# Steric Effects in Isolated Molecules: Gas-Phase Basicity of Methyl-Substituted Acetophenones

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The energies of 14 methyl-substituted acetophenones and of their protonated forms were calculated within the framework of the density functional theory at the B3LYP/6-311+G(d,p) level. The gas-phase basicities of some members of this series were measured using Fourier transform ion cyclotron resonance mass spectrometry in order to complete the known data. The protonated forms exist in two configurations differing in the position of the hydrogen atom; their equilibrium depends strongly on the substitution pattern. Taking into account all conformational equilibria, the experimental and calculated basicities agreed to within 2.7 kJ mol$^{-1}$. Substituent effects were tentatively resolved into polar and steric contributions by comparing the corresponding *ortho* and *para* derivatives. The steric effect of the *ortho*-methyl groups defined in this way has a clear physical meaning proven by several correlations; it destabilizes the neutral acetophenone molecules but destabilizes the cations even more. Hence it is base-weakening relative to the steric effect on the acidity of substituted benzoic acids, which is acid-strengthening.

## Introduction

Steric effects of *ortho* substituents in aromatic systems are most evident in their acid–base properties in solution.[1] The interpretation of these steric effects has often not sufficiently taken into account the fact that they result from a difference between the effect in the neutral molecule and in the ion: any reference to steric effects in the acid (or base) molecule assumes implicitly that such an effect is less important in the anion (or cation). Moreover, the actual magnitude of the effect was difficult to prove since solvation strongly influences the effective size of ions. Recently we evaluated the substituent effects in the isolated molecules of the neutral species and in the ions separately[2–6] on the basis of experimental gas-phase acidities (basicities) and gas-phase enthalpies of formation. Sometimes the latter were replaced by quantum chemical calculations. Some of our conclusions were at variance with those suggested on the basis of solution data. In particular, the theory of steric inhibition of resonance[7] (SIR) was not confirmed[2] in all cases in which it had been advocated.[8] Also the concept of a buttressing effect[9] (BE) was redefined[2a] and observed even in some nonclassical examples.[4]

The *ortho* effect of substituted benzoic acids on acidity has been studied most closely. The classical interpretation[1,8a,8d] relied on van der Waals interactions (vdW) or primary steric effects in the case of planar molecules and SIR in nonplanar molecules. However, we found this explanation not to be sufficient[10] since the volumes of the COOH and COO$^-$ groups are almost equal and so we took into consideration pole/induced dipole interactions that stabilize the anion.[11] However, this model is not applicable to the basicities of *ortho*-substituted aromatic carbonyl bases. In both acetophenones[12] and methyl benzoates[2a] with methyl groups in the *ortho* position, the basicity is reduced whereas electrostatic induction should stabilize equally any charged particles, both cations and anions. Even the basicity of acetophenones or benzoic acids in solution is weakened by *ortho* substitution.[13]

In this paper, we extend the investigation of steric effects in *ortho*-substituted aromatic compounds to their basicities which have been much less studied than their acidities.[14] We have chosen polymethyl-substituted acetophenones **1**–**14** as models (Table 1). These compounds were one of the model series on which the SIR theory was originally created.[7] While SIR has not been confirmed in the case of the

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Table 1. Calculated energies of methyl-substituted acetophenones and their protonated forms.

