Solvation and steric hindrance in methyl-substituted benzoic acids

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Dissociation constants of all isomers of methyl-substituted benzoic acids have been measured in methanol and in dimethyl sulfoxide. From the p*K* values, the substituent effects of the methyl groups are calculated and tentatively divided into polar and steric effects. Also, in the case of polymethyl derivatives, the buttressing effect is calculated with reference to monomethyl derivatives. These quantities are processed within the framework of correlation analysis using as reference the corresponding quantities in the gas phase. The steric effects may be classified as steric hindrance to resonance—observed only in derivatives with two *ortho* methyl groups, and electrostatic induction in the deprotonated molecules—observed in all derivatives. Both effects make the acids stronger and both are attenuated in solution, in methanol more than in DMSO. The electrostatic effect is attenuated in a specific way: the effect of more distant methyl groups is practically cancelled and only that of the *ortho* groups remains. As a result, the overall substituent effects are rather different in the two solvents and in the gas phase.

Introduction

Methyl-substituted benzoic acids were one of the first sets of compounds on which steric effects were investigated.[1–4] They represent a suitable model for studying steric effects since the methyl group has a defined size and polarizability but is itself practically nonpolar. On the basis of their dissociation constants in water, the terms of steric hindrance to conjugation[1] and of the buttressing effect[5] were defined. The series of dimethylbenzoic acids was extended to trimethyl by Lüning[4] but no additional effects were observed. Problems with solubility have prevented extension of the investigations to higher members of the series.

All the results obtained in aqueous solution have an essential weakness: they are contaminated with unknown effects of solvation and its steric hindrance.[3,6] Therefore, a systematic reinvestigation of these classical concepts was undertaken according to a uniform scheme,[6] based experimentally on the gas-phase ionization equilibrium constants[7–10] and gas-phase enthalpies of formation.[11,12] The analysis revealed that the term 'steric effect' can include several different features. Just in the case of methylbenzoic acids several results were obtained,[8–10] differing from those observed in water. Contrary to common opinion,[13–16] any *ortho* substituent need not raise distortion of planarity and steric hindrance to resonance. Among methylbenzoic acids this takes place only in a subset of acids bearing two methyl groups in the positions 2 and 6; the remaining acids occur in equilibrium of two planar conformations.[8,10,17] In both groups, the inductive (and/or hyperconjugative) and steric effects were tentatively separated[8,10] by comparison of *ortho* and *para* derivatives. On first sight, steric effects in anions were proportional to, and weaker than, the steric effects in the acids:[10] their difference was observed in the experimental acidities. This was rather curious considering the fact that the size and steric requirements of the COOH and COO$^-$ groups are practically identical.[18] Hence we suggested[19] that the apparent 'steric' effect on the acidity does not originate in the raised energy of the acid but rather in the energy of the anion lowered by pole-induced dipole interaction.[20,21] While polar effects are generally additive,[22–25] steric effects in dimethyl acids are always greater than the sum of the effects in mono methyl derivatives[8–10] (buttressing effect[5]). We redefined the buttressing effect in a more rigorous way and found it in the gas phase also for more remote substituents,[9] where it cannot be observed in solution. In trimethyl derivatives there is no additional increase and in pentamethylbenzoic acids the steric effects seem to have reached a state of saturation.[10]

For more detailed comparison with the classical theories, it would be necessary to carry out the above analysis also with solution data. The dissociation constants in water of tetra- and penta-methyl derivatives could not be obtained because of their low solubility; even some literature data about trimethylbenzoic acids[4] seem not to be quite dependable. In this paper we report p*K* values in two pure solvents, one protic (methanol) and one nonprotic (dimethyl sulfoxide). Use of pure solvents was preferred to mixed solvents, in which special problems arise depending on their composition.[26] Pure solvents, and particularly methanol and DMSO, have been used systematically in our laboratories for studies of substituent effects.[24,25,27–31] Acidities in DMSO were studied for a broad range of structures.[32]

