Acidity of *ortho*-substituted benzoic acids: an infrared and theoretical study of the intramolecular hydrogen bonds†

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The structures of *ortho*-substituted benzoic acids with substituents bearing hydrogen atoms (OH, NH_2, COOH and SO_2NH_2) were investigated by means of IR spectroscopy and of density functional theory at the B3LYP/6-311 + G(d,p) level. All possible conformations, hydrogen bonds, tautomeric forms and zwitterions were taken into consideration and particular attention was given to intramolecular H-bonds and their effect on acidity. Strong H-bonds in the anions of all four acids, were revealed by calculations. In three cases they were confirmed by the IR spectra of the tetrabutylammonium salts in tetrachloromethane solution, while the salt of 1,2-benzenedicarboxylic acid was not sufficiently soluble. The H-bonds are of different strengths but in all cases they are the main cause of the strengthened acidity of these acids in the gas phase and also in solution, although their effect is opposed by weaker H-bonds present in the undissociated acid molecules. The substituent effect on the acidity was evaluated in terms of isodesmic reactions, separately in the acid molecules and in the anions. While the acidity of the 2-OH and 2-NH_2 acids is determined essentially by the H-bonds, that of the 2-COOH and 2-SO_2NH_2 acids is strengthened by the polar effect operating in the undissociated molecule in addition to the H-bond in the anion. The steric inhibition of resonance (SIR), estimated from model conformations with fixed torsional angles, is of little importance. This analysis goes significantly beyond the classical explanation obtained from the acidities in solution but essentially conforms with it.

Introduction

Benzene *ortho* derivatives, represented very often by 2-substituted benzoic acids, have been studied less extensively than their *meta* and *para* isomers, nevertheless they are still objects of interest.[1,2] The main problem is that their reactivity and physical properties are controlled by more complex substituent effects,[3,4] which cannot be described by a simple relationship like the Hammett equation. As a formal description, the effects of *ortho* substituents were either assumed to be controlled by similar components to those present in the *meta* and *para* isomers (inductive effects and resonance) but in a different proportion, or alternatively, additional factors were considered, often not exactly defined:[3–6] primary steric effects, steric inhibition to resonance, short-range field effects, hydrogen bonds, steric inhibition to solvation. In numerous treatments of this subject, certain of these effects received more or less attention, sometimes they were even expressed by an empirical equation with a limited success.[5–7] Alternatively, separation of the effects is abandoned and they are brought together under the term 'ortho effect'. As an extreme opinion, reactivities of *ortho* derivatives were explained without referring to any steric effects,[8] either by a blend of inductive and resonance effects[8a,b] or simply by correlation with the reactivities of *para* derivatives.[8c] In our previous analysis,[9] we tried to distinguish theoretical concepts of two kinds. Some of them are purely models, sometimes poorly defined: for instance one can hardly distinguish what is a short-range field effect and what is a primary steric effect. On the other hand, there are theoretical concepts immediately related to observable facts: for instance the steric inhibition of resonance[4,7] (SIR) assumes a nonplanar minimum-energy conformation and this assumption can be tested.[10,11] Of particular importance is the effect of hydrogen bonds, involving either a hydrogen atom of the substituent or of the functional group;[1–3,5,7] the presence of both can be checked directly by experiment. Note that most of the named terms were defined and experimentally proven on the model of 2-substituted benzoic acids. One reason for this may be that, besides the availability of these compounds, their *meta* and *para* isomers served as a standard model in connection with the Hammett equation.

In our opinion, the main shortcoming of the outlined treatment of the ortho effect is that it has been mainly based on the dissociation constant (less frequently on the rate constant) in water or in aqueous solvents. In the basic model of 2-substituted benzoic acids, the substituent effect is defined by the Gibbs energy (or enthalpy) of the isodesmic reaction:

$$\text{2-XC}_6\text{H}_4\text{COOH} + \text{C}_6\text{H}_5\text{COO}^- \rightleftharpoons \text{2-XC}_6\text{H}_4\text{COO}^- + \text{C}_6\text{H}_5\text{COOH} \qquad (1)$$

More recently, this reaction[12] and other acidobasic equilibria[13] were also investigated in the gas phase. The results can be correlated with the structures of isolated molecules more closely

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than the acidities in solution. However, there still remains a fundamental shortcoming: that the substituent effect is given by a difference between the effect in the acid molecule and in the anion. It may happen that the two effects are of similar magnitude and their difference is difficult to interpret.[10,11] In order to separate the two effects on ionization, we used the principle of isodesmic reactions[14] and applied it systematically to inductive,[15] resonance,[16] and other[10,11] effects. When this principle is applied to *ortho* substituted benzoic acids, the isodesmic (and also homodesmotic[17]) reactions have the form of eqns (2) and (3).

$$C_6H_5COOH + C_6H_5X \rightleftharpoons 2\text{-}XC_6H_4COOH + C_6H_6 \qquad (2)$$

$$C_6H_5COO^- + C_6H_5X \rightleftharpoons 2\text{-}XC_6H_4COO^- + C_6H_6 \qquad (3)$$

The reaction enthalpies of these reactions, Δ_2H° or Δ_3H°, are a measure of the substituent effects in the acid molecule and in the anion, respectively. The values of Δ_2H° could be obtained, in principle, from the enthalpies of formation of all species involved, but the available values[18] are not sufficiently accurate.[9] Therefore, we preferred[9,16b] calculations within the framework of the density functional theory[19] (DFT).

In our previous work, we divided 2-substituted benzoic acids into three subsets according to the character of the substituent: alkyl groups, polar substituents without an acidic hydrogen atom and substituents bearing such H atoms. Alkyl groups exhibited steric effects[10]–including SIR[11]–of similar magnitude in the acid and in its anion; acidity was controlled mainly by polarization in the anion.[11] Polar substituents without hydrogen represent a more complex problem. We tentatively divided the substituent effects into four parts:[9] H-bond in the acid molecule, SIR, polar effect mediated through the benzene ring (PE) and steric van der Waals effect (*SE*); the two last effects were merely fictive.

In this article, we extended our investigation to the last group of substituents, those bearing an acidic hydrogen atom. We dealt with four 2-substituted benzoic acids: 2-OH, 2-NH_2, 2-COOH and 2-SO_2NH_2. The H-bonds, assumed to be the most important factor influencing the acidity, were examined both theoretically and from the IR spectra of the acids (in part already well described) and of their tetrabutylammonium salts; this was possible only with three of the named acids. The DFT calculations were carried out at the same level as previously;[9] great attention was given to all possible conformations, H-bonds and zwitterions. By these methods it was possible to clearly distinguish strong and weak H-bonds and to estimate roughly their relative energies. In all cases the H-bonds were found both in the acid molecule and in the anion, even when they were of different strengths or when their effects on the acidity partly compensated.