| | Substituents | Acetophenone base[a] | | | | Protonated form (*E*) | | | | Protonated form (*Z*) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *E*(DFT) [a.u.] | $\phi$ [°] | % | *d*(C–C) [Å] | *E*(DFT) [a.u.] | $\phi$ [°] | % | *d*(C–C) [Å] | *E*(DFT) [a.u.] | $\phi$ [°] | % | *d*(C–C) [Å] |
| **1** | H | –385.0016932 | 0.0 | | 1.502 | –385.3435345 | 0.0 | | 1.422 | –385.3404997 | 0.0 | | 1.433 |
| **2** | 2-Me *sp* | –424.3251100 | 0.5 | 98.1 | 1.500 | –424.6706219 | 0.0 | 97.0 | 1.419 | –424.6690528 | 0.1 | 98.5 | 1.433 |
| | *ac* | –424.3213794 | 148.4 | 1.9 | 1.508 | –424.6673517 | 179.9 | 3.0 | 1.425 | –424.6650687 | 157.2 | 1.5 | 1.434 |
| **3** | 3-Me *sp* | –424.3295711 | 0.0 | 57.9 | 1.501 | –424.6748431 | 0.0 | 54.8 | 1.421 | –424.6721738 | 0.0 | 53.8 | 1.431 |
| | *ap* | –424.3292696 | 180.0 | 42.1 | 1.501 | –424.6746609 | 180.0 | 45.2 | 1.421 | –424.6720290 | 180.0 | 46.2 | 1.431 |
| **4** | 4-Me | –424.3300643 | 0.0 | | 1.498 | –424.6784801 | 0.0 | | 1.415 | –424.6755187 | 0.0 | | 1.425 |
| **5** | 2,3-$Me_2$ *sp* | –463.6491420 | 23.8 | 95.5 | 1.501 | –463.9971558 | 0.0 | 98.2 | 1.420 | –463.9959029 | 0.0 | 99.8 | 1.434 |
| | *ac* | –463.6462679 | 138.3 | 4.5 | 1.507 | –463.9933618 | 180.0 | 1.8 | 1.426 | –463.9901080 | 180.0 | 0.2 | 1.438 |
| **6** | 2,4-$Me_2$ *sp* | –463.6536231 | 0.0 | 98.5 | 1.496 | –464.0054113 | 0.0 | 96.6 | 1.413 | –464.0038000 | 0.2 | 98.8 | 1.426 |
| | *ap* | –463.6496947 | 151.3 | 1.5 | 1.506 | –464.0022406 | 180.0 | 3.4 | 1.418 | –463.9996553 | 159.9 | 1.2 | 1.427 |
| **7** | 2,5-$Me_2$ *sp* | –463.6525710 | 0.8 | 97.5 | 1.499 | –464.0015394 | 0.0 | 96.3 | 1.418 | –464.0002829 | 0.0 | 99.5 | 1.432 |
| | *ac* | –463.6491203 | 148.3 | 2.5 | 1.508 | –463.9984654 | 180.0 | 3.7 | 1.424 | –463.9953339 | 180.0 | 0.5 | 1.435 |
| **8** | 2,6-$Me_2$ | –463.6457513 | 73.3 | | 1.510 | –463.9897017 | 21.3 | | 1.423 | –463.9893823 | 28.1 | | 1.435 |
| **9** | 3,4-$Me_2$ *sp* | –463.6573014 | 0.0 | 59.7 | 1.498 | –464.0084663 | 0.0 | 57.0 | 1.414 | –464.0058613 | 0.0 | 54.2 | 1.424 |
| | *ap* | –463.6569285 | 180.0 | 40.3 | 1.498 | –464.0082014 | 180.0 | 43.0 | 1.414 | –464.0057014 | 180.0 | 45.8 | 1.424 |
| **10** | 3,5-$Me_2$ | –463.6569911 | 0.0 | | 1.501 | –464.0056098 | 0.0 | | 1.419 | –464.0032339 | 0.0 | | 1.429 |
| **11** | 2,3,4-$Me_3$ *sp* | –502.9742208 | 24.5 | 95.8 | 1.499 | –503.3276139 | 5.8 | 95.1 | 1.414 | –503.3266384 | 10.6 | 96.2 | 1.426 |
| | *ac* | –502.9712674 | 141.1 | 4.2 | 1.505 | –503.3248087 | 167.4 | 4.9 | 1.417 | –503.3235853 | 156.9 | 3.8 | 1.428 |
| **12** | 2,4,6-$Me_3$ | –502.9734556 | 68.6 | | 1.507 | –503.3241393 | 19.0 | | 1.417 | –503.3235408 | 25.7 | | 1.429 |
| **13** | 3,4,5-$Me_3$ | –502.9817839 | 0 | | 1.498 | –503.3359498 | 0.0 | | 1.413 | –503.3336555 | 0.0 | | 1.427 |
| **14** | 2,3,5,6-$Me_4$ | –542.2972744 | 90.0 | | 1.516 | –542.6429374 | 30.1 | | 1.423 | –542.6439812 | 37.2 | | 1.435 |

[a] See ref.[15]

electronic spectra,[15] it was used to interpret many other properties of these compounds,[16] in particular their gas-phase basicities.[12]

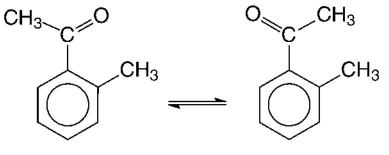
We examined this model both experimentally and theoretically. The gas-phase basicities reported for mono- and dimethylacetophenones[12] were extended to sterically more hindered derivatives and the results were anchored on a recent scale of proton affinities.[17] The energies of **1**–**14** and of their protonated forms were calculated within the framework of DFT[18] at the B3LYP/6-311+G(d,p) level. This theoretical model proved good for molecules of similar size.[19] The substituent effects were evaluated in terms of isodesmic reactions[20] and were tentatively resolved into polar and steric effects. Our final goal was to achieve a better understanding of the apparent difference between the steric effects of substitution on acidity and on basicity.

## Results and Discussion

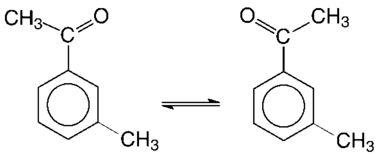
### Conformation of the Bases and Their Protonated Forms

The conformation of methyl-substituted acetophenones has been the object of much controversy since most of theexperimental data can be interpreted in two ways. For instance compound **2** was assumed to exist in equilibrium**2A** ⇋ **2B**,[21] or in a nonplanar conformation.[16,22] According to our calculations[15] (Table 1, columns 4 and 5) the derivatives with one *ortho*-methyl group exist in an equilibrium of two nearly planar forms, for example, **2A** and **2B**, however **2A** strongly prevails. The *meta* derivatives **3** and **9** exist in an equilibrium of two planar forms of similar energy, for instance **3A** ⇋ **3B**. Derivatives with two *ortho*-methyl groups, **8**, **12** and **14**, prefer a nonplanar conformation,[16,22] like **8**, with the torsion angle $\phi$ rather close to 90°. Derivatives **5** and **11** represent transitional cases: owing to the buttressing effect[2b,9] even the prevailing form is slightly nonplanar but it is still classified as having an *sp* conformation (the C=O and C1–C2 bonds are in a synperiplanar position). Further minor forms, similar to **2B**, are seldom planar, (*ap*, antiperiplanar), and are more often nonplanar (*ac*, anticlinal); Table 1 gives the exact torsion angles.

