Acidity of Substituted Benzenes − An Ab Initio Study of the Influence of Methoxy, Trifluoromethyl and Trifluoromethoxy Groups by a Novel Trichotomy Formula

Borislav Kovačević,[a] Zvonimir B. Maksić,*[a,b] and Miljenko Primorac[c]

Keywords: Acidity / Aromaticity / Electrostatic field effect / Substituent effects

The acidities of mono- and polysubstituted benzenes incorporating one, two, or three OCH_3, OCF_3, or CF_3 groups were investigated by use of reliable ab initio theoretical models. The calculated deprotonation energies are in very good agreement with available experimental data, although these are unfortunately sparse. A recently developed novel trichotomy formula proved useful for interpretation of predicted variation in acidity in the monosubstituted compounds. In particular, the long-range final state effect in OCF_3 and CF_3 derivatives is confirmed. It is reflected in the stabilization of the lone-pair electrons formed upon deprotonation at the *meta* and *para* positions. The theoretically established long-range influence of OCF_3 and CF_3 substituents is in accordance with empirical knowledge obtained by experimental chemical reactivity studies. The acidities of multiply substituted benzenes exhibit additivity properties based on the ISA (independent substituent approximation) model established earlier. It is conclusively shown that the combination of the additivity rule and the trichotomy formula offers a powerful tool for interpretation of the acidity of polysubstituted benzenes and of other multiply substituted aromatics, thus shedding new light on this very old and important problem.

Introduction

The exploration of gas-phase reactions has significantly contributed to understanding of structure-reactivity correlation thanks to the absence of solvation effects, implying that the results were directly related to immanent or intrinsic reactivities,[1−4] which in turn were not "contaminated" by the environment. The study of gas-phase acidities has been a major undertaking in this field of intensive research for a number of decades.[5−8] It is therefore not surprising that many experimental and theoretical efforts have been devoted to the elucidation of acidity in widely different molecular systems[9−13] in order to identify the underlying principles and ultimately to help in the design of new acidic substances, with particular emphasis on superacidic compounds.[14−18] We would like to point out that interpretation of acidity on the basis of simple concepts such as Koopmans' ionization potentials, anionic relaxation energy and homolytic CH energy[19] has proved very useful, since it offered a penetrating insight into the relative contributions to the deprotonation process of the initial and final states and their interplay. This not only provides better understanding of the preponderant effects and mechanisms governing the acidity of some Brønsted acids, but also sheds new light on acid-base chemistry in general, thus providing a new vehicle for investigations. A somewhat different, but related, interpretation of the origin of acidity was recently presented by Exner and Čàrsky.[20] Furthermore, it is also worth mentioning that substituent effects in aromatics appear to follow an interesting and surprisingly simple additivity rule,[21−25] which determines the C−H acidity of the aromatic ring in polysubstituted compounds. It is based on the independent substituent approximation (ISA) model,[21] in which each substituent behaves as if all the others were non-existent. This feature parallels the basicities of polysubstituted aromatic bases[26,27] and facilitates interpretation of acidity in heavily substituted aromatic compounds, which are not easily understood otherwise. Needless to say, in order to apply the ISA model it is necessary to estimate and understand the behaviour of each substituent separately. One of the most intriguing substituent groups is the trifluoromethoxy moiety, which affects the aromatic ring proton acidity by a long-range electron-withdrawing mechanism.[28] Its outstanding anion-stabilizing capacity is reflected in the extraordinary ease that characterises hydrogen/metal exchange reactions. The aim of this work is to examine the influence of the OCF_3 group on the acidity of the benzene moiety, to compare it with the effect of other substituents such as OCH_3 and CF_3, and to offer some rationale for its behaviour. Last but not least, we would

---

[a] Quantum Organic Chemistry Group, Ruđer Bošković Institute, 10000 Zagreb, Croatia,
E-mail: zmaksic@spider.irb.hr
[b] Faculty of Science and Mathematics The University of Zagreb, Marulićev trg. 19, 10000 Zagreb, Croatia
[c] Faculty of Forestry, The University of Zagreb, Svetošimunska c. 25, 10000 Zagreb, Croatia

DOI: 10.1002/ejoc.200300391

like to test the additivity rule in polysubstituted benzenes incorporating the groups described above. It would appear that the additivity rule[21] and trichotomy formula[19] provide powerful means for interpretation of the acidities of polysubstituted benzenes in general, thus placing this study in a wider perspective.

Theoretical Background

According to Brønsted, acidity is the capability of a molecule to give up a proton.[29] Hence, acidity is given by the Gibbs energy change $\Delta_r G^\circ$ for the reaction:

$$RH \rightarrow R^- + H^+ \quad (1)$$

As criteria for the acidity, instead of the Gibbs energy, we shall adopt: (a) the change in enthalpies of formation of the species occurring in Equation (1) as far as the G2(MP2) method (vide infra) is concerned and, alternatively, (b) deprotonation energy (*DPE*) for the MP2 model described below. Further, for interpretative purposes, the proton affinity of the corresponding conjugate base $PA(R_a^-)$ will be used interchangeably, because $PA(R_\alpha^-) = DPE(RH_\alpha)$. At the MP2 level of theory (vide infra) the latter is estimated by use of the general Equation (2).