Experimental

Tetrabutylammonium salts **2**, **4**, **6** and **8** were prepared by titration of the acids **1**, **3**, **5** and **7**, respectively, with the solution of tetrabutylammonium hydroxide exactly to the equivalence point. The solution was evaporated to dryness and the glassy residue subjected to spectroscopy. The purity was checked by NMR spectra; no signals of impurities were detected.

Infrared absorption spectra were recorded on a Bruker Equinox 55 FTIR spectrometer in the region 400–3800 cm^{-1} in tetrachloromethane solutions and, in a few cases, also in chloroform. Wide intervals of concentrations were used, from 10^{-1} to 10^{-6} mol l^{-1}, depending on the solubility of individual compounds. Nevertheless, some bands of the carboxylic acid dimers could not be completely eliminated by dilution. The cell thickness was changed, depending on concentration, from 0.1 mm to 10 cm. Several solid state spectra were recorded in KBr pellets, spectra of the partially deuterated samples of **3** in paraffin oil mulls.

The spectral data are collected in Tables S1 to S6 (supplementary information†).

Calculations

Energies of 2-substituted benzoic acids and of their anions were calculated by the DFT method at a B3LYP/6-311 + G(d,p) level with the GAUSSIAN 03 program.[19] Planarity or any symmetry was never anticipated. Geometry optimization was carried out with redundant internal coordinates. All reasonable conformations were taken into consideration and calculations were started from the pertinent near structures; tautomeric and zwitterionic forms were also considered as given by the formulas **1–8**. All optimized structures were checked by vibrational analysis and behaved as energy minima.

The calculated energies *E*(DFT), without corrections to zero-point energies, are listed in Table 1 together with the most important geometric parameters, further geometric parameters are given in Table S7 (supplementary information), the parameters connected directly to H-bonds are given also in Table 2. Population of conformers was estimated for 298 K in two ways: either from the calculated $\Delta G^\circ(298)$ or with the assumption $\Delta G^\circ(298) \cong \Delta E(\mathrm{DFT})$. Since the calculated vibrational frequencies sometimes differed rather a lot from the experimental values, we were of the opinion that the latter estimates are more reliable. Nevertheless, the differences between the two sets of values were mostly negligible. The only case when they were not is given in Table 1, footnote f, nevertheless even in this case the impact on the final values is minute. The effective energies were then evaluated for the equilibrium mixture. The energies Δ_2E° and Δ_3E° of the isodesmic reactions of eqns (2) and (3), further the relative acidities Δ_1E° (Table 3) relate always to this equilibrium mixture at 298 K.

The infrared frequencies were calculated using the same program;[19] they were scaled by a factor[20] of 0.9679 but still remained significantly greater than the experimental values. The calculated frequencies are given in Table S7.

The frozen conformations of some 2- and 4-substituted benzoic acids with a fixed dihedral angle Φ were calculated in such a way that all remaining geometry parameters were optimized with internal coordinates. The results are given in Table S8.

Results and discussion

The problems of structure and acidity are rather different with the four acids. Therefore, the results will be reported separately.

2-Hydroxybenzoic acid (1)

This acid has been studied extensively. There seems to be no contradiction in the literature that the strong acidity[1a] ($pK = 2.99$ in water) is attributed[1,4,7] to the H-bond in the anion (**2b**, Scheme 1) but both spectroscopic experiments[21] and calculations at different

Table 1 DFT energies and some geometric parameters of *ortho*-substituted benzoic acids

Substituent	Conformation [a]		Dihedral angles[b] φ_1	φ_2	DFT energy/a. u.	Relat. E[c]/kJ mol^{-1}	Population[d] (%)
2-OH	**1a**	*sp*,*sp*-HB	0.0		**−496.2056825**	0	99.7
	1b	*ap*,*sp*-HB	180.0		−496.2002301	14.30	0.3
	1c	*ap*,*ap*-HB	176.7		−496.1902134	40.60	
	1d	*ap*,*ap*	180.0		−496.1885893	44.86	
	1e	*sp*,*ap*	0.0		−496.1879379	46.57	
Anion-Ph[e]	**2a**	*ap*-HB	180.0		**−495.6731258**	0	75.3
	2c	*ap*	180.0		−495.6435371	77.66	
	2d	*sp*	0.0		−495.6412893	83.56	
Anion-Ca[e]	**2b**	*sp*,*sp*-HB	0.0		−495.6720633	2.76	24.7
	2e	*sc*,*ap*	76.4		−495.6320693	107.77	
2-NH_2	**3a**	*sp*,*sp*-HB	0.8	7.0	**−476.3311607**	0	99.2
	3b	*ap*,*sp*-HB	176.7	12.8	−476.3265439	12.10	0.8
	3c	*ap*,*ac*-HB	166.1	15.0	−476.3178081	35.04	
Anion	**4a**	*sp*,*sp*	6.4		**−475.7813756**		
2-COOH	**5a**	*sp*,*ac*	22.0	234.7	**−609.5709966**	0	36.3[f]
	5b	ac^+,ac^+	141.3	141.3	−609.5707100	0.75	26.8[f]
	5c	*sp*,*ap*-HB	21.9	200.7	−609.5705234	1.24	22.0[f]
	5d	sc^+,sc^+	33.4	44.0	−609.5701600	2.20	14.9[f]
Anion	**6a**	*sp*,*ap*-HB	1.3	181.6	**−609.0577479**	0	100
	6b	*sp*,*ac*	0.0	111.3	−609.0300078	72.83	
2-SO_2NH_2	**7a**	sc^+,sc^+-HB	35.6	48.5	**−1024.9565881**	0	96.3
	7b	ac^+, ac^-	135.4	222.2	−1024.9534333	8.28	3.4
	7c	ac^+,sc^+-HB	142.3	55.7	−1024.9509626	14.77	0.3
Anion	**8a**	sc^+,sc^+-HB	39.2	57.4	**−1024.4337535**		

[a] Conformation on the bonds C1–C(O) and C2–X; the hydrogen bond is indicated in all conformations where it exists; Zw stands for zwitterion. [b] Dihedral angles C2–C1–C=O and C1–C2–X–Y, respectively. [c] Relative energy with respect to the most stable form. [d] Approximate population in the equilibrium mixture at 298 K calculated from ΔE values. [e] Phenolate and carboxylate anion, respectively. [f] From ΔG° we got the population 39.8, 34.2, 20.8 and 5.2%.