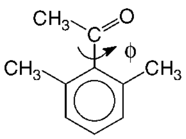
The conformational equilibria have little impact on the calculated energy. We calculated first the population of the rotamers and then the effective energy of the equilibrium mixture. We obtained values that were only slightly greater than the energy of the more stable conformer,[23] by 0.4 kJ mol–1 at most.



**2A** **2B**



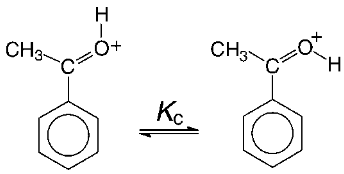
**3A** **3B**



**8**

The protonated forms **$1H^+$**–**$14H^+$** reveal that the C1–C(O) bond has essentially the same conformation as the parent acetophenones **1**–**14**, even the angles $\varphi$ and the population of the rotamers are rather similar (Table 1). Hence, the impact of these conformations on the basicity is negligible.

The most important stereochemical feature was discovered when calculating the structures of the protonated forms: they exist in an equilibrium of two configurations differing only in the position of the proton, for instance (*E*)-**$1H^+$** ⇋ (*Z*)-**$1H^+$**. The equilibrium constant $K_c$ (Table 2, column 3) changes with the structure. For acetophenone and its sterically unhindered derivatives, the (*E*) configuration strongly prevails; for nonplanar derivatives the populations of the (*E*) and (*Z*) configurations are comparable. In the following discussion, the equilibrium mixture will be taken into consideration when comparison is made with the experimental results, while the individual (*E*) and (*Z*) configurations will be referred to when evaluating the substituent effects.



*E*-**$1H^+$** *Z*-**$1H^+$**

### Calculated and Experimental Basicities

To calculate the anticipated basicity, we took into consideration all existing equilibria. The only problem, although not crucial, may be with the statistical weight of the conformers. Nonplanar conformers are racemates and should be given, in principle, a doubled statistical weight (for instance, **2**-*ac* relative to **2**-*sp*). However, this is not a straightforward decision since some angles $\phi$ are very small and/or the rotational barrier is very low (for instance,[15] 0.7 kJ mol$^{-1}$ for **2**-*ac*). Therefore, we decided to give equal statistical weight to all conformations in the Boltzmann distribution and believe that this is the best approximation. Note that the impact of this problem on the calculated basicities is only a few tenths of a kJ mol$^{-1}$.

The calculated relative basicities $\Delta_1 E$ of **1**–**14** (given in Table 2, column 4) thus relate to the isodesmic reaction (1) with each formula representing the Boltzmann equilibrium mixture of all the configurations and conformations. These values were correlated to the experimental gas-phase basicities $\Delta_1 H°(298)$ (Table 2, column 5). The fit is very satisfactory with a correlation coefficient of $R = 0.962$ and a standard deviation from the regression of $s = 2.7$ kJ mol$^{-1}$, which is comparable to the experimental uncertainty (see ref.[12] and Table S1); the slope $b = 0.99 \pm 0.08$ is not significantly different from unity. The agreement with the experimental relative basicities gives confidence to the following analysis based on the calculated values.

### Substituent Effects

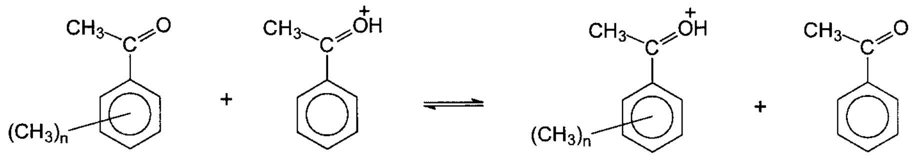
The substituent effects will be evaluated separately according to the principle of isodesmic reactions.[20] The reaction energy of reaction (2), $\Delta_2 E$, represents the substituent effect of the methyl groups on the acetyl group in uncharged molecules. Similarly, the substituent effects in the two configurations of the protonated forms are represented by either reaction (3) or (4) and are denoted $\Delta_3 E$ and $\Delta_4 E$, respectively. Reactions (1)–(4) are all isodesmic and homodesmotic.[24]

The reaction energies $\Delta_2 E$–$\Delta_4 E$ are given in Table 2, columns 6–8. While $\Delta_3 E$ and $\Delta_4 E$ have a close correlation ($R = 0.977$), $\Delta_2 E$ and $\Delta_3 E$ are only roughly similar (Figure 1, part A). This can be explained by the simultaneous action of polar and steric effects: the polar effects influence the cations much more than neutral molecules while steric ef-