Since the enthalpies of formation in methanol or DMSO solutions are not known, we cannot separate the substituent effects in the acid and in the anion as has been done[8,10] in the gas phase. We can only discuss the energy difference between the acid and anion and our reasoning could have a weakness similar to that which we criticised in the case of classical aqueous solution data. However, we can make a direct comparison with previous gas-phase ionization data.[8–10]

Experimental

Benzoic acids **1**–**20** (Table 1) have been characterized in a previous paper.[10] The technique used for p*K* measurement with a glass electrode has been described in some detail.[27] All p*K* values were obtained only relatively with respect to a literature reference value for benzoic acid.[27] This is the main weakness of this method but for our purposes the relative values are sufficient. Experimental p*K* values are listed in Table 1.

Results and discussion

Total substituent effects on the acidity

The measured quantities will be processed by standard methods of correlation analysis using the corresponding gas-phase

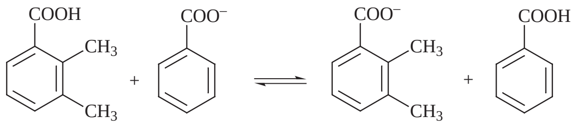
Table 1 Ionization of methyl-substituted benzoic acids (kJ mol^{-1}, 298 K)

		Solvent methanol					Solvent DMSO					Gas phase[a]	
No.	Methyl position	pK	$\delta\Delta G^\circ_{acid}$	PE[b]	SE[b] [react. (2)]	ΔBE[c] [eqn. (5)]	pK	$\delta\Delta G^\circ_{acid}$	PE[b]	SE[b] [react. (2)]	ΔBE[c] [eqn. (5)]	SE[b] [react. (2)]	ΔBE[c] [eqn. (5)]
1	H	9.41[d]	0	0	0	0	11.00[d]	0	0	0	0	0	0
2	2	9.31[e]	−0.6	1.1	−1.7	0	11.07[e]	0.3	1.8	−1.5	0	−5.1	0
3	3	9.47[f]	0.3	0.3	0	0	11.26[g]	1.1	1.1	0	0	0	0
4	4	9.61[f]	1.1	1.1	0	0	11.42[g]	1.8	1.8	0	0	0	0
5	2,3	8.98	−2.4	1.4	−3.8	2.1	11.09	0.4	2.9	−2.5	1.0	−8.0	2.9
6	2,4	9.50	0.5	2.2	−1.7	0.0	11.42	1.8	3.6	−1.8	0.3	−6.1	1.0
7	2,5	9.29	−0.7	1.4	−2.1	0.4	11.36	1.5	2.9	−1.4	−0.1	−6.3	1.2
8	2,6	8.38[h]	−5.9	2.2	−8.1	4.7	10.68[h]	−1.3	3.6	−4.9	1.9	−12.3	2.1
9	3,4	9.58[i]	1.0	1.4	−0.4	0.4	11.38[i]	1.6	2.9	−1.3	1.3	0.7[k]	−0.7
10	3,5	9.51[j]	0.6	0.6	0.0	0.0	11.29[j]	1.2	2.2	−1.0	1.0	0.3[k]	−0.3
11	2,3,4	9.19	−1.3	2.5	−3.8	2.1	11.26	1.1	4.7	−3.6	2.1	−10.1	5.0[k]
12	2,3,5	9.05	−2.1	1.7	−3.8	2.1	11.24	1.0	4.0	−3.0	1.5	−9.4	4.3[k]
13	2,3,6	8.42	−5.7	2.5	−8.2	4.8	11.07	0.3	4.7	−4.4	1.4	−17.0	6.8[k]
14	2,4,5	9.60	1.1	2.5	−1.4	−0.3	11.58	2.4	4.7	−2.3	0.7	−7.3	2.2
15	2,4,6	8.57	−4.8	3.3	−8.1	4.7	10.88	−0.5	5.4	−5.9	2.8	−12.7	2.5
16	3,4,5	9.66	1.4	1.7	−0.3	0.3	11.54	2.3	4.0	−1.7	1.7	−1.2	1.2
17	2,3,4,5	9.24	−1.0	2.8	−3.8	2.1	11.58	2.4	5.8	−3.4	1.8	−8.3	3.2
18	2,3,4,6	8.61	−4.6	3.6	−8.2	4.8	11.17	0.7	6.5	−5.8	2.7	−16.3	6.1
19	2,3,5,6	8.51	−5.1	2.8	−7.9	4.5	10.89	−0.5	5.8	−6.3	3.2	−14.9	4.7
20	2,3,4,5,6	8.66	−4.3	3.9	−8.2	4.8	11.31	1.3	7.6	−6.3	3.2	−16.2	6.0
s.d.[l]		0.02	0.1	0.2	0.3	0.3	0.06	0.2	0.5	0.7	0.7	1	1