$$DPE(RH_\alpha) = E(R_\alpha^-) + ZPVE(R_\alpha^-) - [E(RH) + ZPVE(RH)] + (5/2)\,RT \quad (2)$$

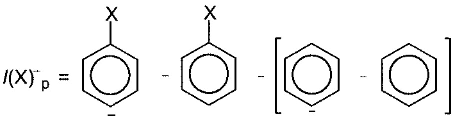
E signifies the total molecular electronic energy, RH and R^- stand for the acid in question and its conjugate base, respectively, while α denotes the site of deprotonation. The zero−point vibrational energy is given in a shorthand notation as *ZPVE*. Excellent agreement with experiment can be obtained by the G2 procedure.[30] However, the G2 approach is too impractical to be used in larger systems involving heavy atoms, such as those examined in this work. A more efficient and economical alternative, with a fairly small sacrifice in accuracy, is represented by a simplified G2(MP2) procedure.[31] However, we would also like to examine an even simpler theoretical model provided by the MP2(fc)/6-311+G**//HF/6-31+G* (abbreviated as MP2) computational strategy,[21] which would be more practical than G2(MP2) procedure. It consists of the HF/6-31+G* optimization of the molecular structures and the MP2(fc)/6-311+G** estimates of the total molecular electron energies obtained by the single-point calculations. The *ZPVE* values are obtained at the HF/6-31+G* level by employment of a weighting factor of 0.915, as customary.[32] Another theoretical route useful in calculation of *DPE*s is offered by some density functional theory (DFT) methods.[8] They are quite efficient, but in our experience somewhat less reliable than the MP2 model. All calculations were carried out with the aid of the Gaussian 98 suite of programs.[33]

Results and Discussion

Increments

The systems studied are depicted in Figure 1. Let us first discuss the effect of the monosubstituents; results are presented in Table 1. The first observation to be made is that G2(MP2) deprotonation energies obtained by calculation of enthalpies for the deprotonation process according to Equation (1) are in excellent agreement with a few available experimental data. The *DPE* of benzene at 293.15 K is 401.7[34] and 400.7,[35] for instance, which compares well with the G2(MP2) result (399.8 kcal/mol). This kind of agreement is satisfactory, if it is taken into account that a typical experimental error is ±3 kcal/mol. Similarly, the measured *DPE* value for **8** of 387.1 kcal/mol[35] is consistent with the G2(MP2) estimate (386.3 kcal/mol obtained for the *ortho* position). There is, however, a discrepancy with experimental findings for methoxybenzene **2**, for which the reported *meta* and *para* deprotonation energies are 394±3 and 394±3 kcal/mol, respectively.[36] Whether this is a consequence of a known tendency of anisole anion to undergo fragmentation or not is an open question. However, the reported *DPE* for the *ortho* deprotonation site (391±3 kcal/mol[36]) is in good agreement with our G2(MP2) and MP2 estimates (390.8 and 389.9 kcal/mol, respectively) for this position. In view of the paucity of experimental data, the calculated *DPE*s − discussed below − are particularly useful, because their accuracy is similar to that of the experiment alone. Going back to a survey of the theoretical results displayed in Table 1, it may be said that the MP2 *DPE*s are in good agreement with G2(MP2) predictions. We conclude that both theoretical models are satisfactory, being able to discriminate among various acidic position on the benzene perimeter despite the fact that the relative values for alternative positions within a molecule are sometimes rather small. This is of importance since they cannot as a rule be easily distinguished by experiment.

Modification of the acidity at the *para* position due to a substituent X is given by Equation (3).



(3)

$I(X)_p^-$ denotes the increment in *DPE* relative to a free benzene, where X represents OCH_3, OCF_3, and CF_3 substituents. Analogous expressions hold for the *ortho* and *meta* increments $I(X)_o^-$ and $I(X)_m^-$, respectively. A survey of the increments presented in Table 1 shows that they are little dependent on the methods applied here, since both G2(MP2) and MP2 procedures yield similar values. We discuss both G2(MP2) and MP2 increments below, however, because the former are somewhat more accurate, whereas the latter can be tested within the additivity rule against the actual PA(MP2) calculations for polysubstituted benzenes

Table 1. Total molecular enthalpies (in au) of benzene, its monosubstituted derivatives and the corresponding data relating to their deprotonated species as obtained by the G2(MP2) method; the resulting proton affinities are compared with those calculated by the MP2 model. Koopmans' ionization potential and decomposition of PA according to Equation (4) are presented in the lower part of this table (in kcal/mol)