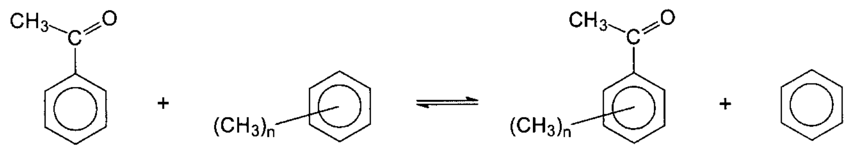
Table 2. Calculated and experimental energies of the isodesmic reaction of methyl-substituted acetophenones.[a]

| | Substituents | $K_c$ ([*E*]/[*Z*]) | Basicity $\Delta_1 E$ calcd.[b] | Basicity $\Delta_1 H°$ exp.[d] | $\Delta_2 E^{[b,c]}$ Base | $\Delta_3 E^{[b,c]}$ Cation (*E*) | $\Delta_4 E^{[b,c]}$ Cation (*Z*) | $\Delta_2 E_{st}$ Base | $\Delta_3 E_{st}$ Cation (*E*) | $\Delta_4 E_{st}$ Cation (*Z*) |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | H | 24.87 | 0 | –861.1[e] | 0 | 0 | 0 | 0 | 0 | 0 |
| **2** | 2-Me | 5.04 | –9.21 | –866.1[e] | 11.01 | 1.45 | –2.51 | 13.19 | 20.89 | 17.13 |
| **3** | 3-Me | 16.61 | –9.04 | –868.2[e] | –0.55 | –9.68 | –10.68 | 0 | 0 | 0 |
| **4** | 4-Me | 23.01 | –17.25 | –875.5[e] | –2.18 | –19.44 | –19.64 | 0 | 0 | 0 |
| **5** | 2,3-$Me_2$ | 3.56 | –15.99 | –874.6[e] | 13.69 | –2.68 | –7.50 | 16.42 | 26.44 | 22.82 |
| **6** | 2,4-$Me_2$ | 5.19 | –25.64 | –882.6[e] | 8.15 | –17.84 | –21.72 | 12.51 | 21.04 | 17.56 |
| **7** | 2,5-$Me_2$ | 3.45 | –18.26 | –873.5[e] | 10.55 | –8.09 | –12.99 | 13.28 | 21.03 | 17.33 |
| **8** | 2,6-$Me_2$ | 1.40 | –5.50 | –857.0[e] | 28.66 | 23.13 | 16.00 | 33.02 | 62.01 | 55.28 |
| **9** | 3,4-$Me_2$ | 15.11 | –24.46 | –882.8[e] | –7.68 | –32.25 | –33.49 | –4.95 | –3.13 | –3.17 |
| **10** | 3,5-$Me_2$ | 12.38 | –17.64 | –876.0[e] | –0.85 | –18.64 | –20.37 | 0.25 | 0.72 | 0.99 |
| **11** | 2,3,4-$Me_3$ | 2.75 | –29.93 | –887.8[f] | 11.03 | –19.26 | –24.72 | 15.94 | 29.30 | 25.24 |
| **12** | 2,4,6-$Me_3$ | 1.88 | –22.98 | –875.2[f] | 27.54 | 4.33 | –2.07 | 34.08 | 62.65 | 56.85 |
| **13** | 3,4,5-$Me_3$ | 11.35 | –32.18 | –890.8[f] | –9.15 | –41.51 | –43.45 | –5.87 | –2.71 | –2.45 |
| **14** | 2,3,5,6-$Me_4$ | 0.33 | –12.40 | –869.6[f] | 23.74 | 13.71 | 3.00 | 29.20 | 71.95 | 63.64 |

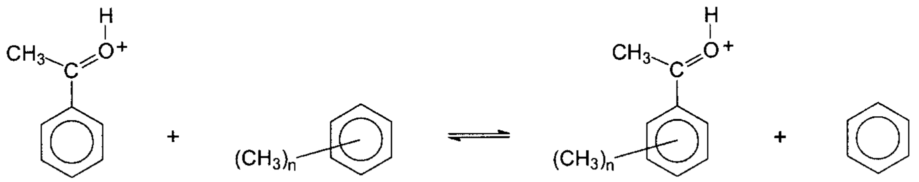
[a] Energy values are given in kJ mol$^{-1}$. [b] The subscript corresponds to the number of the defining isodesmic equation. [c] The enthalpies of the isodesmic reactions (1) and (2) were calculated from the *E*(DFT) values in Table 1 and the *E*(DFT) values for methyl-substituted benzenes from ref.[15] [d] Equals the proton affinity with the sign inversed. [e] Values taken from ref.[17], the value for **2** was taken directly from ref.[12] and adjusted by reference to the value of $\Delta_1 H°$ for **1**. [f] This work, Table S1 in the Supporting Information.



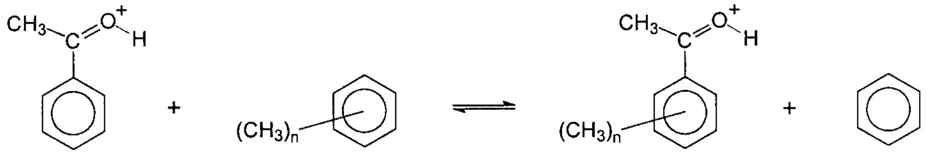
(1)



(2)



(3)



(4)

