

**ANALYSIS OF THE ORTHO EFFECT: BASICITY OF 2-SUBSTITUTED BENZONITRILES**Otto EXNER<sup>a,\*</sup> and Stanislav BÖHM<sup>b</sup><sup>a</sup> *Institute of Organic Chemistry and Biochemistry, 166 10 Prague 6, Czech Republic; e-mail: exner@uochb.cas.cz.*<sup>b</sup> *Department of Organic Chemistry, Institute of Chemical Technology, Prague, 166 28 Prague 6, Czech Republic; e-mail: bohms@vscht.cz*Received June 2, 2006  
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*Dedicated to Professor Antonín Holý on the occasion of his 70th birthday in recognition of his outstanding contribution to bioorganic chemistry.*

Energies of 18 *ortho*-substituted benzonitriles and their protonated forms were calculated within the framework of the density functional theory at the level B3LYP/6-311+G(d,p). The substituent effects were evaluated in terms of isodesmic reactions as the effects on the basicity on the one hand and separately in the nitrile molecules and in the cations on the other. The *ortho* effect was defined as the difference when compared to the 4-substituted isomers. It is smaller than in the case of *ortho*-substituted benzoic acids but not negligible (up to 25 kJ mol<sup>-1</sup>). In unprotonated molecules it may be classified as purely steric effect, in spite of the small dimension of the CN group and estimates made with the calotte models. In the protonated forms, polar properties of the substituent are decisive. In addition, a new, quite important substituent effect was discovered with the substituents OH, SH, CHO and COOCH<sub>3</sub>, which is controlled by different conformation of protonated and unprotonated molecules. Substituents OH, SH and NH<sub>2</sub> form also weak hydrogen bonds in unprotonated nitriles. In summary, 2-substituted benzonitriles allowed evaluating of several, partly new substituent effects but cannot serve as model molecules without an *ortho* effect, although the constant functional group CN is sterically little pretentious.

**Keywords:** Isodesmic reactions; Steric effects; Substituent effects; Basicity; Hydrogen bonds; Conformation analysis; Nitriles; Benzenes; Ab initio calculations.

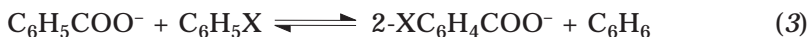
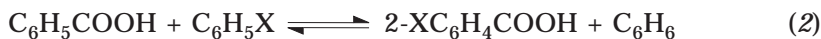
The effects of substituents in the *ortho* position of the benzene ring are complex in character and difficult to predict. They were denoted together as *ortho* effect<sup>1,2</sup>, or were divided into a number of effects, defined more or less exactly<sup>3-6</sup>. Alternatively it was argued that the *ortho* effect can be interpreted only by inductive and resonance effects, without referring to any

steric component<sup>1,6-8</sup>, but this treatment was criticized<sup>4</sup>. The classical problem is of standing interest<sup>7-10</sup>.

We started the analysis by dividing the suggested effects into two categories<sup>2</sup>. Some of them exist undoubtedly in the real structure and can be in principle experimentally proved or at least disproved: H-bonds, steric inhibition of resonance (SIR). The other are merely artificial constructions: the van der Waals steric effect, short-range polar effect, polar effects transmitted through the benzene ring. Some of these effects could be quantitatively estimated by means of suitable model compounds<sup>2</sup>; in other cases this was not possible<sup>11</sup>. Our results<sup>2,11</sup> and most of the literature data<sup>3-7</sup> were obtained on 2-substituted benzoic acids, mainly on their dissociation constants in solution. In terms of isodesmic<sup>12</sup> (and homodesmotic<sup>13</sup>) reactions the dissociation reaction is formulated as Eq. (1).



More recently, this reaction was investigated also free of solvent effects by measuring its Gibbs energy in the gas phase<sup>14</sup>. The results can be correlated with common chemical formulas more closely but there is still another shortcoming that the substituent effect is given by the difference between the effect in the acid molecule and in the anion. It may happen that the two effects are of similar magnitude and their difference is difficult to interpret<sup>2,15</sup>. We tried to separate them by the isodesmic reactions<sup>2,11</sup>, Eqs (2) and (3), describing separately the substituent effect in the acid and in its anion, respectively. This principle was already applied to substituent effects of various kind<sup>12,15-18</sup>.