Molecule	G2MP2(Enth.)	*PA*(G2MP2)	*PA*(MP2)[a]	$I^{-}(X)_{\alpha}$[b]	$I^{-}(X)_{\alpha}$[c]
1	−231.77080	–	–	–	–
$\mathbf{1}_1$	−231.13603 (−231.08635)	399.8	400.0	–	–
2	−346.11976	–	–	–	–
$\mathbf{2}_2$	−345.49931 (−345.43477)	390.8	389.9	−9.0	−10.1
$\mathbf{2}_3$	−345.48690 (−345.43538)	398.6	399.0	−1.2	−1.0
$\mathbf{2}_4$	−345.48385 (−345.43305)	400.5	400.1	0.7	0.1
$\mathbf{2}_5$	−345.48566 (−345.43507)	399.6	400.6	−0.2	0.6
$\mathbf{2}_6$	−345.49064 (−345.43168)	396.3	397.1	−3.5	−2.9
5	−643.61839	–	–	–	–
$\mathbf{5}_2$	−643.01016 (−642.93011)	383.2	382.1	−16.6	−17.9
$\mathbf{5}_3$	−643.00064 (−642.93238)	389.1	388.3	−10.7	−11.7
$\mathbf{5}_4$	−642.99863 (−642.93147)	390.4	389.7	−9.4	−10.3
8	−568.48341	–	–	–	–
$\mathbf{8}_2$	−567.87020 (−567.79558)	386.3	386.2	−13.5	−13.8
$\mathbf{8}_3$	−567.86540 (−567.79700)	389.3	388.3	−10.5	−11.7
$\mathbf{8}_4$	−567.86594 (−567.79711)	389.9	388.4	−9.9	−11.6
	$-IP(X^{-})_{a}^{Koop}$	$(IP)_{1}^{ad}$	$E(ei)_{rex}^{(\alpha)}$	$(BDE)_{\alpha}^{\bullet}$	PA(tri)
$\mathbf{1}_1$	−66.2	31.2	35.0	117.2	399.6
$\mathbf{2}_2$	−74.5	40.5	34.0	117.6	390.7
$\mathbf{2}_3$	−69.5	32.3	37.2	117.2	398.5
$\mathbf{2}_4$	−66.9	31.9	35.0	118.6	400.3
$\mathbf{2}_5$	−68.9	31.7	37.2	117.4	399.3
$\mathbf{2}_6$	−71.4	37.0	34.4	119.5	396.1
$\mathbf{5}_2$	−89.3	50.2	39.1	119.6	383.0
$\mathbf{5}_3$	−80.2	42.8	37.4	118.2	389.0
$\mathbf{5}_4$	−78.7	42.1	36.6	118.8	390.3
$\mathbf{8}_2$	−85.4	46.7	38.7	119.3	386.2
$\mathbf{8}_3$	−80.2	42.9	37.3	118.4	389.1
$\mathbf{8}_4$	−81.9	43.2	38.7	118.4	388.8

[a] *PA*(MP2) proton affinities obtained by the MP2(fc)/6-311+G**//HF/6-31+G* + *ZPVE*(HF/6-31+G*) model. Total molecular enthalpies of radical generated by ejection of an electron from anionic lone pair are given in parentheses. They are calculated by the G2MP2 unrestricted approach. [b] Increments obtained by the G2MP2 method. [c] Increments obtained by the MP2 model.

studied here and possibly in some other compounds considered in the future. Specifically, it appears that OCH_3 considerably activates the *ortho* position, has a very small effect on the *meta* position, and affects the *para* position to a negligibly small extent. In other words, the OCH_3 group exerts a short-range *ortho* effect. In contrast, the trifluoromethoxy group OCF_3 exhibits a long-range effect, as evidenced by $I(X)_o^{-}$, $I(X)_m^{-}$, and $I(X)_p^{-}$, which assume −17.9, −11.7, and −10.3 kcal/mol, respectively. It appears that the *para* position is activated by OCF_3 much as the *ortho* position is affected by OCH_3. The same conclusion about the long-range influence is valid for a CF_3 substituent, with one notable difference: its activation of the *ortho* position lies between those found for the methoxy and the trifluoromethoxy groups. It thus follows that OCF_3 acidifies the *ortho* position by far the most. The question arises of which electronic features influence the acidity of the benzene ring in its monosubstituted derivatives and govern variations in the *DPE*s described above. A useful tool for interpretation of the acidities of neutral organic molecules has been developed recently.[19] Briefly, it is embodied in the trichotomy formula according to Equation (4), describing protonation of the corresponding anion (a reverse DP reaction).

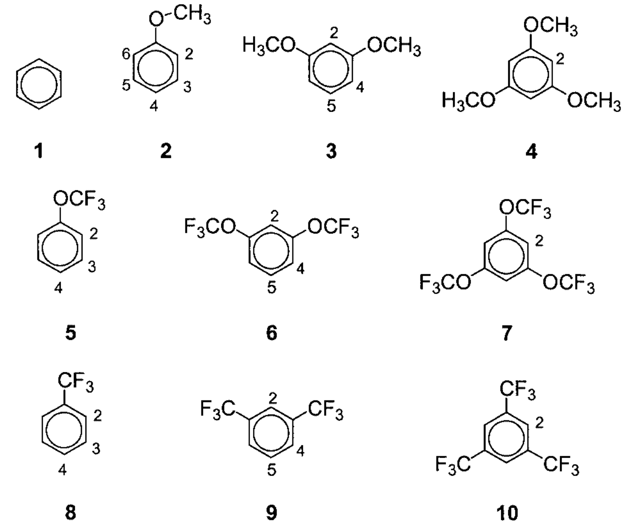


Figure 1. Schematic representation of substituted benzenes and the numbering of atoms

$$PA(X^-)_\alpha = -IP(X^-)_\alpha^{\mathrm{Koop}} + E(\mathrm{ei})_{\mathrm{rex}}^{(\alpha)} + (\mathrm{BDE})_\alpha^{\bullet} + 313.6\ \mathrm{kcal/mol} \quad (4)$$