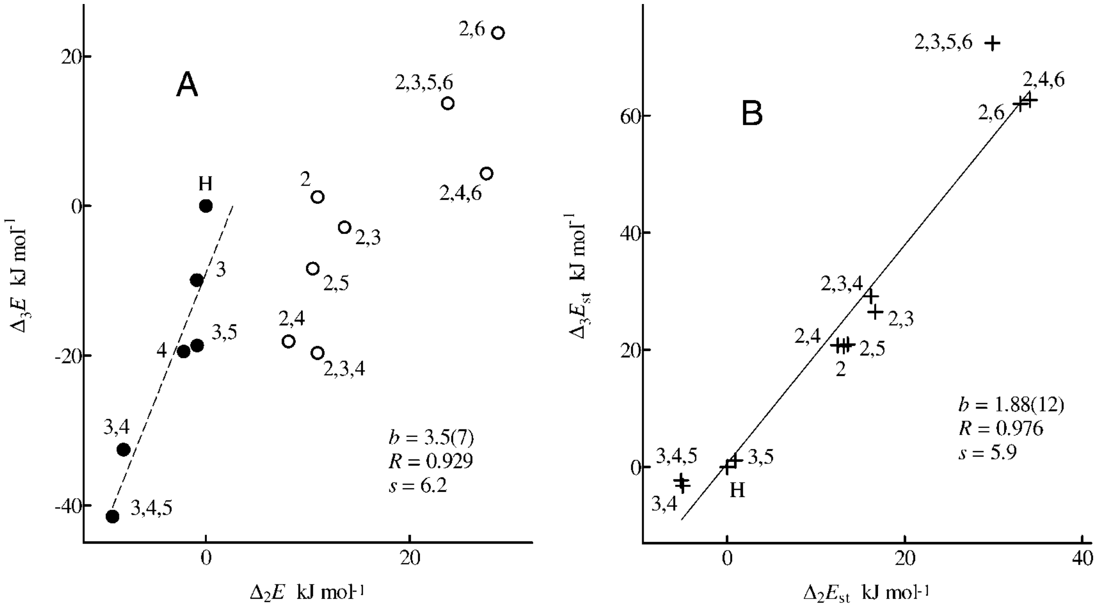


Figure 1. Dependence of the substituent effects $\Delta_2E$ of the methyl groups in methyl-substituted acetophenones **1**–**14** and the substituent effects $\Delta_3E$ in their protonated forms: A) total substituent effects and B) only the steric component, separated according to Equation (5); ●: compounds without steric hindrance obey the Hammett equation (the statistics and the regression line belong to this subgroup).

fects are of comparable magnitude. In Figure 1 (part A) the six compounds without *ortho* substituents obey the Hammett equation (extended to polysubstitution) and lie nearly on a line. Its slope, $b = 3.5$, reveals a much stronger polar effect in the cations than in the nonprotonated acetophenones. The large deviations of the remaining points disclose strong steric effects.

### Separation of Steric Effects

The attempted separation of steric effects uses the known principle,[2–5] comparison of *ortho* and *para* derivatives. This is based on three assumptions. a) Steric effects are negligible in the *meta* and *para* positions. b) Polar effects are equal in the *ortho* and *para* positions. c) Polar effects are additive. For instance, the steric effect $\Delta_2E_{st}$ in 2,3-dimethylacetophenone is obtained from the total substituent effect by subtracting the substituent effects in 4-methylacetophenone and in 3-methylacetophenone [Equation (5), $i = 2$]. The same procedure was used for the protonated forms ($i = 3$ or 4).

$$\Delta_iE_{st}(2,3\text{-Me}_2) = \Delta_iE(2,3\text{-Me}_2) - \Delta_iE(3\text{-Me}) - \Delta_iE(4\text{-Me}) \qquad (i = 1\text{–}4) \qquad (5)$$

Assumption b) was doubted: polar effects in the *ortho* position were assumed to be either smaller or greater than in the *para* position.[25,26] However, we left the original definition based on assumptions a) and b), as exemplified in Equation (5), since the polar effect of the methyl group is weak and the correction would have a negligible impact. Moreover, by introducing an empirical correction, Equation (5) would lose the character of an isodesmic reaction.

The calculated steric effects $\Delta_2E_{st}$, $\Delta_3E_{st}$ and $\Delta_4E_{st}$ are given in the last three columns of Table 2. They are zero by definition for compounds **1**, **3** and **4**; for **9**, **10** and **13** they would be zero when the above assumptions were exactly valid. The negative values for **9** and **13** suggest some deviations from the additivity of polar effects but these can be neglected. The positive values indicate strong steric hindrance and their physical meaning can be proven in several ways. First, the $\Delta E_{st}$ values for the acetophenones and their cations have a close correlation (Figure 1, part B), while the original reaction energies $\Delta_2E$ and $\Delta_3E$ do not (Figure 1, part A). Further, very convincing proof was obtained from purely experimental values: There is no correlation between the gas-phase basicities of **1**–**14** and the $^{13}$C NMR chemical shifts of the carbonyl carbon atom[27] (Figure 2, part A) since the basicities are much more sensitive to polar effects than are the $^{13}$C chemical shifts. When the steric effect is separated, it is evident that it affects both quantities in a similar way (Figure 2, part B).

The steric effects on the protonated forms depend somewhat on the configuration, (*E*) or (*Z*), but are closely proportional in both: $R = 0.9995$, and a slope of $b = 1.19(10)$ means that they are slightly greater in form (*E*). The steric effects are stronger in both cations than in the nonprotonated acetophenones (Figure 1, part B); the difference determines the effect on the basicity. The values of $\Delta E_{st}$ are a measure of the steric hindrance in both the planar and nonplanar derivatives. They are roughly three times stronger in nonplanar compounds, but even in planar compounds the values close to 20 kJ mol$^{-1}$ are not negligible.