[a] Values from ref. 10. [b] Estimated polar and steric parts of the substituent effect, respectively, see Discussion section. [c] Buttressing effect as defined in ref. 9. [d] Reference values, see refs. 24, 25. [e] Ref. 29. [f] Ref. 28. [g] Ref. 31. [h] Ref. 30 gives 8.57 and 10.64 in methanol and DMSO, respectively. [i] Ref. 24 gives 9.63 and 11.46 in methanol and DMSO, respectively. [j] Ref. 25 gives 9.59 and 11.29 in methanol and DMSO, respectively. [k] These values have been slightly corrected compared to ref. 10. [l] Standard deviation.

values as reference. Twenty compounds are sufficient to reveal some outliers or different behaviour within subgroups.

Let us begin with the total substituent effect of all methyl groups on the acidity. This may be given either in terms of the pK values relative to benzoic acid (pK^H), *i.e.* as pK^H − pK, or in the pertinent Gibbs energies as $\delta\Delta G^\circ_{acid} = \Delta G^\circ_{acid} - G^\circ{}_{acid}{}^{H}$. The latter values are also given in Table 1 and have a simple physical meaning: they represent the Gibbs energy of an isodesmic reaction. For example, in the case of 2,3-dimethylbenzoic acid, see reaction (1). In general, the substituent effects



(1)

$\Delta H_1^\circ(g) = -3.5$ kJ mol^{-1} (ref. 10)

$\Delta G_1^\circ(me) = -2.4$ kJ mol^{-1}

$\Delta G_1^\circ(DMSO) = +0.4$ kJ mol^{-1}

in a solvent are smaller than in the gas phase (attenuation). A close parallel between both is to be expected only for *meta* and *para* derivatives in agreement with the Hammett equation. Since our set contains many *ortho* derivatives, the proportionality is only rough, see the statistical data in Table 2, lines 1 and 4. [In the gas phase, we prefer using $\Delta H^\circ(g)$ to $\Delta G^\circ(g)$ because of pure symmetry effects affecting $\Delta G^\circ(g)$.[6,33] In our case the difference is immaterial.] More telling than the rough correlations is a graphical representation (Fig. 1). The five compounds without *ortho* substitution determine with reasonable accuracy a straight line with a slope of 0.26. For common, mostly strongly polar substituents, a slope of 0.14 would be obtained from dissociation constants measured in methanol[28] and in the gas phase.[21] The disagreement is understandable with respect to the weak polar effect of the methyl substituent which has small influence on the overall dependence when stronger substituents are present.[33] In any case the full line in Fig. 1 should correspond to the polar (inductive and/or hyperconjugative) effects of the methyl groups and its small slope expresses attenuation of polar effects: a less delocalized charge is better solvated and substituent effects and solvent effects partly compensate. Deviations of the remaining points from this line may be interpreted as specific steric and solvent effects. They increase with the number of methyl groups. Most marked are the deviations of all 2,6-dimethyl derivatives whose molecules are not planar.[8,17] Apparently, a non-planar anion is better solvated than a planar anion[27] and the acid is stronger.