α is the site of protonation, $IP(X^-)_a^{\mathrm{Koop}}$ is the Koopman's ionization potential of the anion calculated in the frozen electron density and clamped nuclei approximation, and $E(\mathrm{ei})_{\mathrm{rex}}^{(\alpha)}$ is the relaxation energy, which gives the reorganisation effect upon electron ejection by ionization of the anion [Equation (5)].

$$E(\mathrm{ei})_{\mathrm{rex}}^{(\alpha)} = IP(X^-)_\alpha^{\mathrm{Koop}} - (IP)_1^{\mathrm{ad}} \quad (5)$$

Here the first adiabatic potential of the anion is denoted by $(IP)_1^{\mathrm{ad}}$. Note that $IP(X^-)_\alpha^{\mathrm{Koop}}$ is not necessarily the first Koopmans' ionization potential, since it depends on the site and/or functional group to be deprotonated. It is very important to stress here that Koopman's ionization potential mirrors the initial state features of bases and the final state properties of acids, whereas the second term $E(\mathrm{ei})_{\mathrm{rex}}$ describes the relaxation of the electron cloud during the protonation/deprotonation processes. Finally, the bond dissociation energy describing homolytic C−H bond formation in the protonation or its scission in the deprotonation process at position α is given by the $(BDE)_\alpha^{\bullet}$ term. The use of Koopmans' IPs is a crucial step. It provides a description of the true initial/final state electronic characteristics of bases/acids, enabling subsequent introduction of the relaxation process as an interplay of the initial and final states. Thus employment of Koopmans' approximation offers a distinct advantage over the use of conventional adiabatic ionization potentials. Finally, a word on terminology is appropriate here. We have named a trichotomy formula [Equation (4)] for obvious reasons, but alternatively it can be denoted as triadic formula. Two important points should be kept in mind. Firstly, the deprotonation is considered in reverse (i.e., as protonation of the corresponding conjugate base as mentioned above). Secondly, triadic analysis [Equation (4)] is performed at the G2(MP2) level of theory, whilst Koopmans' ionization potentials are calculated by the restricted HF/6-311+G(3df,2p)//MP2(full)/6-31G* model. Bond dissociation energy $BDE_\alpha^{\bullet}$ is calculated by use of the unrestricted G2(MP2) approach. Earlier we showed that the triadic formula (4) proved useful in interpretation of the relative acidities of some small neutral acids.[19] It appears that the same interplay of three contributions given in Equation (4) determines the acidities in monosubstituted benzenes, as this analysis indicates. Particularly important in this respect, however, is the variation in Koopmans' ionization potentials $IP(X^-)_\alpha^{\mathrm{Koop}}$, which dominates changes in the acidity. Some characteristic results presented in Table 1 substantiate this assertion. It can be observed that the bond dissociation energy $(BDE)^{\bullet}$ obtained by the G2(MP2) method is fairly constant, being in a narrow gap between 117.2 and 119.6 kcal/mol. It can hence safely be stated that it does not influence the variation in the acidity to any appreciable extent. The relaxation energy $E(\mathrm{ei})_{\mathrm{rex}}^{(\alpha)}$ exhibits a somewhat more pronounced spread of the values in the range between 34.0 and 39.1 kcal/mol. The largest variation, however, is found in the changes in the ionization potentials of the resulting conjugate bases calculated in the frozen electron density distribution and fixed nuclei approximation (i.e., within Koopmans' theorem $-IP(X^-)_a^{\mathrm{Koop}}$, meaning that the acidities of these compounds are determined by the final state features. In our model then, the $IP(X^-)^{\mathrm{Koop}}$ term mirrors the genuine properties of the resulting anions. Relative acidities, be it between two different compounds or between different sites in the same compound, are conveniently described by changes in the characteristic contributions written in the form of a triad expressible as: $\Delta(DPE)_{\alpha(\mathbf{m},\mathbf{n})} = \Sigma[\Delta(-IP(X^-)_{\alpha(\mathbf{m},\mathbf{n})}^{\mathrm{Koop}};\Delta E(\mathrm{ei})_{\mathrm{rex}}^{(\alpha(\mathbf{m},\mathbf{n}))};(BDE)_{\alpha(\mathbf{m},\mathbf{n})}^{\bullet}]$, in which summation is extended over three terms given within the square parentheses and a subscript $\alpha(\mathbf{m},\mathbf{n})$ denotes the α positions in two different molecules **m** and **n**, which relinquish the proton. The difference Δ of two corresponding magnitudes in the triadic formula is always taken as **m** − **n**. It is important to keep in mind that the change in the ionization potential IP^{Koop} should be entered into this formula with a negative sign. Similarly, one can consider changes between different positions (α and β) in different molecules ($\mathbf{m} \neq \mathbf{n}$): $\Delta(DPE)_{\alpha(\mathbf{m}),\beta(\mathbf{n})} = \Sigma[\Delta(-IP(X^-)_{\alpha(\mathbf{m}),\beta(\mathbf{n})}^{\mathrm{Koop}};\Delta E(\mathrm{ei})_{\mathrm{rex}}^{\alpha(\mathbf{m}),\beta(\mathbf{n})};\Delta(BDE)_{\alpha(\mathbf{m}),\beta(\mathbf{n})}^{\bullet}]$. In a special case, **m** could be equal to **n** ($\mathbf{m} = \mathbf{n}$). If, for instance, benzene is taken as an *etalon* (gauge) of basicity, one can easily identify the origin of the strong long-range effect exerted by the OCF_3 group, or the lack of it, as in the case of the OCH_3 constituent. Specifically, for the *para*-deprotonated positions in **5**(OCF_3) and **2**(OCH_3) the corresponding triads obtained by the G2(MP2) approach read: $\Sigma(-12.5;1.6;1.6) = -9.3$ kcal and $\Sigma(-0.7;0.0;1.4) = 0.7$ kcal/mol, respectively, implying that the increase in acidity of the former molecule relative to benzene is a consequence of the long-range influence of the OCF_3 group on the