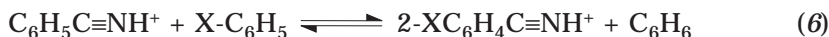
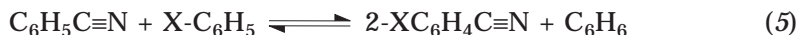


Separation of the effects in the anion and in the acid molecule enabled us to describe the substituent effects more properly<sup>2,11</sup> than in previous studies<sup>3-8</sup>. Nevertheless, our conclusion was that the acidities of 2-substituted benzoic acids are not the best model for studying the ortho effect because it is too complex; for instance, it was not feasible to separate the effects of strong hydrogen bonds of the substituents like OH or NH<sub>2</sub> from their steric

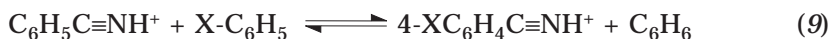
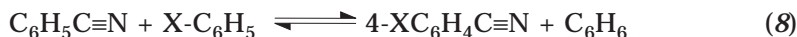
effects<sup>11</sup>. In this communication, we are dealing with a simpler model, protonation of 2-substituted benzonitriles, Eq. (4).



With this model, steric inhibition of resonance was a priori excluded and hydrogen bonds seemed to be very improbable. It was already investigated, both theoretically and experimentally<sup>17</sup>, but only for X = alkyl; the result was that steric effects are observable only for large substituents such as C(CH<sub>3</sub>)<sub>3</sub>. In this work, we investigated 2-substituted benzonitriles with 18 common substituents (Table I). Energies of the protonated forms and parent bases were estimated separately according to the isodesmic reactions, Eqs (5) and (6), and the relative basicities expressed by Eq. (4).



Calculations were carried out within the framework of the density functional theory<sup>19</sup> (DFT) at the same level as in our previous work<sup>2,11,18</sup>. The results were compared with the isomeric 4-substituted benzonitriles, i.e. with Eqs (7) to (9).



3- And 4-substituted benzonitriles were already investigated both theoretically<sup>18,20</sup> and experimentally<sup>20,21</sup>. In absence of experimental data on the 2-isomers<sup>21</sup> we must rely to the agreement in this previous work<sup>18</sup> as evidence that our theoretical model is sufficiently dependable. Comparison of *ortho* and *para* isomers is a traditional approach when evaluating the *ortho* effect<sup>4</sup>. It was assumed originally that purely polar effects would be equal from the two positions, when there were no steric or short-range interactions of the *ortho* substituents. Later investigations claimed that the polar

effects are a little stronger<sup>10</sup> or weaker<sup>2,7,8,22</sup> from the *ortho* position. We hoped that 2-substituted benzonitriles could contribute even to this problem.

TABLE I  
Calculated energies of 2-substituted benzonitriles

Compd	Substituent	$E(\text{C}\equiv\text{N})$ a.u.	$E(\text{C}\equiv\text{NH}^+)$ a.u.	Population, %	
				C $\equiv$ N	C $\equiv$ NH <sup>+</sup>
<b>1</b>	H	-324.5777606 <sup>a</sup>	-324.9015658 <sup>a</sup>		
<b>2</b>	CH <sub>3</sub>	-363.9057384 <sup>b</sup>	-364.2334543 <sup>b</sup>		
<b>3</b>	C(CH <sub>3</sub> ) <sub>3</sub>	-481.8659371 <sup>b</sup>	-482.1992781 <sup>b</sup>		
<b>4</b>	CH <sub>2</sub> Cl	-823.5246644	-823.8473786		
<b>5</b>	CF <sub>3</sub>	-661.7188041	-662.0359631		
<b>6</b>	CN	-416.8366259	-417.1502385		
<b>7a</b>	CHO <i>sp</i>	-437.9265565	-438.2564153	1.71	100.00
<b>7b</b>	CHO <i>ap</i>	-437.9303828	-438.2434519	98.29	0.00
<b>8a</b>	CO <sub>2</sub> CH <sub>3</sub> <i>sp</i>	-552.5155943	-552.8522264	18.60	99.99
<b>8b</b>	CO <sub>2</sub> CH <sub>3</sub> <i>ap</i>	-552.5169886	-552.8439833	81.40	0.01
<b>9</b>	NH <sub>2</sub>	-379.9584462	-380.2900921		
<b>10</b>	N(CH <sub>3</sub> ) <sub>2</sub>	-458.5790057	-458.9214188		
<b>11</b>	NO <sub>2</sub>	-529.1275482	-529.4473723		
<b>12a</b>	OH <i>sp</i>	-399.8275957	-400.1448699	98.39	0.00
<b>12b</b>	OH <i>ap</i>	-399.8237115	-400.1556131	1.61	100.00
<b>13a</b>	OCH <sub>3</sub> <i>sp</i>	-439.1286304	-439.456494	0.54	0.00
<b>13b</b>	OCH <sub>3</sub> <i>ap</i>	-439.1335540	-439.4693309	99.46	100.00
<b>14a</b>	SH <i>sp</i>	-722.7916720	-723.1121712	91.10	1.68
<b>14b</b>	SH <i>ap</i>	-722.7894752	-723.1160164	8.90	98.32
<b>15</b>	F	-423.8423376	-424.1624684		
<b>16</b>	Cl	-784.1958288	-784.5174372		
<b>17</b>	O <sup>-</sup>	-399.2876159	-399.7803572		
<b>18</b>	NH <sub>3</sub> <sup>+</sup>	-380.2886274	-380.4727391		