Table 2 Statistics of correlations between thermodynamic quantities of methyl-substituted benzoic acids in gas and in solution (kJ mol^{-1}, 298 K)

Explanatory variable	Response function	Slope b	R^a	s.d.[a]	N^a
1 $\delta\Delta G_{acid}(g)$	$\delta\Delta G_{acid}(me)$	0.58 ± 0.06	0.910	1.08	20
2 $SE_{acid}(g)$	$SE_{acid}(me)$	0.52 ± 0.04	0.956	1.00	20
3 $\Delta BE_{acid}(g)$	$\Delta BE_{acid}(me)$	0.70 ± 0.12	0.806	1.26	20
4 $\delta\Delta G_{acid}(g)$	$\delta\Delta G_{acid}(DMSO)$	0.17 ± 0.05	0.661	0.79	20
5 $SE_{acid}(g)$	$SE_{acid}(DMSO)$	0.33 ± 0.03	0.930	0.80	20
6 $\Delta BE_{acid}(g)$	$\Delta BE_{acid}(DMSO)$	0.33 ± 0.08	0.712	0.80	20
7 $\delta\Delta G_{acid}(me)$	$\delta\Delta G_{acid}(DMSO)$	0.29 ± 0.07	0.731	0.72	20
8 $SE_{acid}(me)$	$SE_{acid}(DMSO)$	0.61 ± 0.04	0.957	0.64	20
9 $\Delta BE_{acid}(me)$	$\Delta BE_{acid}(DMSO)$	0.44 ± 0.07	0.831	0.63	20

[a] Correlation coefficient, standard deviation and number of data, respectively.

A similar dependence in DMSO solvent (not shown) would differ from Fig. 1 in two respects. Firstly, there is more scattering, partly also due to the lower experimental accuracy. Secondly, the attenuation of polar effects is greater, also the steric effects are weaker as is seen particularly on 2,6-dimethyl derivatives. In addition to a smaller solvation of the anions in DMSO,[27] one could also consider solvation of the neutral acid molecules in this basic solvent: both effects would make the acids weaker. For these reasons also the mutual dependence of $\delta\Delta G_{acid}$ in the two solvents is strongly scattered (Table 2, line 7).

Separation of polar and steric effects

A better insight into the substituent effects can be attempted by separating polar and steric effects. A simple approach was made

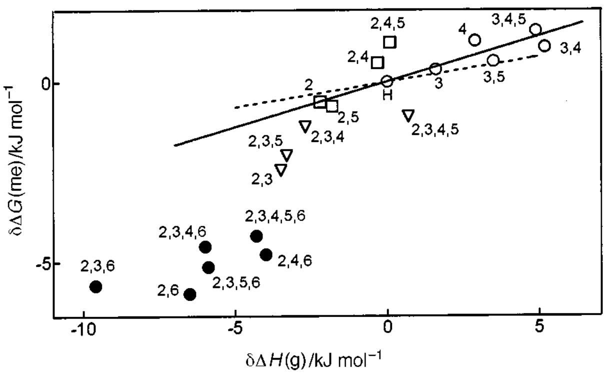
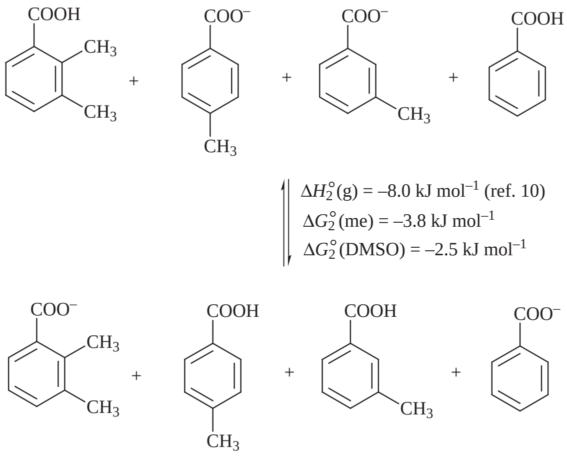