Koopmans' ionization potential, which in turn is substantially increased relative to benzene and to its derivative **2**. Analogously, one can analyse variation in acidity (*DPE*s) within a single molecule. For example, it appears that all five positions in methoxybenzene **2** are non-equivalent. Let us first examine why OCH_3 group is an *ortho*-directing substituent and not a *meta*- or *para*-acidifying factor. The corresponding $\Delta(DPE)_{o(\mathbf{2}),m(\mathbf{2})} = \Sigma[-5.0;-3.2;0.4] = -7.8$ kcal/mol and $\Delta(DPE)_{o(\mathbf{2}),p(\mathbf{2})} = \Sigma[-7.6;-1.0;-1.0] = -9.6$ kcal/mol values, where o, m, and p stand for *ortho*, *meta*, and *para* positions, respectively, indicate that the largest influence on a decrease in acidity at more distant positions in this compound is due to more loosely bound lone pairs in the corresponding conjugate bases. A difference in *DPE*s between positions C(2) and C(6) in **2**, estimated by assuming that the $O-CH_3$ fragment does not exhibit an internal rotation around the O−C (aryl) bond, is relatively small, but significant: $\Delta(DPE)_{2(\mathbf{2}),6(\mathbf{2})} = \Sigma[-3.1;-0.4;-1.9] = -5.4$ kcal/mol. This is a result of the more stable (by 3.1 kcal/mol) lone pair at C(2), which is at least partly due to interaction between the two C−H bonds of the methyl group positioned above and below the molecular plane around the anionic $C(2)^-$ site, thus forming a weak three-centre double hydrogen bond configuration and a homolytic C(6)−H bond energy slightly stronger by ca. 2 kcal/mol. Further, it is plausible to assume that the $C(6)^-$ lone pair in the deprotonated acid **2** suffers a small but nonvanishing repulsion with oxygen lone pairs of the $O-CH_3$ group, thus contributing to a difference $\Delta(-IP(\mathbf{2}^-)_{2(\mathbf{2}),6(\mathbf{2})}{}^{koop})$ of −3.1 kcal/mol and that there is some repulsion between the C(2)−H bond and the CH_3 group in the initial acid, thus giving rise to the difference in BDEs$^{\cdot}$ of 2 kcal/mol described above. The *ortho*-directing effect of the OCF_3 group in **5** in comparison with the *para* position suggests the same conclusion: $\Delta(DPE)_{2(\mathbf{5}),4(\mathbf{5})} = \Sigma(-10.6;2.5;0.8) = -7.6$ kcal/mol, which illustrates the overwhelming influence of the lone-pair ionization potential computed in Koopmans' approximation. The question arising is why OCF_3 should have such a long-range effect on the lone pairs formed upon deprotonation at *meta* and *para* positions. A plausible explanation is offered by the fact that the lone pairs in the σ-plane are localized to a high extent. Consequently, they are influenced the most by the intramolecular electrostatic potential. It is therefore fair to say that the OCF_3 group is a long-range acidifying factor, because it produces a strong long-range electrostatic field, which stabilises m and p lone pairs. The same conclusion also holds for CF_3 substituents.

Since the OCF_3 group is of particular interest, we considered the effect of the internal rotation of the CF_3 group around the aryl C(1)−O bond in the anion generated by deprotonation at the C(2) carbon atom. Let us denote the angle of torsion $C(F_3)-O-C(1)-C(2)$ as Θ. The energy landscape for deprotonated $\mathbf{5}^-$ against Θ is depicted in Figure 2. A part of the potential energy, within the range Θ = 0−100°, is almost completely flat, with two shallow minima at Θ = 50° and 100°, lower than $E(\Theta = 0°)$ by only 0.2 kcal/mol. The barrier between the two minima is 0.1 kcal/mol. This is negligible and one is tempted to conclude that there is a free libration of the CF_3 group around the deprotonated C(2) position for the Θ range between −90° and 90°, which has no influence on the total energy (of deprotonation). The energy for the *anti* position Θ = 180° is 2 kcal/mol higher than that for Θ = 100°, implying that the CF_3 group can rotate almost freely with a very small influence (if any) on the acidity of the *ortho* positions in **5** (see later). The rotational barrier of neutral acid **5** has been studied by several research groups both experimentally (MW, matrix IR) and theoretically by ab initio and DFT methods.[37−40] The most sophisticated calculations were performed by Karpfen et al.,[40] who found that the ortho [o]-conformation of $O-CF_3$ group relative to the benzene plane is 0.5 kcal/mol more stable than the eclipsed [e]-conformation by MP2/cc-pVTZ and B3LYP/cc-pVTZ procedures. These conformations correspond to two minima on the potential surface, separated by a low barrier with a height of about 0.2 kcal/mol above the [e] conformation. This finding was also confirmed by MP4(SDTQ) computations.[40] It follows that there is almost free rotation in the initial compounds **5**, which should increase the total energy by approximately 0.5 kcal/mol. Taking into account that the internal rotation should also effectively increase the energy of deprotonated **5** at position $C(2)^-$ by roughly 0.5 kcal/mol, we can safely conclude that acidity of **5** should not be affected by rotational motion of the OCF_3 group.