<sup>a</sup> Ref.<sup>24</sup>; <sup>b</sup> Ref.<sup>18</sup>

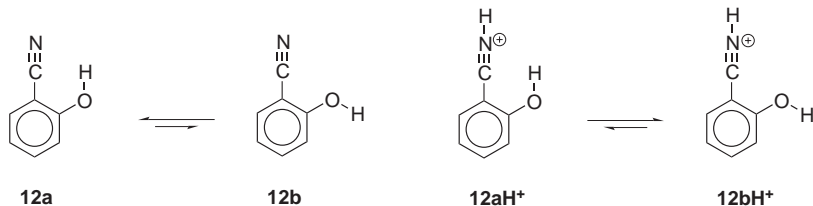
## CALCULATIONS

DFT calculations were performed at the B3LYP/6-311+G(d,p) level according to the original proposal<sup>19</sup> exploiting the Gaussian 03 program<sup>23</sup>. This level was chosen according to previous experience with similar compounds<sup>2,11</sup>. Full-energy optimization and vibrational analysis were carried out in all cases. The minimum-energy forms were searched for starting from two or more initial structures; these can differ only in the conformation within the substituent group. The calculated energies are listed in Table I for all stable conformations. Their approximate population was estimated with the assumption that their difference of Gibbs energy equals the difference of calculated DFT-energy. The populations are given also in Table I.

## RESULTS AND DISCUSSION

*Conformation and Hydrogen Bonds*

The DFT-calculated energies of 2-substituted benzonitriles **1–18** and of their protonated forms **1H<sup>+</sup>–18H<sup>+</sup>** are given in Table I, columns 3 and 4, respectively. With five compounds, **7**, **8**, **12**, **13** and **14**, two conformations of the substituent were revealed, although their stability was very different: in most cases only one conformer is virtually present at equilibrium. The calculated populations are given in Table I, the last two columns. It is most interesting that the stable conformation of the protonated form is almost always reversed to the conformation of the nitrile itself. Thus in 2-hydroxybenzonitrile the conformer **12a** is almost exclusively present, while the protonated form has conformation **12bH<sup>+</sup>**. Dealing with the basicity, Eq. (4), we must consider the equilibrium, **12a**  $\rightleftharpoons$  **12bH<sup>+</sup>**, while the substituent effects in the unprotonated molecule are given by Eq. (5) with **12a** and in the protonated form by Eq. (6) with **12bH<sup>+</sup>**. The reaction energies  $\Delta_4E$  to  $\Delta_6E$  given in Table II relate to these equilibria as they have been just defined.



The preference of conformation **12a** over **12b** must be attributed to a weak hydrogen bond that was assumed when interpreting the IR spectra<sup>25</sup> and was also in agreement with <sup>1</sup>H NMR<sup>26</sup>. In the discussion of the acidities of phenols this H-bond was not taken into consideration<sup>14,27</sup>. We collected in Table III several quantities indicating the H-bond. Although these descriptors may give individually somewhat different results, the conclusion is that the H-bonds in **12a**, **14a** and **9** are very weak. With **12a** it follows particularly from the small difference of the O–H vibration frequency<sup>25</sup> of **12a** and **12b**, further from the small energy of the H-bond,  $\Delta_{\text{HB}}E$ , which was approximately identified with the energy difference of **12a** and **12b**. The H-bond should be described as interaction of the hydrogen atom with  $\pi$ -electrons of the C $\equiv$ N bond rather than with any atom. Even in

TABLE II  
Calculated energies of the isodesmic reactions of 2-substituted benzonitriles (in kJ mol<sup>-1</sup>)