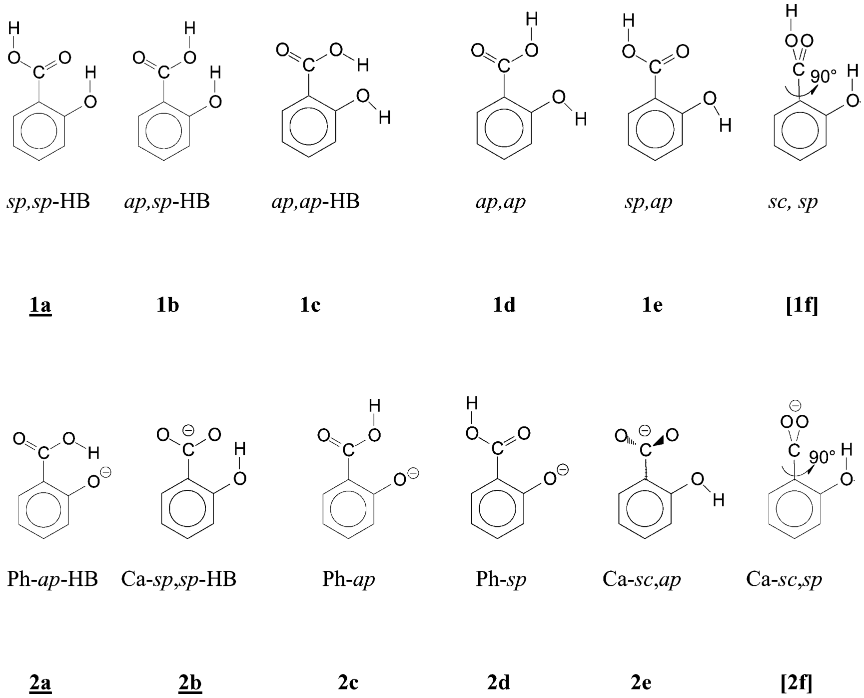
Table 2 Quantities characterizing the hydrogen bond

Compound	Structure	X–H/Å	H. . .Y/Å	∠X–H. . .Y/°	ΔE[a]/kJ mol^{-1}	$\Delta\nu$ calc./cm^{-1}	$\Delta\nu$ exp./cm^{-1}
1a	O–H. . .O=	0.971	1.76	145	−26	359[b]	395[b]
1b	O–H. . .O	0.970	1.80	141	−12	141	
1c	O–H. . .O	0.971	1.79	145		68	
2a	O–H. . .O^-	1.038	1.48	158	−73	not reliable	342[c]
2b	O–H. . .O^-	1.052	1.45	158		not reliable	264[b]
3c	O–H. . .N	0.983	1.83	143		343	—
5c	O–H. . .O=	0.986	1.62	162		408	
6a	O–H. . .O^-	1.184	1.19	179		not reliable	
3a	N–H. . .O=	1.010	1.95	129	−10	158[d]	133[d]
3b	N–H. . .O=	1.006	1.97	126		120[d]	—
4a	N–H. . .O^-	1.032	1.76	141	−14	393[d]	245[d]
7a	N–H. . .O=	1.018	2.03	139		134[e]	119[e]
8a	N–H. . .O^-	1.054	1.66	160		not reliable	201[e]

[a] Estimated energy change when the two groups connected by a H-bond are brought together, see text. [b] Related to ν(O–H) of phenol. [c] Related to ν(O–H) of to benzoic acid. [d] Difference of ν_{as} and ν_s of the NH_2 group, it is to be compared with $\Delta\nu$ of aniline, calculated 97 cm^{-1}, experimental 80 cm^{-1}. [e] Difference of ν_{as} and ν_s of the NH_2 group, compared with $\Delta\nu$ of benzenesulfonamide, calculated 109 cm^{-1}, experimental 201 cm^{-1}.

levels[22] deal only with the H-bond in the acid molecule and exclusively prefer the form **1a**. Acidity is commonly discussed in comparison with the weaker 4-hydroxybenzoic acid.[4,22] However, the latter behaves in the gas phase as a substituted phenol and its deprotonation proceeds on the phenolic OH group.[12,16b] Therefore, one must also take into consideration the phenolic OH acidity in the case of **1**. We calculated the energies of the acid and perhaps of the anion in all possible conformations, **1a–e** and **2a–e**, respectively; the relative energies and populations are given in Table 1, the last two columns.

As expected, the planar structure **1a** is the only detectable form of the acid, in agreement with previous calculations,[22] with our IR investigation and with previous spectral data.[21] A strong H-bond was observed at all concentrations, independently of the equilibrium of **1a** with its dimer (Table S1, ESI†). The form **1b** can be neglected since the energy difference between **1b** and **1a** is 14.3 kJ mol^{-1} (in satisfactory agreement with calculations[22a] at a slightly lower level, 12.1 kJ mol^{-1}.) Concerning the structure of the anion, we obtained probably the first direct experimental proof of the H-bond from the IR spectrum of the tetrabutylammonium salt in tetrachloromethane. Moreover, we found two structures with a H-bond. Calculations predicted the planar structures **2a** and **2b**, differing only by the position of the hydrogen atom. Within the framework of our theoretical model they should be



Scheme 1 Conformations of 2-hydroxybenzoic acid **1** and of its anion **2** in the sequence of increasing energy. (Conformers populated in the equilibrium mixture by more than one percent are underlined; structures for which no energy minimum was obtained are in square brackets).

Table 3 Estimated substituent effects in 2-substituted benzoic acids (in kJ mol^{-1})

Substituent		HB + SE	SIR	PE	Total ΔE^a
2-OH	Acid (**1**)	−23	0	−4	−26.7
	Anion (**2**)	−75	0	−1	−75.6
	Acidity	**−52**	**0**	**3**	**−48.9**
2-NH_2	Acid (**3**)	−8	0	−8	−16.1
	Anion (**4**)	−29	0	7	−21.7
	Acidity	**−21**	**0**	**15**	**−5.6**
2-COOH	Acid (**5**)	20	14	4	37.5
	Anion (**6**)	−44	0	−19	−63.4
	Acidity	**−64**	**−14**	**−23**	**−100.9**
2-SO_2NH_2	Acid (**7**)	3	13	5	21.1
	Anion (**8**)	−44	21	−32	−54.9
	Acidity	**−47**	**8**	**−37**	**−76.0**

[a] Substituent effect in the acid molecule ($\Delta_2 E$), or in the anion ($\Delta_3 E$), or the effect on the acidity ($\Delta_1 E$), as the case may be.

in equilibrium but separated only by a very low energy barrier of 1.75 kJ mol^{-1}. In agreement with this, two IR bands were observed (Table S1) differing by 150 cm^{-1}; calculation yielded a difference of 119 cm^{-1} but the individual frequencies were calculated wrongly. The agreement of calculated and experimental frequencies was generally bad, even with the recently suggested correction factor;[20] relative values agreed better. Qualitatively, calculations and IR spectra agree well: Calculations predict that the phenolate anion **2a** is more populated and its ν(O–H) is at higher frequencies; in the spectra the higher-frequency band is more intense.

