, and the substituent effect can be expressed by a single substituent constant, σ_i. Figure 3 reveals linearity for our five-donor groups (class II); classes I and III are not separated, as it is often the case. In Figure 4 the fit is slightly worse. In our opinion, the meta/para relationship described in terms of three classes is oversophisticated: our original simpler picture[44a] with one

(45) (a) Pytela, O. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1502−1528. (b) Pytela, O. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1191−1204.

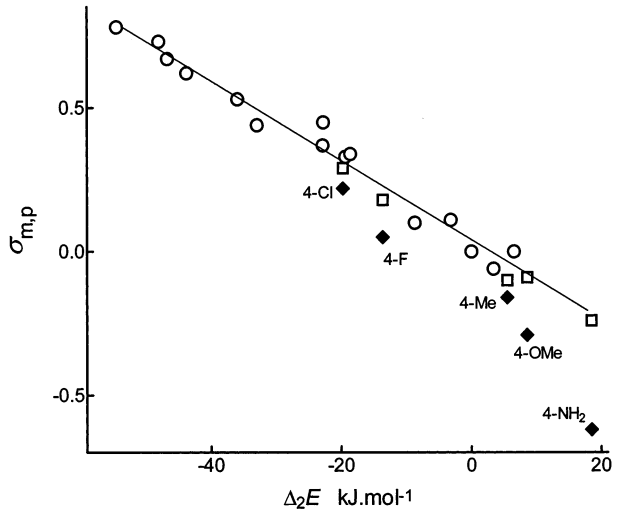


FIGURE 5. Plot of calculated acidities of substituted benzoic acids, Δ_2E, vs the substituent constants $\sigma_{m,p}$ (ref 5): donor substituents in the para position, ◆; the same substituents versus the normal constants σ_p° (ref 41), □; acceptor substituents in the para position and all meta substituents, ○; the regression line belongs to the last group.

line and deviating points as given in Figures 3 and 4 seems better.[46]

Relation to Constants σ Determined in Water. The standard values of Hammett substituent constants σ_m or σ_p have been defined by eq 1 when log K means the dissociation constant in water and ρ equals unity by definition. Constants determined in this way were recently reviewed and reliable values selected.[5a,b] Their relation to our Δ_2E is shown in Figure 5. A kind of correlation could be anticipated because also experimental Δ_2G° correlated[23,24a] with $\sigma_{m,p}$. In Figure 5, the para donor substituents must be omitted, similarly as in Figure 2 and for the same reason. Then the correlation in Table 2, line 14, is of comparable precision to the other correlations in this table. When the correlation equation is written with $\sigma_{m,p}$ as response function, eq 12,

$$\sigma_{m,p} = 0.042 - 0.0137\Delta_2E \qquad R = 0.987$$
$$s = 0.046 \quad N = 15 \quad (12)$$

it may be used as a source of new values of σ_m or σ_p for substituents that cannot be investigated by standard procedures. However, the standard deviation SD is relatively great and this precision is not sufficient for standard σ values.

Conclusions

The success of the Hammett equation for meta and para derivatives of benzene (and its failure for ortho

(46) A linear meta/para dependence for donor substituents is perhaps possible for sets of selected similar groups: Exner, O.; Lakomý, J. *Collect. Czech. Chem. Commun.* **1970**, *35*, 1371−1386. McDaniel, D. H. *J. Org. Chem.* **1961**, *26*, 4692−4694. However, one could certainly find groups with an intermediate conjugation and weak inductive effect belonging between classes I and II. Such groups, as for instance NHOH, $NHCONH_2$, and $SeCH_3$, have been little investigated and the available constants σ_m and σ_p are little reliable. The meta/para relationship offers also an additional opportunity of testing the entropy effect. If there is a linear dependence meta/para of Δ_2E(DFT) for certain substituents including hydrogen, a similar dependence of experimental Δ_2G should reveal a deviation of hydrogen by R ln 2. This was not observed.

derivatives) has been commonly explained by the benzene ring eliminating steric effects.[1] In addition, through-conjugation of the substituent with the reaction center should be absent.[41] Our dissection of substituent effects into Δ_3E and Δ_4E revealed that the system is particularly suitable as a model since the substituent effects are observable also in uncharged particles (Δ_3E). One might suggest that even the presence of the π-electron system could be favorable by making the molecule more sensible to electron withdrawing; however, the energy relations in some alicyclic molecules are similar.[28] On the other hand, the π-electron system is responsible for the well-known deviations[41] of para donor substituents, observed in the values Δ_3E. We can thus confirm the suggestion[47] that, strictly speaking, the range of the Hammett equation should be split into meta and para derivatives: only for the former the simple mathematical form could be retained. The original choice of benzene derivatives as model was mainly due to the historical availability of data.

Last but not least, the success of the Hammett equation—and of many other empirical relationships—is also due to repeated use of simple standard substituents, including those strongly electron withdrawing, which are usually decisive for the fit: less regular effects of weaker substituents are masked.[32]

Calculations

Energies of the meta- and para-substituted benzoic acids **1**−**25** and of their anions were calculated by the DFT method[20] at the B3LYP/6-311+G(d,p) level, exploiting the GAUSSIAN 94 program.[39] The planarity was not assumed from the beginning, but structure refinement finished in planar conformations in all cases. All possible conformations were then taken into account, in particular all combinations of the resulting planar conformation of the COOH group (*ap* and *sp*) and of the planar substituents (*ap* and *sp*). All final structures were checked by vibrational analysis. In the case of parent benzoic acid and its anion, also tight SCF calculations were carried out: the results have not changed. Sums of electronic and thermal enthalpies, $\Delta H°(298)$, and entropies, $S°(298)$, were calculated according to the same program.[39]

Supporting Information Available: Energies in au of substituted benzoic acids **1**−**25** and of their anions in all planar conformations calculated at a B3LYP/6-311+G(d,p) level, bond lengths C_{ar}–C(O) (Table S1); calculated Cartesian coordinates of **1**−**25** and of their anions (Table S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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(47) Ludwig, M.; Wold, S.; Exner, O. *Acta Chem. Scand.* **1992**, *46*, 549−554.