Compd	Substituent	$\Delta_4E$ Eq. (4)	$\Delta_5E^a$ Eq. (5)	$\Delta_6E^a$ Eq. (6)	$\Delta_7E^b$ Eq. (7)
<b>1</b>	H	0	0	0	0
<b>2</b>	CH <sub>3</sub>	-10.27	-1.15	-11.42	-14.68
<b>3</b>	C(CH <sub>3</sub> ) <sub>3</sub>	-25.04	19.98	-5.06	-20.86
<b>4</b>	CH <sub>2</sub> Cl	2.87	6.82	9.69	-9.17
<b>5</b>	CF <sub>3</sub>	17.45	22.42	39.87	29.85
<b>6</b>	CN	26.76	20.11	46.87	36.56
<b>7</b>	CHO <sup>c</sup>	-5.86	13.68	7.83	24.31
<b>8</b>	CO <sub>2</sub> CH <sub>3</sub> <sup>c</sup>	-30.02	20.06	-9.96	8.29
<b>9</b>	NH <sub>2</sub>	-20.59	-11.28	-31.86	-50.05
<b>10</b>	N(CH <sub>3</sub> ) <sub>2</sub>	-48.86	4.11	-44.74	-66.12
<b>11</b>	NO <sub>2</sub>	10.45	35.66	46.11	46.07
<b>12</b>	OH <sup>c</sup>	-11.06	-6.41	-17.47	-19.16
<b>13</b>	OCH <sub>3</sub> <sup>c</sup>	-31.43	1.39	-30.04	-29.97
<b>14</b>	SH <sup>c</sup>	-1.42	0.28	-1.13	-15.35
<b>15</b>	F	9.65	11.28	20.93	8.80
<b>16</b>	Cl	5.77	12.79	18.56	7.46
<b>17</b>	O <sup>-</sup>	-443.54	-71.18	-514.73	
<b>18</b>	NH <sub>3</sub> <sup>+</sup>	66.77	32.33	399.10	

<sup>a</sup> Calculated with the energies of monosubstituted benzenes taken from ref.<sup>24</sup>, <sup>b</sup> Ref.<sup>18</sup>, <sup>c</sup> The data relate to the prevailing conformations (see text).

intermolecular H-bonds between a phenol and a nitrile, such structure was preferred<sup>28</sup> to a linear structure with the hydrogen atom bonded to nitrogen.

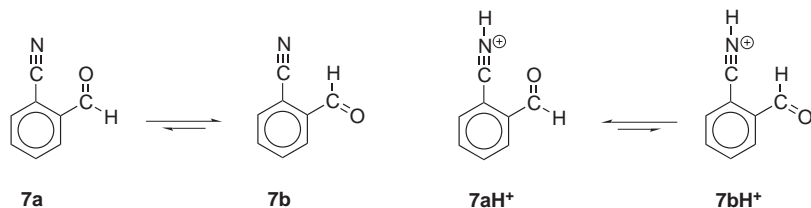
With the thiol **14** we encountered the same conformers as with **12**; the H-bond is still distinctly weaker (Table III). Even in the amino derivative **9** a kind of weak H-bond was taken into consideration when interpreting the IR<sup>29</sup> or <sup>1</sup>H NMR<sup>30</sup> spectra but no H-bond was mentioned in the discussion of the basicity<sup>31</sup> of **9** (protonation on the NH<sub>2</sub> group). In the data of Table III the H-bond is seen most clearly in the difference  $\Delta\nu$  of the symmetrical and antisymmetrical NH<sub>2</sub> frequencies: this increases when one of the NH<sub>2</sub> hydrogens is engaged in a H-bond. The experimental value<sup>29</sup> of  $\Delta\nu = 103 \text{ cm}^{-1}$  is smaller than for 2-aminobenzoic acid ( $133 \text{ cm}^{-1}$ ) but distinctly greater than in the reference aniline ( $87 \text{ cm}^{-1}$ ) indicating a weak bond. On the contrary, other spectroscopic properties of **9** suggested that a H-bond is absent<sup>29</sup>. This confirms the opinion<sup>32</sup> that the strength of intramolecular H-bonds can be assessed quite differently depending on various descriptors. We were interested mainly in the energy  $\Delta_{\text{HB}}E$  and attempted to estimate it in a rather complex way using the fixed conformation: the nonplanar NH<sub>2</sub> group situated symmetrically to the ring with the hydrogen atoms turned

TABLE III  
Some quantities characterizing the strengths of intramolecular hydrogen bond in 2-substituted benzonitriles