### Steric Inhibition to Resonance

The physical properties of substituted acetophenones,[7,16] in particular their gas-phase acidities,[12] have been commonly explained in terms of SIR. This explanation is evidently invalid for the planar derivatives as has

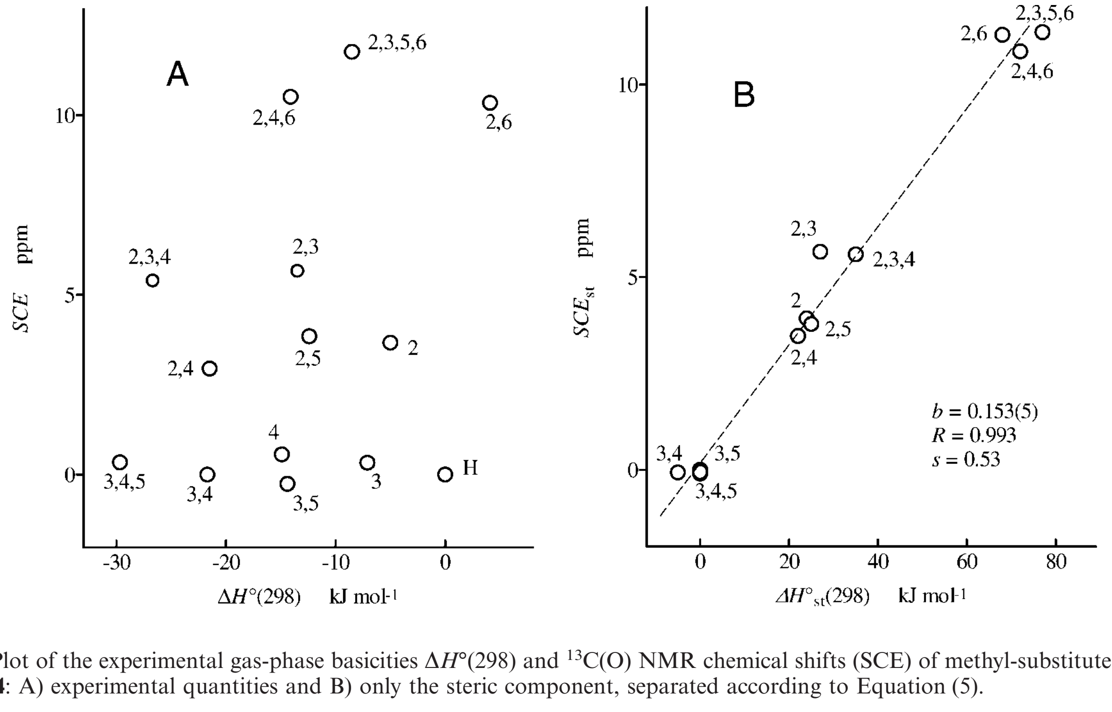


Figure 2. Plot of the experimental gas-phase basicities $\Delta H°(298)$ and $^{13}$C(O) NMR chemical shifts (SCE) of methyl-substituted acetophenones **1**–**14**: A) experimental quantities and B) only the steric component, separated according to Equation (5).

already been stated in the analysis of the electronic[15] and NMR spectra.[27] In the case of nonplanar derivatives **8**, **12** and **14**, the SIR can be estimated by means of a previously suggested[10] model involving artificial molecules with a fixed conformation.

In reaction (6) $\phi$ represents the actual torsion angle in the minimum-energy conformation of the substituted acetophenone; it is fixed at the same value in unsubstituted acetophenone. The reaction energy $\Delta_6E$ may include any steric effect other than SIR, the contribution of which is obtained by subtracting $\Delta_6E$ from the total effect, $\Delta_2E$. SIR in the cations is estimated in the same way. The results are given in Table 3. SIR is important in neutral molecules, but much less important in the (*E*) or (*Z*) cations. There is partial compensation for the effect of SIR on basicity. In any case, SIR cannot be used to explain the effect of substitution on basicity:[12] SIR would have a directly opposite effect, viz. base-strengthening. However, as in other cases,[10,14] SIR has rather little effect on the acid–base properties.

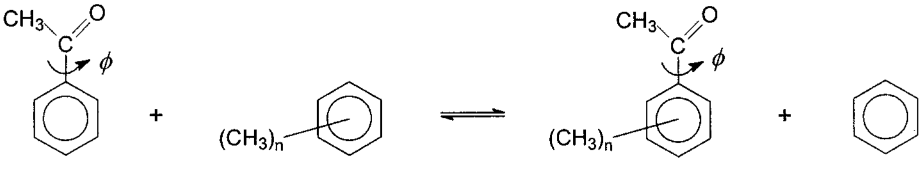
### Steric Effects on Acidity and Basicity

In the previous sections, we attempted to estimate the steric effects on the basicity of substituted acetophenones in the same way as previously the steric effects on the acidity of equally substituted benzoic acids had been estimated.[2,10] When we compare the two series, the effects are opposite: benzoic acids are made stronger acids (the ionic form is stabilized) while acetophenones are made weaker bases (the ionic form is destabilized). This difference is not easy to rationalize.