Fig. 1 Plot of the acidities of methyl-substituted benzoic acids in methanol *vs.* their acidities in the gas phase: ○ acids without *ortho* methyl groups, □ with one *ortho* methyl group, ▽ with methyl groups in the positions 2,3, ● with two *ortho* methyl groups. The solid line was drawn through the derivatives without *ortho* substituents, the broken lines has a slope determined from *meta* and *para* substituted benzoic acids with polar substituents.

previously on the gas-phase acidities in the same series of acids:[8,10] the effect of an *ortho* methyl group transmitted through the benzene ring (*i.e.* inductive, resonance or hyperconjugative) was assumed equal as in the *para* position in 4-methylbenzoic acid, the effect of a *meta* methyl group was taken from 3-methylbenzoic acid. Although this crude approximation may be criticised,[29] it may work reasonably well since the through-ring effects are rather small. It was also successful to the extent that the obtained steric effects SE were approximately proportional when calculated from two independent quantities: from the enthalpies of formation on the one hand and from the gas-phase acidities on the other (see Fig. 4 of ref. 10). When the concept of SE is to be expressed by an isodesmic reaction, this reaction is apparently complex [see reaction (2)]. The steric



$\Delta H_2^\circ(g) = -8.0$ kJ mol^{-1} (ref. 10)
$\Delta G_2^\circ(me) = -3.8$ kJ mol^{-1}
$\Delta G_2^\circ(DMSO) = -2.5$ kJ mol^{-1}

(2)

effects defined in this way are based on a thermodynamically defined equation but it is given no more physical meaning than a difference between the behaviour of a substituent in the *ortho* and *para* position. (The term proximity effect would be also acceptable.)

The SE values calculated in this way for solution are given in Table 1 (columns 6 and 11) for comparison with SE values in the gas phase (column 13). Although some of the values may be near to the experimental uncertainty, their reliability is reinforced by the fact that all values are negative—stabilizing the anion. The SE values in methanol are plotted *vs.* SE in the gas phase in Fig. 2. A good correlation (Table 2, line 2), much better than for crude substituent effects, gives some support to the simple kind of calculation. The slope of 0.52 expresses attenuation even of steric effects. However, a particular feature emerges from Fig. 2. SE values in methanol are grouped into four subgroups: acids with no *ortho* methyl substituent, with one *ortho* methyl, with two methyls in the position 2 and 3, and with two *ortho* methyl groups. Within each group, the gas phase values are sufficiently different but the values in methanol are not. Finer steric effects are thus observable in the gas phase, caused by more remote substituents. Such effects are not evident from the space-filling molecular models and can be denoted as non-classical.[9] In methanol solution, these finer effects are leveled. For instance, one must accept that there is a non-zero interaction between the two methyl groups in 2,4-dimethylbenzoic acid, but this interaction is cancelled in solution: one can imagine that the methyl groups are separated by a solvent molecule. A corresponding plot for DMSO solution (Fig. 3) gave similar results, taking into account the mentioned greater uncertainty of measurements in DMSO than in methanol. A still smaller slope of 0.33 (Table 2, line 5) can be interpreted by reduced solvation of the anions, or also by solvation of the neutral acid molecules as in the preceding section.