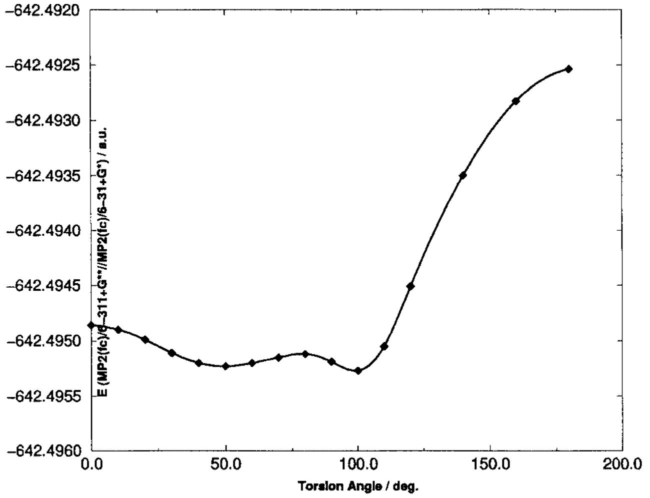


Figure 2. Total electronic energy profile of deprotonated trifluoromethoxy benzene (**5**), deprotonated at the C(2) position, as a function of the torsion angle describing internal rotation of the CF_3 group around the aryl-O bond (energy in au, angle in degrees)

Polysubstituted Benzenes and the Additivity Rule

The additivity rule governing the acidity of multiply substituted benzenes developed by us[21] and experimentally confirmed by Schlosser et al.[22−24] not only provides a useful rule of thumb, but also offers semiquantitative information on the deprotonation energies in a quick and inexpensive way. The corresponding formula reads:

$$DPE(\text{subst. benzene})_\alpha = DPE(\text{benzene}) + \Sigma I(\text{S})_{\alpha(\text{s})}{}^{-} \quad (6)$$

In which the summation is over all substituents S and α(s) denotes the position of the substituents relative to the deprotonation site (α = o, m, p). The underlying concept is that of the independent substituent approximation (ISA) as mentioned earlier. The formula according to Equation (6) performs surprisingly well in spite of its utmost simplicity.[21,22−24] However, some caution is always necessary when approximate model descriptions are employed. In some systems interactions between substituents might be significant, thus resulting in non-additivity. One such example is provided by chloroarenes studied by Schlosser et al[41] This, however, does not undermine the utility of the additivity formula; it merely shows that the additivity formula has its limitations and that it can be employed as a probe for some special non-additive effects, which have to be separately scrutinised. Perusal of the data presented in Table 2 shows that the additive *DPE*s reproduce the actual ab initio results in both doubly and triply substituted benzenes very well. This conclusion holds for both sets of additivity values obtained by MP2 and G2(MP2) increments. Hence, the additivity formula (6) offers a very useful means indeed for estimation of *DPE*s (acidity) in substituted benzenes. However, there is one additional very important benefit originating from the additivity formula. Since it works so well in most cases, it straightforwardly follows that the interpretation of acidity provided by the trichotomy formula (4) for monosubstituted benzene holds for polysubstituted benzenes as well. Consequently, it can be concluded that the acidities of compounds **2−10** are predominantly affected by the ionization potentials of the carbon atom lone pairs formed upon deprotonation, estimated in the clamped nuclei and frozen electron density Koopmans' approximation. In other words, the final state effect has a decisive role in determining the acidic behaviour of the aromatic compounds discussed in this study. The most acidic molecule is **7**, followed by **10**, which is in agreement with the corresponding increments for OCF_3 and CF_3 groups given in Table 1. We conclude that the additivity rule of Equation (6) in conjunction with the trichotomy formula of Equation (4) offers an illuminating insight into the acidity of polysubstituted benzenes. There is no doubt that the same conceptual framework (trichotomy interpretation) used simultaneously with a simple computational tool (additivity formulas) can interpret the acidities of other larger aromatics and their multiple derivatives along similar lines.