Better insight is gained when the effects are divided into those operating in the acetophenone molecules ($\Delta_2E_{st}$, Table 2) and in the cations. Since there are two cations, we shall use, instead of $\Delta_3E_{st}$ and $\Delta_4E_{st}$, the values pertinent to the equilibrium mixture in the Boltzmann distribution and denote them $\Delta_{34}E_{st}$. Now $\Delta_2E_{st}$ and $\Delta_{34}E_{st}$ can be compared with the corresponding quantities for benzoic acids: $\Delta E_{st}(Bz)$ for the acids[2b] and $\Delta E_{st}(Bz^-)$ for the benzoate anions.[2b] This comparison is straightforward. All four quantities increase with steric hindrance, roughly correlate with each other (*R* is from 0.914 to 0.995), but are of different magnitude: the values of $\Delta_2E_{st}$ and $\Delta E_{st}(Bz)$ for the neutral molecules are nearly equal, the values of $\Delta_{34}E_{st}$ are greater by a factor of 1.9 (Figure 1, part B) and $\Delta E_{st}(Bz^-)$ are smaller by a factor of 0.6 (see Figure 2 in ref.[10]). Therefore the steric effect on the cations, $\Delta_{34}E_{st}$, is much stronger than on the anions $\Delta E_{st}(Bz^-)$ (Figure 3, part A).

When we now return to the acidities and basicities, the steric effect of substitution on the basicities of the acetophenones is given by the difference $\Delta_{34}E_{st} - \Delta_2E_{st}$ and is still positive (weaker bases) while the effect on the acidities of the benzoic acids is given by the difference $\Delta E_{st}(Bz^-) - \Delta E_{st}(Bz)$ and the sign is to negative (stronger acids; Figure 3, part B). From this there is a simple and clear conclusion that can be made: the acidities or basicities are not the best quantities for following their dependence on structure and various substituent effects. The energies of the individual ions are more suitable for this, although they are difficult to obtain experimentally and in practice must be based on calculations.

A less important problem is why the anions and cations are affected so differently by steric hindrance. In the case of benzoic acids we argued that the purely van der Waals demands of the groups COOH and $COO^-$ must almost be equal and we tentatively attributed the observed effects to electrostatic phenomena (interaction pole/induced dipole).[10] The same reasoning does not apply in the case of acetophenones. The geometries of 2-methylacetophenone and its cation (Figure 4) are not equal and steric effects may be greater in the cation. However, electrical effects must play a role and an explanation involving induced dipoles would lead to a false prediction. We tried to prove that the charge distribution in the cations (of acetophenones) and in the anions (of benzoic acids) is quite different since the charge is more delocalized in the latter. For comparison we chose protonated 2,4-dimethylacetophenone and the 2,4-dimethylbenzoate anion since their molecules are planar. The electron-density maps (see the Supporting Information, Figures S1 and S2) reveal different charge distributions but



(6)

Table 3. Estimates of the extent of the steric inhibition of resonance on the basicity of nonplanar substituted acetophenones.[a]

| Compound | Acetophenones | | Cations *E* | | Cations *Z* | | Basicity | |
|---|---|---|---|---|---|---|---|---|
| | SIR[b] | Non-SIR[c] | SIR[b] | Non-SIR[c] | SIR[b] | Non-SIR[c] | SIR[b] | Non-SIR[c] |
| **8** | 24.0 | 5.0 | 4.6 | 57.4 | 4.7 | 50.6 | –19.4 | 49.6 |
| **12** | 23.6 | 5.2 | 5.0 | 57.6 | 4.3 | 52.5 | –18.7 | 50.6 |
| **14** | 27.0 | 13.1 | 10.3 | 61.6 | 12.8 | 50.9 | –14.9 | 40.4 |

[a] Measured in $kJ\,mol^{-1}$. [b] Equal to the difference $\Delta_2E - \Delta_6E$. [c] Equal to the reaction energy $\Delta_6E$ of reaction (6).

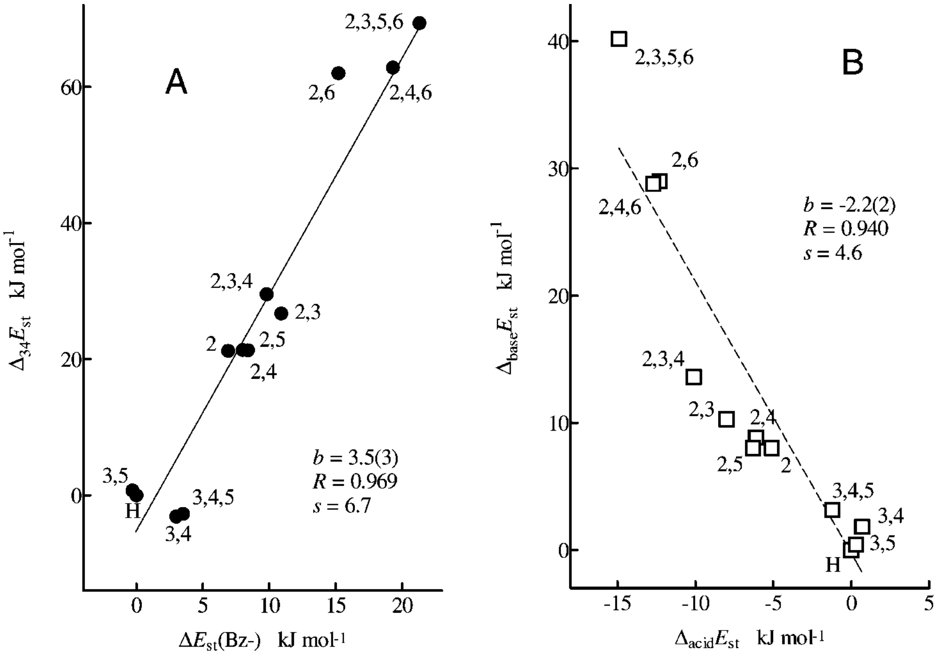


Figure 3. Comparison of steric effects on the acidity of methyl-substituted benzoic acids (*x* axis) and on the basicity of equally substituted acetophenones (*y* axis): A) in terms of the energy of anions versus the energy of the cations and B) in terms of acidity versus basicity.