When we calculated the relative acidity $\Delta_1 E$, eqn. (1), from the forms **1a**, **2a** and **2b** present in equilibrium, we got −48.9 kJ mol^{-1} compared with the experimental $\Delta_1 G^\circ$ in the gas phase −58.2 kJ mol^{-1}. The fit is not good compared to the much better fit for *meta*- and *para*-substituted benzoic acids[16b] (s = 2.69 kJ mol^{-1}) and even for *ortho*-substituted acids without hydrogen bonds.[9] Moreover, when a disagreement of DFT calculated and experimental substituent effects was observed, these effects were always overestimated (in absolute values) by calculations, never underestimated.[15a,16,23] We examined the possibility that the difference could be due to the entropy[24] and calculated $\Delta_1 G^\circ$ of eqn. (1) in spite of our rather bad experience[23] with calculation by statistical thermodynamics within the framework of DFT. We obtained only a slight improvement to −51.1 kJ mol^{-1}.

The H-bonds in **1a**, **2a** and **2b** are strong according to common criteria[25] (Table 2) but quantitatively these criteria need not give concordant results.[25] According to the distance H…O, the H-bonds in **2a** and **2b** are much stronger than in **1a**, according to the shift $\Delta\nu$ of the ν(O–H) frequency, there is little difference. Values of ν (O–H) were related to benzoic acid or to phenol for the sake of simplicity and these relative values were predicted by calculations in fair agreement with the IR spectra (Table 2). For evaluating the effect on acidity, the deciding property of the H-bond would be its energy defined as an energy difference between the real structure and any reference structure without the H-bond. However, the latter cannot be evidently defined in an unambiguous way.[22a] We used a rather sophisticated model which can also be applied to the acid **3** and to the anions **2** and **4**. When the carboxyl group was rotated out by 90° and fixed in this conformation (**1f**), the H-bond was broken but the conjugation was also inhibited (SIR). The latter component was estimated from the isomeric 4-hydroxybenzoic acid (Table S8) and subtracted. In the same way, the energy of the H-bond in the anion **2a** ⇌ **2b** was also estimated (**2f**). According to Table 2 the H-bond is rather strong in the acid **1a** but much stronger in the anion and makes the acid **1** stronger.

2-Aminobenzoic acid (3)

The acidity of **3** in water ($pK_2 = 4.85$) and aqueous solvents was the object of much speculation but the crucial problem was the presence and population of the zwitterion, **3e** or **3f**. Its population in water was estimated differently,[26] in any case it diminishes in less polar solvents.[27] Even the X-ray structure is partly controversial.[28] Acidity in the gas phase was interpreted by a H-bond in the anion,[12] not directly proven, but no proof in favour of a H-bond was found in the chemometrical analysis of reactivities in various solvents.[7] The H-bond in the acid molecule found by IR spectroscopy in the gas phase was classified as weak;[29] nevertheless it was claimed even in various solutions.[21b,30] Semiempirical calculations[31] predicted two conformers of **3**.

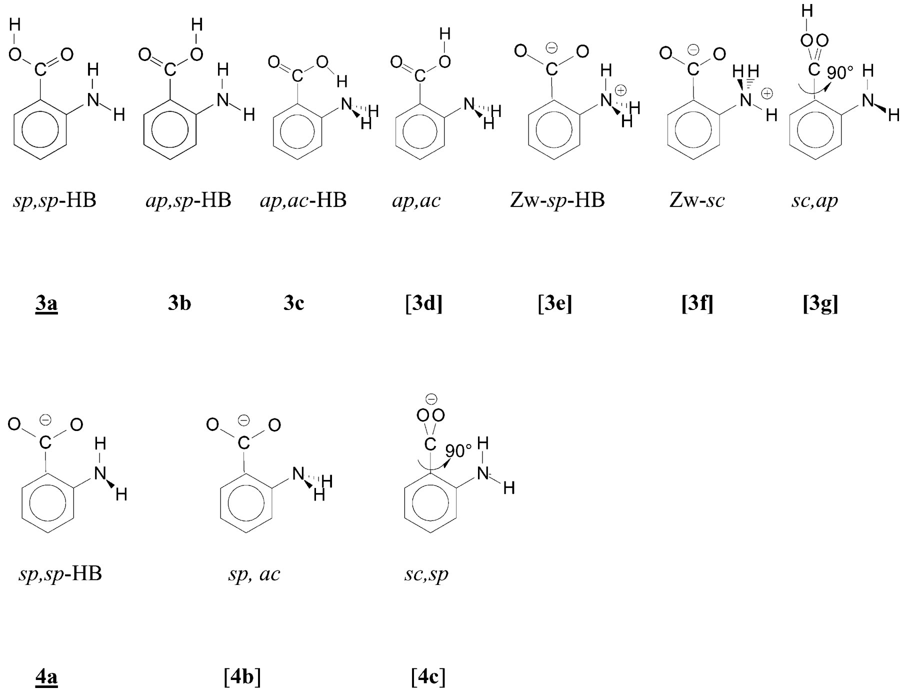
We tried to calculate energies of all possible forms (Scheme 2) but we reached no energy minima for the zwitterions **3e** or **3f**, and also no minima for a conformation near to **3d**, or for a form of anion near to **4b**. The ionization is sufficiently represented by the acid in the conformation **3a** and anion in **4a**; the forms **3b** and **3c** are negligibly populated (Table 1). Both species contain H-bonds, observed also from the IR spectra, but these H-bonds are of different strengths as seen from various criteria (Table 2). The relative acidity $\Delta_{\text{I}}E$ of **3** was calculated from the energies of **3a** and **4a** as −4.4 kJ mol^{-1} compared to the experimental[12] $\Delta_{\text{I}}G^\circ(298)$ −11.7. The difference may have similar grounds as with the acid **1**. Note that the deviations, although significant for the individual acids, are of little importance in the perspective of the whole series.[9,16b]