Table 2. Total molecular energies of polysubstituted benzenes and their deprotonated species as calculated by the MP2 Model (in au); the *ZPVE*s obtained by the scaled HF/6-31+G* results and the corresponding *PA*(MP2) values are given in kcal/mol; they are compared with the additivity estimates obtained by G2MP2 and MP2 increments

Molecule	M(I)	$ZPVE_{sc}$	*PA*	*PA*(add)[a]	*PA*(add)[b]
3	−460.09817	102.2	–	–	
3_2	−459.48070	93.1	379.9	379.8	381.8
3_4	−459.46445	93.1	390.2	390.1	391.5
3_5	−459.45243	93.3	397.8	398.0	397.4
4	−574.35769	122.5	–	–	
4_2	−573.73807	113.3	381.1	379.9	382.5
5	−643.11288	67.9	–	–	
6	−1054.64068	74.0	–	–	
6_2	−1054.04751	64.9	364.6	364.3	366.6
6_4	−1054.03482	65.0	372.7	371.9	373.8
6_5	−1054.02677	65.0	377.7	376.7	378.4
7	−1466.16668	80.0	–		
7_2	−1465.58738	70.9	355.9	354.0	357.2
9	−904.49682	68.3	–	–	
9_2	−903.89105	59.5	372.8	372.4	372.8
9_4	−903.88666	59.5	375.6	374.6	376.4
9_5	−903.88346	59.5	377.6	376.6	378.8
10	−1240.94983	71.5	–	–	
10_2	−1240.36100	62.7	362.2	361.5	362.9

[a] Additivity values obtained by MP2 increments. [b] Additivity values estimated by G2MP2 increments.

Concluding Remarks

The acidities of the benzene aromatic moieties in monosubstituted methoxy, trifluoromethyl and trifluoromethoxy derivatives has been considered by G2(MP2) and MP2(fc)/6-311+G**//HF/6-31+G* theoretical models. Good agreement between the results obtained by both models has been found. They are also consistent with some available measured values, thus enabling their assignment. A notable exception is to be found in methoxybenzene (**2**), in which the experimentally determined deprotonation energies[36] for the *meta* and *para* positions deviate from both G2(MP2) and MP2 predictions. However, the extent of agreement achieved for the *ortho* position in **2** and in other compounds provides justification for the use of the MP2 model in polysubstituted benzenes and in larger heavily substituted aromatics. Perusal of the predicted deprotonation energies reveals that the previously established additivity rule, based on the independent substituent approximation (ISA),[21−24] works very well in compounds **3**, **4**, **6**, **7**, **9**, and **10**, with good accuracy. Use of the additivity feature in conjunction with trichotomy formula (4) yields a penetrating insight into the origin of acidity in multiply substituted benzenes. The latter is able to explain the effects of specific substituents in terms of three pertinent contributions given in Equation (4). For example, it has been conclusively shown that the overwhelming influence on acidity in the studied systems **2−10** is the final state effect mirrored in the ionization potential of the lone pair formed upon deprotonation, which in turn is estimated in Koopmans' approximation. This last can explain the variation in acidity within the same molecule and between various molecules belonging to the family of related compounds, as exemplified by molecules examined here. However, it should be strongly emphasized that the interpretation based on formulas (4) and (6) is valid generally, meaning that they should be equally useful in other polysubstituted aromatics. Finally, it should be pointed out that the long-range effect of the OCF_3 group has been interpreted here for the first time. It can safely be attributed to a strong long-range electrostatic field stabilization effect exerted on the lone pair electrons in **5** at the *meta* and *para* positions. Last but not least, it has also been found that the G2(MP2) and MP2 theoretical models can provide useful *DPE*s of aromatics. This is an important source of information, since experimental data are scarce.

Acknowledgments

We would like to thank the Computing Centre of the University of Zagreb (SRCE) for granting computation time on the ISABELLA cluster.

---

[1] E. M. Arnett, *Acc. Chem. Res.* **1973**, *7*, 404.

[2] M. Meot-Ner (Mautner), *Acc. Chem. Res.* **1984**, *17*, 186.

[3] F. Cacace, *Acc. Chem. Res.* **1998**, *21*, 215.

[4] K. M. Ervin, *Chem. Rev.* **2001**, *101*, 391−444.

[5] S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin, G. W. J. Mallard, *Phys. Chem. ref. Data* **1988**, *17*, Suppl. 1; E. P. L. Hunter, S. G. Lias, *J. Phys. Chem. Ref. Data* **1998**, *27*, 413−656.

[6] G. A. Harrison, *Chemical Ionization Mass Spectrometry*, CRC Boca Raton, **1989**.

[7] J.-F. Gal, P.-C. Maria, E. D. Raczyńska, *J. Mass. Spectr.* **2001**, *36*, 699−716.

[8] M. Alcami, O. Mó, M. Yāñez, *Mass. Spectr. Rev.* **2001**, *20*, 195−245.

[9] M. T. Molina, W. Bouab, M. Esseffar, M. Herreros, R. Notario, J.-L. M. Abboud, O. Mó, M. Yāñez, *J. Org. Chem.* **1996**, *61*, 5485−5491.

[10] O. Mó, M. Yāñez, M. Esseffar, A. El-Hammadi, M. Herreros, R. Notario, J.-L. Abboud, *J. Org. Chem.* **1997**, *62*, 3200−3207.

[11] J. F. Gal, M. Decouzon, P. C. Maria, A. I. González, O. Mó, M. Yāñez, S. El Chaouch, J. C. Guillemin, *J. Am. Chem. Soc.* **2001**, *123*, 6353−6359.

[12] O. Mó, M. Yāñez, J. C. Guillemin, E. H. Riague, J. F. Gal, P. C. Maria, C. Dubin-Poliart, *Chem. Eur. J.* **2002**, *8*, 4919−4924.

[13] I. Alkorta, J. Elguero, *Tetrahedron* **1997**, *53*, 9741−9748.