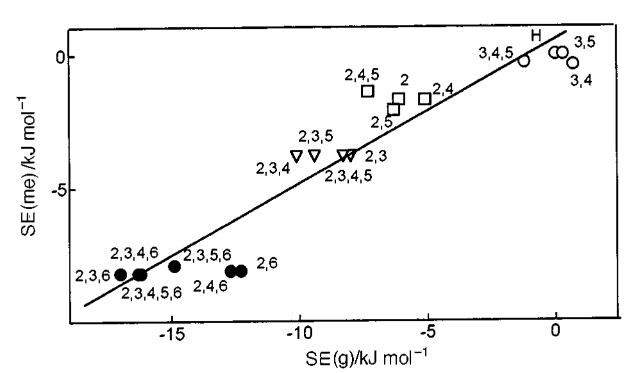


Fig. 2 Plot of steric components SE of the substituent effect in the acidities of methyl-substituted benzoic acids, in methanol *vs.* in the gas phase: the line is the regression line for all points, the points are denoted as in Fig. 1.

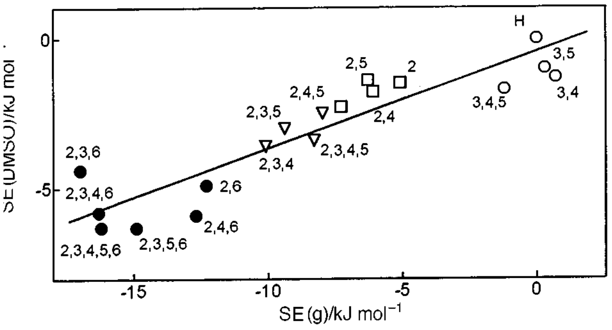


Fig. 3 Plot of the steric components SE of substituent effect in methyl-substituted benzoic acids in dimethyl sulfoxide *vs.* in the gas phase: the line is the regression line for all points, the points are denoted as in Fig. 1.

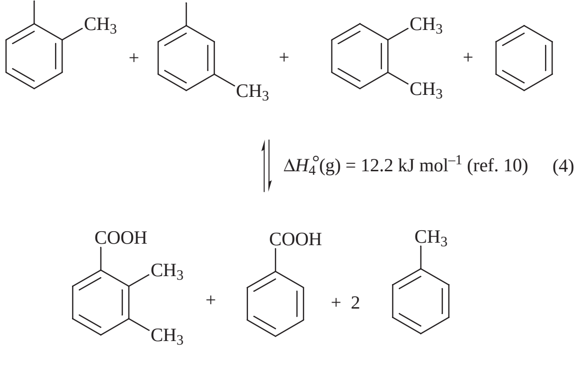
Our interpretation of the above facts differs from the views generally accepted. Commonly it has been believed[1–3,34] that molecules of all *ortho* methyl substituted benzoic acids are non-planar, the substituent effects being due to steric hindrance to resonance since resonance is important in the molecule of the acid but negligible in the anion. Variations of the effect in individual acids was attributed to differences in the torsion angle φ.[13–16] According to proof presented by us,[8,17,35] the methyl-substituted benzoic acids are in a planar conformation unless they have methyl groups in both *ortho* positions. In the planar molecules, the substituent effect called simply steric cannot be due to van der Waals interaction as defined by the well known function[36] of r^{-6} and r^{-12}, since the steric requirements of the groups COOH and COO$^-$ are practically equal.[18] In addition, the geometries of 2-methylbenzoic acid and of its anion, calculated using the 6-31+G** basis set[19] are not significantly different. We suggested[19] as the most probable interpretation that the apparent steric effect on acidity is not to be found in a greater destabilizing interaction in the acid but rather in an additional stabilizing interaction in the carboxylate anion, approximately described as electrostatic interaction.[20] The energy of interaction between the charge q and the dipole moment induced in a polarizable medium is expressed as a function of the distance r and polarizability a in eqn. (3). The effective relative permittivity