The strength of the H-bonds in **3a** and **4a** is best characterized in the IR spectra by the difference of the antisymmetrical and symmetrical NH$_2$ frequencies, $\Delta\nu = \nu_{\text{as}}(\text{NH}_2) - \nu_{\text{s}}(\text{NH}_2)$. When one of the N–H bonds is engaged in a H-bond, the coupling is weaker and $\Delta\nu$ increases. For the weak H-bond in **3a** we found $\Delta\nu = 133$ cm^{-1} compared to 97 cm^{-1} in aniline; this H-bond is weaker in the dimer of **3a** and still weaker in the solid state. For the stronger H-bond in **4a** we got $\Delta\nu$ 393 cm^{-1}. The values of $\Delta\nu$ were also calculated with a fair fit to experiments (Table 2), although the fit for the frequencies themselves was much worse. In any case, the calculations predict the great difference between the weak H-bond in **3a** and strong bond in **4a** well, which is further confirmed by the geometric parameters (Table 2). The energy of the H-bonds was estimated in the same way as above with the species **1** and **2**. In the fixed perpendicular conformations **3g** and **4c** the H-bonds are broken; for SIR a correction is calculated from the isomeric 4-aminobenzoic acid (Table S8) and subtracted. Remarkably only a small difference was found between these energies for **3a** and **4a** (Table 2); consequently the H-bond should have only small effect on the acidity of **3**.

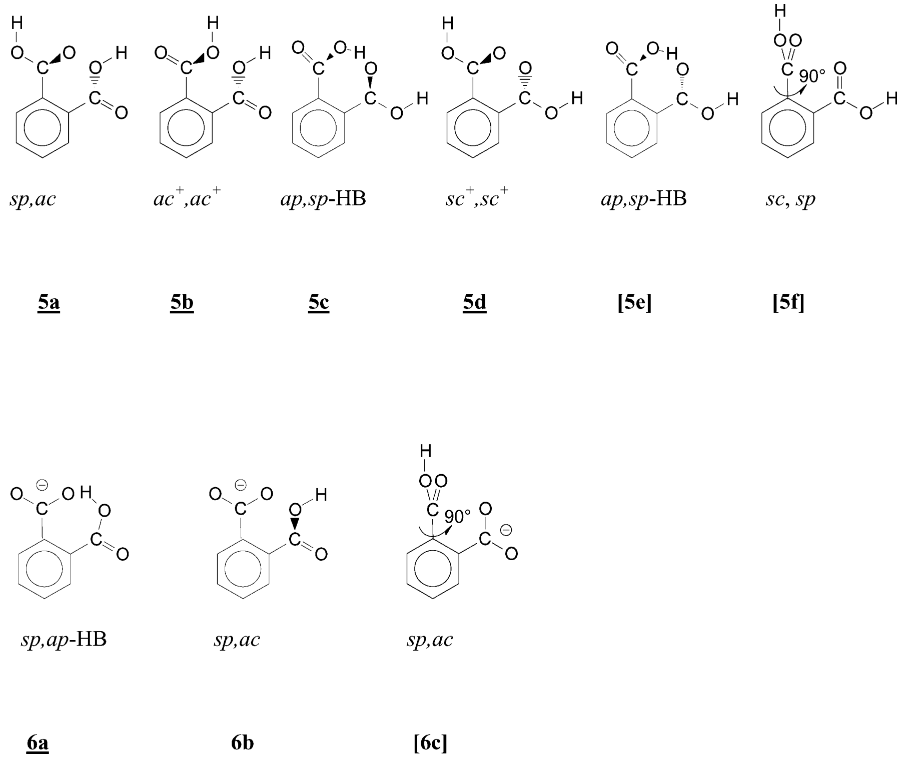
Benzene-1,2-dicarboxylic acid (5)

Discussion of the acidity of **5** was almost always restricted[4] to the ratio of the two dissociation constants K_1 and K_2. (in water $pK_1 = 2.94$, $pK_2 = 5.40$). A possible H-bond in the monoanion, requiring a seven-membered ring, was rarely taken into consideration. On the basis of correlation analysis it was assumed in dimethylformamide but not in water;[1b] no proof for it was found in kinetics in various solvents.[7] From direct comparison of K_1 and K_2, this H-bond was anticipated to be very weak in water, stronger in dimethyl sulfoxide.[32] Conformation of the undissociated acid **5** was investigated in tetrachloromethane on the basis of the experimental dipole moment and the Cotton–Mouton effect[33] with the result that several nonplanar conformers are populated.[34] Even in crystal form, the conformation is unexpected[35] (somewhat distorted nonplanar **5d**, Scheme 3).

IR investigation was in this case prevented by the low solubility of the acid in tetrachloromethane or chloroform; the acid salt



Scheme 2 Conformations of 2-aminobenzoic acid and of its anion in the sequence of increasing energy. (See Scheme 1.)



Scheme 3 Conformations of phthalic acid and of its monoanion in the sequence of increasing energy. (See Scheme 1.)

could not be investigated because of its disproportionation into neutral salt and acid. In our opinion, we can rely on the calculations due to good agreement with the experiments in the preceding cases. We obtained four forms of the acid, **5a–d**, all of comparable stability, with a H-bond only in **5c**. Although this bond could be strong according to the calculated $\Delta\nu$, its energy is counterbalanced by unfavourable conformation on the C–O bond. Let us consider the equilibrium of the four forms **5a** to **5d**: when **5c** is removed from the equilibrium mixture, the energy would practically not change, only by some hundredths of kJ mol^{-1}. We thus take for granted that the H-bond in **5c** has no effect on the acidity.

For the monoanion, only one stable form was found (**6a**) with a remarkably strong H-bond. The seven-membered ring is almost planar and the H-bond is symmetrical, with the H-atom situated in the middle between the two oxygen atoms (Table 2); the geometric parameters are much more favourable than in **5c**. Unfortunately, experimental determination of $\Delta\nu$ was not possible and its calculation was not reliable similarly as with the preceding H-bonds in the anions (**2a** and **2b**). We also found no reliable model for estimating the energy of the hydrogen bonds in **5c** and **6a**; the fixed conformers **5f** and **6c** were of no use since it was not possible to take into account further simultaneous changes of conformation. According to the geometry and calculated IR frequency, the H-bond in **6a** is strong and contributes significantly to the acidity of **5**.