[14] I. A. Koppel, R. W. Taft, F. Anvia, S.-Z. Zhu, L.-Q. Hu, K.-S. Sung, D. D. DesMarteau, L. M. Yagupolskii, Y. L. Yagupolskii, N. V. Ignaťev, N. V. Kondratenko, A. Y. Volkonskii, V. M. Vlasov, R. Notario, P.-C. Maria, *J. Am. Chem. Soc.* **1994**, *116*, 3047−3057.

[15] I. Leito, I. Kaljurand, I. A. Koppel, L. M. Yagupolski, V. M. Vlasov, *J. Org. Chem.* **1998**, *63*, 7868−7874.

[16] P. Burk, I. A. Koppel, I. Koppel, I. Leito, O. Travnikava, *Chem. Phys. Lett.* **2000**, *323*, 482−489.

[17] I. A. Koppel, P. Burk, I. Koppel, I. Leito, T. Sonoda, M. Mishima, *J. Am. Chem. Soc.* **2000**, *122*, 5114−5124.

[18] V. M. Vlasov, I. A. Koppel, P. Burk, I. Koppel, *J. Phys. Org. Chem.* **1995**, *8*, 364−370; I. A. Koppel, I. Koppel, V. Pihl, I. Leito, M. Mishimo, V. M. Vlasov, L. M. Yagupolskii, R. W. Taft, *J. Chem. Soc., Perkin 2*, **2000**, 1125−1133.

[19] Z. B. Maksić, R. Vianello, *ChemPhysChem.* **2002**, 696−700.

[20] O. Exner, P. Čársky, *J. Am. Chem. Soc.* **2001**, *123*, 9564−9570 and references cited therein.

[21] Z. B. Maksić, D. Kovaček, M. Eckert-Maksić, I. Zrinski, *J. Org. Chem.* **1996**, *61*, 6717−6719.

[22] H. H. Büker, N. M. M. Nibbering, D. Espinosa, F. Mongin, M. Schlosser, *Tetrahedron Lett.* **1997**, *38*, 8519−8522.

[23] M. Schlosser, *Angew. Chem. Int. Ed.* **1998**, *110*, 1497−1513.

[24] M. Schloser, F. Mongin, J. Porwisiak, W. Dmowski, H. H. Büker, N. M. M. Nibbering, *Chem. Eur. J.* **1998**, *4* 1281−1286.

[25] D. Kuck, *Angew. Chem. Int. Ed.* **2000**, *39*, 125−130.

[26] M. Eckert-Maksić, M. Klessinger, Z. B. Maksić, *Chem. Eur. J.* **1996**, *2*, 1251−1257.

[27] Z. B. Maksić, M. Eckert-Maksić, in: *Theoretical and Computational Chemistry* (Series Eds.: P. Politzer, Z. B. Maksić), Vol. 5, *Theoretial Organic Chemistry*, (Ed.: C. Parkanyi), Elsevier, Amsterdam, **1998**, p. 203, and references cited therein.

[28] E. Castagnetti, M. Schlosser, *Chem. Eur. J.* **2002**, *8*, 799−804; E. Castagnetti, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 691−695.

[29] N. S. Isaaes, *Physical Organic Chemistry*, John Wiley & Sons, Inc., New York, **1987**.

[30] L. A. Curtiss, K. Raghavachari, G. W. Trucks, J. A. Pople,, *J. Chem. Phys.* **1991**, *94*, 7221−7230; B. J. Smith, L. Radom, *J. Phys. Chem.* **1991**, *95*, 10549−10551.

[31] L. A. Curtis, K. Raghavachari, J. A. Pople, *J. Chem. Phys.* **1995**, *103*, 4192−4200.

[32] A. P. Scott, L. Radom, *J. Phys. Chem.* **1996**, *100*, 16502−16513.

[33] *Gaussian 98 (Revision A.10)*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1998**.

[34] G. E. Davico, V. M. Bierbaum, C. H. De Puy, G. B. Ellison, R. R. Squires, *J. Am. Chem. Soc.* **1995**, *117*, 2590−2599.

[35] M. Meot-Ner (Mautner), S. A. Kafafi, *J. Am. Chem. Soc.* **1988**, *110*, 6297−6303.

[36] G. D. Dahlke, S. R. Kass, *Int. J. Spectrom. Ion. Proc.* **1992**, *117*, 633−645.

[37] D. Federsel, A. Herrmann, D. Christen, S. Sander, H. Willner, H. Oberhammer, *J. Mol. Struct.* **2001**, *567−568*, 127−136.

[38] I. F. Shiskov, H. J. Geise, C. Van Alsenoy, L. V. Khristenko, L. V. Vilkov, V. M. Senyavian, B. Van der Veken, W. Herrebout, B. V. Lokshin, O. G. Garkusha, *J. Mol. Struct.* **2001**, *567−568*, 339−360.

[39] E. G. Kapustin, V. M. Bzhezovsky, L. M. Yagupolskii, *J. Fluor. Chem.* **2002**, *113*, 227−237.

[40] J. Klocker, A. Karpfen, P. Wolschann, *Chem. Phys. Lett.* **2003**, *367*, 566−575.

[41] M. Schlosser, E. Marzi, F. Cottet, H. H. Büker, N. M. M. Nibbering, *Chem. Eur. J.* **2001**, *7*, 3511−3516.

Received June 26, 2003