$$E = -aq^2/32\pi^2\varepsilon_o^2\varepsilon_{ef}^2r^4 \qquad (3)$$

ε_{ef} should possess a value between 1 and 2 in the gas phase. In the literature, eqn. (3) was given (in the CGS system—differing by a factor of $16\pi^2\varepsilon_o^2$) either erroneously,[37] with ε_{ef} instead of ε_{ef}^2, or ε_{ef} was entirely omitted.[20,21] The dependence on r^4 and on ε_{ef}^2 makes the calculation sensitive to the assumptions made, particularly as far as the localization of the charge and of the polarizable medium is concerned. Our calculations according to eqn. (3) yielded a reasonable agreement with experiments for $\varepsilon_{ef} = 2$ and when the charge was localized between the two oxygen atoms and the induced point dipole on the methyl carbon.[19] A previous calculation[21] only for 2-methylbenzoic acid had a comparable success with $\varepsilon_{ef} = 1$ but the value of a was not reported. Generally, this approach must be evaluated in a similar way to the well-known equations describing interactions between two charges or between a charge and a permanent dipole:[38] the electrostatic formulae are only an approximate model of the quantum chemical reality. We thus conclude only that our results in solution support the idea that the apparent steric effect of *ortho* methyl groups is caused by stabilizing interaction in the anion. In any case, we can confirm that generalized steric effects represent an important share in the overall *ortho* effect.[8,10,29] Previous correlations of many reaction series, particularly also of the benzoic acids, with the constants σ_I and σ_R did not reveal any steric effect[14] but these series were dominated by strong polar substituents and the important point for hydrogen was eliminated. In an extension of this work, steric effects were observed at least for some substituents.[39]

Buttressing effect

In polysubstituted derivatives, a general question arises as to whether there is an additional effect exceeding the sum of effects expected on the basis of mono derivatives. In the case of polar effects, these additional effects are mostly negligible and substituent effects are additive.[22–25,40] In the case of the steric effect, the classical term buttressing effect (BE) was coined to describe the non-additive behaviour of two adjoining substituents.[5] We extended this term to the properties of isolated molecules and redefined it with more precision.[8,9] In this conception, BE is an excessive energy of a trisubstituted compound exceeding the value anticipated on the basis of all three bis derivatives. For our example, 2,3-dimethylbenzoic acid, BE can be represented by the isodesmic reaction (4). This concept is applicable to any trisubstituted compound and any quantity representing energy. When it is applied to dissociation, the enthalpy of formation of *o*-xylene is dropped and the differential buttressing effect $-\Delta BE$ is represented by reaction (5).


$\Delta H_4^\circ(g) = 12.2\ \mathrm{kJ\ mol^{-1}}$ (ref. 10) (4)

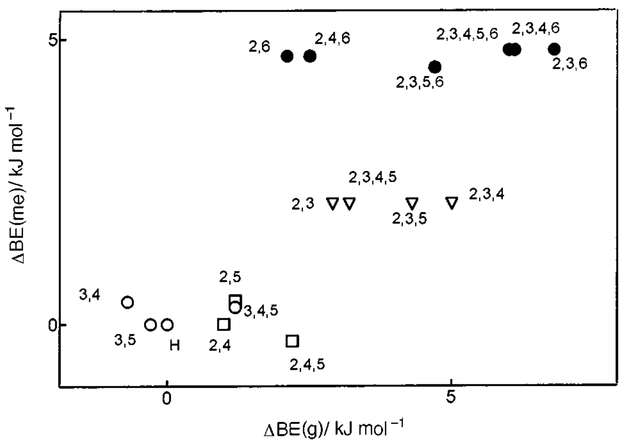
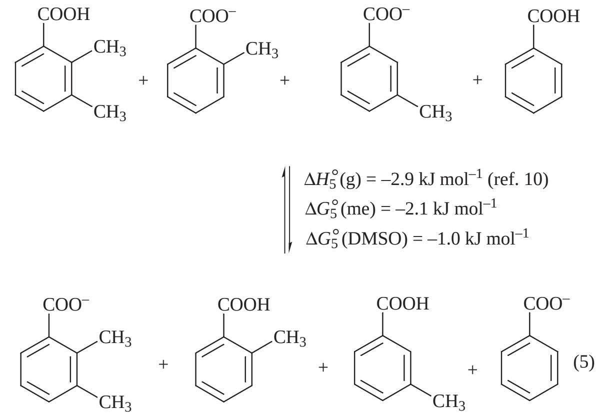