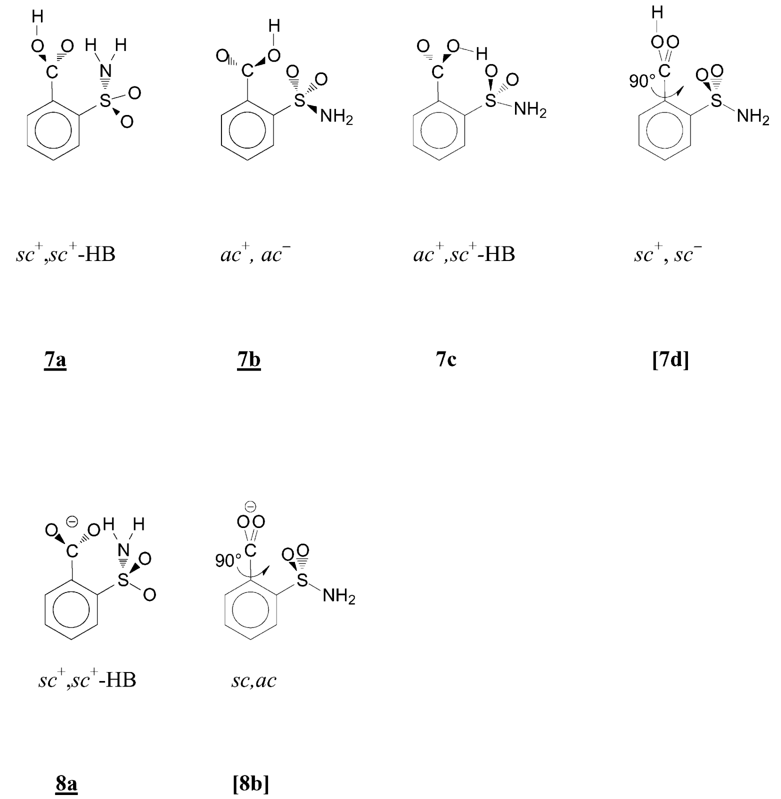
2-Sulfonamidobenzoic acid (7)

This acid has been studied very little due to its low solubility. A weak H-bond in the anion was deduced from chemometrical analysis of the relatively strong acidity in various solvents (p*K* in water[1a] 3.14) but it was not evident from the graphical representation.[1a] A more specified chemometrical investigation restricted to dimethylformamide solution suggested a H-bond in the anion making the acid stronger.[1b] We searched for various conformations of **7**, which all are nonplanar and somewhat less exactly defined. Particular attention was given to various possible conformations of the SO_2NH_2 group but they have small effect on the energy and are mostly unstable. Ultimately we found three conformers, **7a–7c** (Scheme 4), forming an equilibrium mixture but **7a** containing a H-bond represents 96% (Table 1). The H-bond is weak according to its geometry and to calculated $\Delta\nu$. For the anion only one minimum-energy form was found, **8a**, with a much stronger H-bond.

The calculations were in accord with the spectroscopic results. Two conformers of **7** were observed, **7a** and **7b**, but the H-bond in **7a** is very weak according to the frequencies $\nu_{as}(NH_2)$ and $\nu_s(NH_2)$ (Table 2). At higher concentrations an intermolecular bond is observed in addition, probably involving the SO_2 group. On the contrary, the H-bond observed with the tetrabutylammonium salt is strong and the difference between the NH_2 frequencies is striking (Table 2). Also the intermolecular bond at higher concentrations is more apparent. We were unable to estimate the energy of the H-bonds in **7a** and **8a**. The nonplanar conformers **7d** or **8b** could not be fixed in their simple perpendicular conformation since the H-bonds persisted even at the cost of other deformation of the molecule. We had to be satisfied with the qualitative conclusion that the acidity of **7** is strengthened by the H-bond in the anion **8a** while the opposing effect of the H-bond in the acid is negligible.

Comparison of substituent effects

Previously we attempted to divide the ortho effect observed in 2-substituted benzoic acids into real or fictive components;[9] this analysis was restricted to substituents without acidic hydrogen



Scheme 4 Conformations of 2-sulfonamidobenzoic acid and of its monoanion in the sequence of increasing energy. (See Scheme 1.)

atoms. Extension to substituents with a hydrogen atom is not straightforward since the contribution of the H-bonds is difficult to estimate. Let us start with the values of substituent effects separated into the effect in the anion, Δ_3E [eqn. (3)], and in the acid molecule Δ_2E [eqn. (2)]. These values (Table 3, last column) are, in our opinion, reliable and can serve as a firm basis for the analysis. In Fig. 1 Δ_2E are plotted *vs.* Δ_3E together with other 2-substituted benzoic acids and with the 3- and 4-isomers; the purpose of this figure is to show the fundamental difference between substituent effects in the *ortho* position and in the *meta* and *para* positions. A linear dependence for *meta* and *para* derivatives is evident (the Hammett line). Its large negative slope means that the acidity is controlled by a strong polar effect in the anion and slightly supported by the opposite effect in the acid molecule.[16b] Deviations of certain *para* substituents (NH_2 and $N(CH_3)_2$) has been discussed[16b,36] and will not be dealt with here. The *ortho* derivatives without a hydrogen atom (noted ▲) deviate strongly to the right from the Hammett line; the energy of both undissociated molecules and anions is raised (steric hindrance) and the effects on the acidity may partly compensate. Our four acids with acidic hydrogen atoms deviate still more strongly. Their anions are stabilized by H-bonds, while in the acid molecules one observes both destabilizing (2-COOH, 2-SO_2NH_2) and stabilizing interactions (2-OH, 2-NH_2).

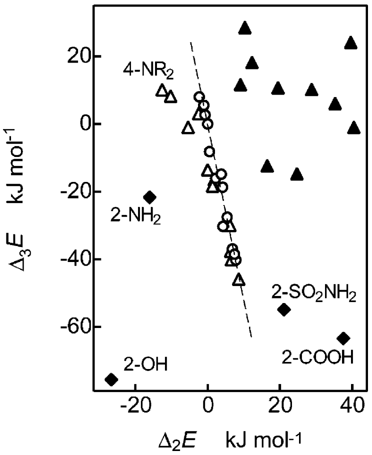


Fig. 1 Calculated substituent effects with the ionization of *ortho*-substituted benzoic acids: *x*-axis effects in the unionized acid, eqn (2), *y*-axis effects in the anion, eqn (3); ◆ substituents with an acidic hydrogen atom, ▲ substituent without an acidic hydrogen atom, ○ *meta* and △ *para* derivatives shown as reference standards.