are difficult to explain in detail. A more significant difference was found in the electron charges calculated within the framework of the Merz–Singh–Kollmann scheme.[28] We considered the C-2 carbon atom to be the critical point. When 2,4-dimethylacetophenone is protonated on the carbonyl oxygen atom, the electron density at C(O) decreases by 0.08 electrons (Table 4) and also decreases at the C-2 atom by 0.04 electrons. When 2,4-dimethylbenzoic acid is deprotonated, the electron density at C(O) increases by 0.06 electrons, but at the C-2 atom it decreases slightly; the charge is strongly delocalized and changes induced in other parts of the molecule are not straightforward. Simple electrostatic models are unsatisfactory; their main shortcoming is in placing the charge or dipole at a particular point. From this point of view even our model of pole/induced dipole interactions[10] was only an ad hoc explanation.

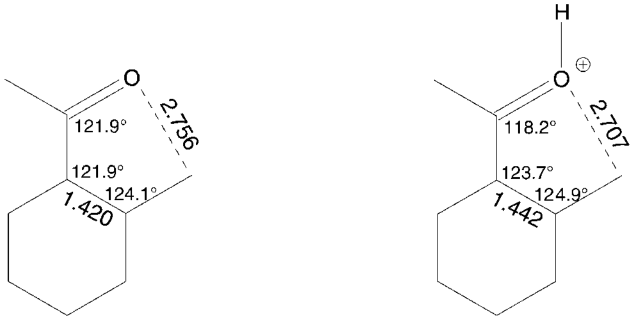


Figure 4. Important geometrical parameters of 2-methylacetophenone **2** and of its protonated form (*E*)-**2H**$^+$ in their most stable conformations (bond lengths in Å).

## Conclusions

The gas-phase basicities may be more difficult to determine by calculations than the acidities since the structure of the protonated form must be resolved. Apart from cases in which protonation of two functional groups is possible, this work has revealed that even protonation of a given atom may generate two cations with different configurations: their ratio is not constant even in a series of structurally similar compounds. If this is the case, one must then take into consideration either the equilibrium mixture of isomers (in relation to the experimental data) or a single isomer (to estimate the substituent effects). In searching for possible isomers and rotamers, quantum chemical calculations are indispensable.

The effects of substituents on basicity can sometimes be difficult to rationalize, particularly when they are compared

Table 4. Charges[a] at selected atoms of 2,4-dimethylacetophenone and 2,4-dimethylbenzoic acid according to Merz–Singh–Kollmann scheme.

| | Charges at the carbonyl oxygen atom | Charges at the C-2 carbon atom |
|---|---|---|
| 2,4-Dimethylacetophenone (**6**) | –0.536 | –0.500 |
| Protonated form, **6H**$^+$ | –0.456 | –0.464 |
| 2,4-Dimethylbenzoic acid | –0.561 | –0.433 |
| Anion | –0.624 | –0.414 |

[a] Charges given in electrons.

with the effects of substituents on the acidity of structurally similar acids. The problem may be unraveled when they are resolved by means of isodesmic reactions into effects in the cation and in the base molecule, similarly in the case of the acidity into the effects in the anion and in the acid molecule. Then the substituent effects become more regular, for instance, being only quantitatively different in the cations and anions.

## Computational Methods

DFT calculations at the B3LYP/6-311+G(d,p) level were carried out according to the original proposal[18] using the Gaussian program.[29] Full geometry optimization was carried out separately for each configuration and conformation given in Table 1. Planarity or symmetry constraints were never assumed. Vibrational analysis was carried out in all cases: All structures were energy-minima conformations. The calculated energies of **1**–**14** and of their protonated forms **1H$^+$**–**14H$^+$** together with some important geometrical parameters are listed in Table 1.

The reaction energies $\Delta_2 E - \Delta_4 E$ of reactions (2)–(4) were obtained from the energies $E$(DFT) of **1**–**14** and of the methyl-substituted benzenes.[15] When several conformers or configurations coexist, the values of $\Delta_2 E - \Delta_4 E$ were corrected to relate to their equilibrium mixture at 298 K. The equilibrium constant and population of the conformers were estimated on the assumption that $\Delta G°(298) \approx \Delta E(\text{DFT})$.

The energies of the frozen conformations of **8**, **12** and **14** with a fixed dihedral angle $\phi$, as defined in Equation (6), were calculated in such a way that all remaining geometry parameters were optimized with respect to internal coordinates. The energies of individual compounds are not reported and only the final results of substituent effects are given in Table 3.

The electron densities were calculated according to the method of Merz–Singh–Kollmann[28] at the B3LYP/6-31+G(d,p)//B3LYP/6-311+G(d,p) level; the results are given in Table 4.

## Experimental Section

The synthesis of compounds **11**–**14** has been described previously.[15]

The gas-phase basicities were determined by Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry.[2a,6]

**Supporting Information:** Supplementary Information contains Table S1, which provides the original experimental data for determining the gas-phase basicities, some details of the experimental procedure and Figures S1 and S2, which show the electron-density map of the protonated 2,4-dimethylacetophenone and the 2,4-dimethylbenzoate anion.

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