Fig. 4 Plot of the buttressing effect ΔBE in the acidities of methyl-substituted benzoic acids in methanol *vs.* in the gas phase, symbols as in Fig. 1


$\Delta H_5^\circ(g) = -2.9\ \mathrm{kJ\ mol^{-1}}$ (ref. 10)
$\Delta G_5^\circ(\mathrm{me}) = -2.1\ \mathrm{kJ\ mol^{-1}}$
$\Delta G_5^\circ(\mathrm{DMSO}) = -1.0\ \mathrm{kJ\ mol^{-1}}$
(5)

The sign of ΔBE was chosen[9] opposite (*i.e.* $\Delta BE = -\Delta H_5$) so that a positive value means stronger acidity of the disubstituted acid as it had been originally defined.[5] The most important result was that ΔBE is positive even in non-adjoining positions, for instance in 2,4-dimethylbenzoic acid [$\Delta BE(g) = 1.0$ kJ mol^{-1}]. As in the preceding section, one must accept that the van der Waals interaction even in the *meta* position is not negligible and the popular Stuart–Briegleb calotte models are misleading for more exact considerations.[9] Reaction (5) may seem rather complex but its purpose is only to show that ΔBE has a strict physical meaning. Actual calculating ΔBE in solution means a simple difference of relative $\delta\Delta G^\circ$ values for the ionization of 2,3-dimethyl-, 2-methyl- and 3-methyl-benzoic acids [eqn. (6)].

$$\Delta BE = -\delta\Delta G^\circ(2{,}3\text{-Me}_2) + \delta\Delta G^\circ(2\text{-Me}) + \delta\Delta G^\circ(3\text{-Me}) \qquad (6)$$

For ionization, the new definition of ΔBE is thus identical with the old concept and ΔBE has the same meaning as deviation from additivity. Compared to SE in the previous section, ΔBE has the advantage of being a purely experimental quantity, not dependent on any assumption or approximation. Calculated values of ΔBE in methanol and in DMSO are given in Table 1 (columns 7 and 12) in comparison with ΔBE in the gas phase[10] (column 14). A graphical comparison is presented in Fig. 4. The same separation into subgroups, mentioned already in Figs. 2 and 3, is observed, even more distinctly. In the gas phase, non-zero values of ΔBE are observable even in non-adjoining positions, *e.g.* 2,4 or 3,4,5; furthermore the values for positions like 2,3 and 2,3,5 are different. In solution, values of

ΔBE are divided into three groups, in which they are almost constant. These groups are signified either by 2,6-disubstitution, or by 2,3-disubstitution—both with significant ΔBE; the remaining derivatives show practically no ΔBE. Previously, ΔBE was observed in solution and only on derivatives with adjoining substituents: the most important proof was comparison of 2,3 and 2,5 derivatives.[5,41] These observations are now confirmed also by our solution data while the effects of more remote groups remain observable only in the gas phase.[9]

Conclusions

Detailed investigation of a restricted series of compounds showed conclusively that the common term steric effects cannot be understood in a unified way: its causes can be quite different in similar molecules or even in different properties of the same molecule. Within the series of methyl-substituted benzoic acids, we have observed van der Waals interaction (on the enthalpies of formation[8]), steric hindrance to resonance (in the case of 2,6-dimethyl derivatives) and electrostatic interaction ion-induced dipole. We have avoided discussion of 'effects' inexactly defined and focused attention on those which can be experimentally distinguished: for instance, one can decide whether an effect is present in the acid molecule or in the deprotonated form, or whether a molecule is planar or distorted. We believe that still further problems of this kind can be solved by the approach used here: the principle of isodesmic reaction and comparison of the acid–base properties in the gas phase and in solution.

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