Fig. 1 gives a true picture of substituent effects, which was not obtainable from the dissociation constants in solution.[4–8] We attempted a still more detailed analysis along the lines given previously[9] but the results are only approximate. Firstly we defined the polar effect PE (Table 3, the last but one column) as proportional to the substituent effect in the pertinent 4-isomers. The proportionality coefficient was subjected to discussion[1a,9,37] but is near to unity and the exact value is of little consequence. We used the value[9] of 0.81. The term PE has no exact meaning in the real world but can serve as a reference; it is evidently important for the anions **6** and **8**. The difference of the total effect ΔE and PE may be called the ortho effect and attributed to at least three components: steric (van der Waals) effects SE, SIR and the effect of H-bonds. SIR is evidently absent in the planar molecules of **1**, **2**, **3**, **4** and **6**; in the remaining species it was estimated by the approach developed previously,[9,15c] referring to the fixed conformation of the pertinent *para* isomer (the energies see Table S8). Their values (Table 3, column 3) have only a limited impact on the acidity.[38] The remaining two components, HB and SE, cannot, in our opinion, be reliably separated. One can imagine that when the two parts of the molecule are approaching, they need some energy to overcome SE (and/or SIR); once the H-bond is formed, a greater energy is gained back; these steps cannot be divided. We obtained the assumed sum of HB + SE (Table 3, column 3) as the difference $\Delta E - \mathrm{PE} - \mathrm{SIR}$. Some of these values may be reliable: the estimates for **1** and **2** are virtually equal to the estimates for **1a** and **2a** (Table 2) made in a quite different way: any SE is negligible. Even for **3** and **4** the agreement is not so bad. The destabilizing effect in **5** may be classified as steric, while the stabilizing effect in the anions **6** and **8** is certainly due to H-bonds overcoming any SE. The substituent effects on the acidity are perhaps somewhat more reliable than those in the anions and in the acid molecules, since some components partly compensate. Summarizing, Table 3 correctly reflects the difference between the acidity of **1** or **3**, controlled by the difference of the H-bonds, and **5** or **7** given by the sum of HB and PE in the anions with smaller contributions from the acid molecules.

The whole foregoing analysis was restricted to the behaviour of isolated molecules while all previous discussions were based on the dissociation constants in water.[4–8] We have some indirect proof that the strong H-bonds persist even in water. In Fig. 2 the acidities of substituted benzoic acids in water are compared with the calculated acidities of isolated molecules; the ortho effect is again, very clearly, apparent. As expected the *meta* derivatives determine the Hammett line; its slope of 0.1 is a measure of attenuation.[12] Some *para* derivatives (4-NH_2, 4-NMe_2, Fig. 2 at the top) deviate—the acids are weaker in water (zwitterions). The acids 2-COOH and 2-SO_2NH_2 are also weaker since the H-bond in the anion is weakened; nevertheless it still exists since these acids are much stronger than their 4-isomers. In the big deviation of 2-NH_2 the two grounds are combined, zwitterion and H-bond. The substituent 2-OH deviates to the opposite side, the acid is stronger in water. Probably the H-bond in the acid molecule has been more weakened in water than the stronger H-bond in the anion. All other *ortho* derivatives deviate in the sense that the acids are stronger or much stronger (2-NO_2) in water. One can speculate about steric hindrance of solvation of the acid molecules or specific hydration of the anions but direct proof is not available to date.

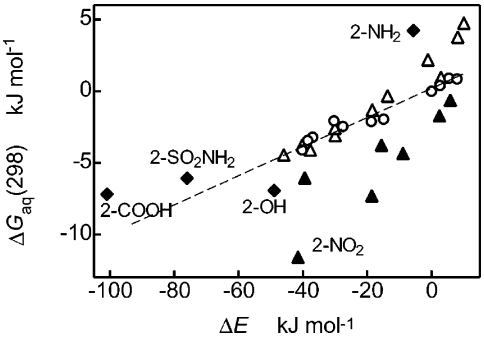


Fig. 2 Substituent effects on the acidity of substituted benzoic acids: *x*-axis calculated energies of isolated molecules, *y*-axis experimental Gibbs energies in water; ◆ substituents with an acidic hydrogen atom, ▲ substituent without an acidic hydrogen atom, ○ *meta* and △ *para* derivatives given as reference.

Conclusions

2-Substituted benzoic acids are certainly not a suitable model for evaluating steric and other substituent effects since these effects may be dissimilar for various substituents and also different in the anions and in the acid molecules. Previous analysis based on the acidities in aqueous solution[1,4–8] could meet only with very limited success. We obtained additional information from quantum chemical calculations of energies when utilizing their values as if they were experimental quantities. The main result was separating the substituent effects in the anion and in the undissociated molecule. Of the individual factors influencing the acidity, the H-bonds are very important and can be reliably proven by a combination of calculations and experiments. Several other factors remain more or less theoretical constructions since they refer to fixed conformations (as SIR) or to comparison with isomers or other molecules (PE and SE).

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References

1 (*a*) O. Pytela and O. Prusek, *Collect. Czech. Chem. Commun.*, 1999, **64**, 1617–1628; (*b*) O. Pytela and J. Kulhánek, *Collect. Czech. Chem. Commun.*, 2002, **67**, 596–608.
2 I. Bauerová and M. Ludwig, *Collect. Czech. Chem. Commun.*, 2001, **66**, 770–784.
3 O. Exner, *Correlation Analysis of Chemical Data*, Plenum Press, New York, 1988, pp. 135–137.
4 (*a*) H. C. Brown, D. H. McDaniel and O. Häfliger, in *Determination of Organic Structures by Physical Methods*, E. A. Braude and F. C. Nachod, eds, Academic Press, New York, 1955, pp. 567–662; (*b*) G. S. Hammond, in *Steric Effects in Organic Chemistry*, M. S. Newman, ed., Wiley, New York, 1956, pp. 425–470; (*c*) J. Hine, *Structural Effects on Equilibria in Organic Chemistry*, Wiley, New York, 1975, Chapter 3–4.
5 (*a*) J. Shorter, in *Advances in Linear Free Energy Relationships*, N. B. Chapman and J. Shorter, eds, Plenum Press, London, 1972, pp. 71–118; (*b*) T. Fujita and T. Nishioka, *Prog. Phys. Org. Chem.*, 1976, **12**, 49–89; (*c*) U. Berg, R. Gallo, G. Klatte and J. Metzger, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1350–1355; (*d*) A. C. Farthing and B. Nam, in *Steric Effects in Conjugated Systems*, G. W. Gray, ed., Butterworths, London, 1958, pp. 131–140; (*e*) M. T. Tribble and J. G. Traynham, *J. Am. Chem. Soc.*, 1969, **91**, 379–388.
6 M. Charton, in *Similarity Models in Organic Chemistry, Biochemistry and Related Fields*, R. I. Zalewski, T. M. Krygowski and J. Shorter, eds, Elsevier, Amsterdam, 1991, p. 629–687.
7 M. H. Aslam, A. G. Burden, N. B. Chapman, J. Shorter and M. Charton, *J. Chem. Soc., Perkin Trans. 2*, 1981, 500–508.
8 (*a*) M. Charton, *Prog. Phys. Org. Chem.*, 1971, **8**, 235–317; (*b*) V. Nummert and M. Pirsalu, *Collect. Czech. Chem. Commun.*, 2002, **67**, 1833–1857; (*c*) K. Bowden and G. E. Manser, *Can. J. Chem.*, 1968, **46**, 2941–2944.
9 S. Böhm, P. Fiedler and O. Exner, *New J. Chem.*, 2004, **28**, 67–74.
10 (*a*) M. Decouzon, P. Ertl, O. Exner, J.-F. Gal and P.-C. Maria, *J. Am. Chem. Soc.*, 1993, **115**, 12071–12078; (*b*) M. Decouzon, J.-F. Gal, P.-C. Maria, S. Bhm, P. Jiménez, M. V. Roux and O. Exner, *New J. Chem.*, 1997, **21**, 561–573.

11 (*a*) S. Böhm and O. Exner, *Chem.–Eur. J.*, 2000, **6**, 3391–3398; (*b*) S. Böhm and O. Exner, *New J. Chem.*, 2001, **25**, 250–254.

12 T. B. McMahon and P. Kebarle, *J. Am. Chem. Soc.*, 1997, **99**, 2222–2230.

13 (*a*) R. T. McIver, Jr. and J. H. Silvers, *J. Am. Chem. Soc.*, 1973, **95**, 8462–8464; (*b*) S. Bhm, M. Decouzon, O. Exner, J.-F. Gal and P.-C. Maria, *J. Org. Chem.*, 1994, **59**, 8127–8131.

14 (*a*) A. Pross, L. Radom and R. W. Taft, *J. Org. Chem.*, 1980, **45**, 818–826; (*b*) O. Exner, *Org. Reactivity (Tartu)*, 1995, **29**, 1–6.

15 (*a*) O. Exner and P. Nauš, *J. Phys. Org. Chem.*, 2000, **13**, 693–698; (*b*) O. Exner and S. Böhm, *Chem.–Eur. J.*, 2002, **8**, 5147–5152; (*c*) O. Exner and S. Böhm, *J. Phys. Org. Chem.*, 2004, **17**, 124–130.

16 (*a*) O. Exner and S. Böhm, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1994–1999; (*b*) O. Exner and S. Böhm, *J. Org. Chem.*, 2002, **67**, 6320–6327.

17 P. George, M. Trachtman, C. W. Bock and A. M. Brett, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1222–1227.

18 G. Pilcher, in *The Chemistry of Functional Groups. Supplement B: The Chemistry of Acid Derivatives, Vol. 2*, S. Patai, ed., Wiley, New York, 1992, pp. 51–94.

19 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03, Revision B.03*, Gaussian, Inc., Pittsburgh, PA, 2003.

20 M. P. Andersson and P. Uvdal, *J. Phys. Chem. A*, 2005, **109**, 2937–2941.

21 (*a*) A. E. Lutskii and Yu. I. Dolzhenko, *Zh. Obshch. Khim.*, 1980, **50**, 440–446; (*b*) A. Ya. Kaminskii, V. M. Ivanova, S. S. Gitis, E. G. Kaminskaya and L. I. Khabarova, *Reakts. Sposobn. Org. Soedin.*, 1971, **8**, 343–362.

22 (*a*) P. I. Nagy, W. J. Dunn, III, G. Alagona and C. Ghio, *J. Phys. Chem.*, 1993, **97**, 4628–4642; (*b*) H. Lampert, W. Mikenda and A. Karpfen, *J. Phys. Chem.*, 1996, **100**, 7418–7425; (*c*) J. Catalán and J. I. Fernandez-Alonso, *J. Mol. Struct.*, 1975, **27**, 59–65; (*d*) F. T. T. Huque and J. A. Platts, *Org. Biomol. Chem.*, 2003, **1**, 1419–1424.

23 S. Böhm and O. Exner, *J. Comput. Chem.*, 2006, **27**, 571–577.

24 The experimental gas-phase acidities are obtained as $\Delta G°$ and their transformation into $\Delta_f H°$ is only approximate: S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin and W. G. Mallard, *J. Phys. Chem.*, 1988, **17**, suppl. 1.

25 S. J. Grabowski, *J. Phys. Org. Chem.*, 2004, **17**, 18–31.

26 (*a*) L. M. Schwartz, R. I. Gelb, J. Mumford-Zisk and D. A. Laufer, *J. Chem. Soc., Perkin Trans. 2*, 1987, 453–460; (*b*) V. I. Zaionts and E. Sh. Gutshabash, *Zh. Org. Khim.*, 1982, **18**, 1912–1917.

27 I. Mentre, *Ann. Chim. (Paris)*, 1973, **8**, 115–122.

28 (*a*) C. J. Brown and M. Ehrenberg, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1985, **41**, 441–443; (*b*) H. Takazawa, S. Ohba and Y. Saito, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1986, **42**, 1880–1881.

29 Yu. Ya. Kharitonov and I. I. Oleinik, *Dokl. Akad. Nauk SSSR*, 1987, **294**, 151–154.

30 Yu. G. Kondrashina, S. G. Vul'fson and A. P. Timosheva, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1994, 859–861.

31 M. A. Palafox, M. Gil and J. L. Nunez, *Vib. Spectrosc.*, 1993, **6**, 95–105.

32 P. J. Choi, K. A. Petterson and J. D. Roberts, *J. Phys. Org. Chem.*, 2002, **15**, 278–286.

33 A. P. Timosheva, S. G. Abdullina, S. G. Vul'fson and L. V. Ermolaeva, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1993, 1568–1571.

34 In ref. 33 the experimental data were complemented by semiempirical calculations but it is not clear which conformations were actually considered. The only safe conclusion seems to be that several conformers are in equilibrium and that they are not planar; this is in agreement with our results.

35 O. Ermer, *Helv. Chim. Acta*, 1981, **64**, 1902–1909.

36 S. Böhm, P. Pařík and O. Exner, *New J. Chem.*, 2006, **30**, 384–391.

37 M. Charton, *Can. J. Chem.*, 1960, **38**, 2493–2499.

38 The generally small importance of SIR was analyzed in detail: J. Kulhánek, S. Böhm, K. Palát, Jr. and O. Exner, *J. Phys. Org. Chem.*, 2004, **17**, 686–693 and references therein.