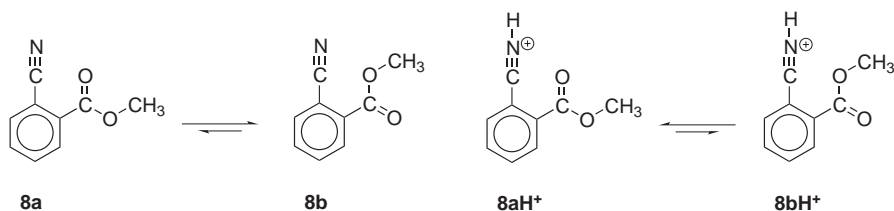
Quantity	<b>12a</b> OH <sup>b</sup>	<b>12b</b> OH	<b>14a</b> SH <sup>b</sup>	<b>14b</b> SH	<b>9</b> NH <sub>2</sub>	<b>7b</b> CHO
$r(\text{H}\cdots\text{C}(\equiv\text{N}))$ , Å	2.35	3.71	2.42	4.24	2.47	2.53
$r(\text{X}\cdots\text{C}(\equiv\text{N}))$ , Å	2.83	2.76	3.15	3.02	2.82	2.93
$\theta(\text{C2}-\text{C1}-\text{C}(\equiv\text{N}))$	118.5	120.4	120.8	120.8	118.9	121.4
$\theta(\text{X}-\text{C2}-\text{C1})$	122.8	117.5	124.3	118.9	121.1	121.4
$\theta(\text{C2}-\text{X}-\text{H})$	110.8	110.3	97.3	95.5	118.7, 118.1	115.7
$\theta(\text{C1}-\text{C}\equiv\text{N})$	176.5	178.3	179.2	179.5	177.3	178.3
$\tau(\text{X}-\text{C2}-\text{C1}-\text{C}(\equiv\text{N}))$	0.0	0.0	0.0	0.0	2.9	0.0
$\nu(\text{X}-\text{H})$ calc., $\text{cm}^{-1}$	3768	3832	2673	2678	3584, 3697	
$\nu(\text{X}-\text{H})$ exp., $\text{cm}^{-1}$	3559 <sup>a</sup>	3586 <sup>a</sup>			3434 <sup>b</sup> , 3537 <sup>b</sup>	
$\Delta_{\text{HB}}E$ , $\text{kJ mol}^{-1}$	10.9		5.8		7.1	

<sup>a</sup> Ref.<sup>25</sup>; <sup>b</sup> Ref.<sup>29</sup>

off from the CN group. This fixed conformation had energy higher by 43.4 kJ mol<sup>-1</sup> than the minimum-energy structure **9**, while for the similarly distorted conformation of 4-aminobezonitrile it is 36.3 kJ mol<sup>-1</sup>. The difference should represent the energy of the H-bond,  $\Delta_{\text{HB}}E$  (Table III). Note that this value is rather uncertain and not strictly comparable with that of **12** or **14**.



With the formyl derivative **7** a similar change of conformations was observed. While in the nitrile the *ap* conformation **7b** is preferred, in the protonated form it changes to *sp* **7aH<sup>+</sup>**. In this case we attributed it not to a H-bond in **7b** but merely to the stabilization energy of **7aH<sup>+</sup>**. For comparison we give in Table III some characteristic features of the structure **7b**; they do not suggest the presence of a H-bond. The methoxycarbonyl derivative **8** reveals similar change of conformations (equilibrium **8b**  $\rightleftharpoons$  **8aH<sup>+</sup>**); in this case any H-bond is not possible. Enhanced stability of **7aH<sup>+</sup>** and **8aH<sup>+</sup>** must be attributed to polar interaction of the negatively charged O atom with positively charged C≡N bond. This explanation is confirmed by comparison with the protonated nitro derivative **11H<sup>+</sup>**, the conformations of which are not possible but the non-bonded interaction is evident from the elongated adjacent N–O bond. (The bond lengths N–O in **11H<sup>+</sup>** are 1.234 and 1.207 Å, respectively, compared to 1.221 and 1.224 Å in **11**.) Of the derivatives with variable conformations only the methoxy derivative **13** behaves in a “regular” way since the *ap* conformation is preferred both in the uncharged nitrile and in its protonated form.





The change of conformation during the acid-base equilibrium is in any case an important feature, which can strongly influence the correlations of acidity or basicity with structure. We are not aware of any other example where it would be observed. It cannot be revealed in the discussions of experimental dissociation constants and its experimental discovery would require rather sophisticated experiments. In water solution it might be particularly difficult to observe and need not be also similar as in the isolated molecules.

### *Substituent Effects on the Basicity*

The DFT-calculated basicities of 2-substituted benzonitriles **1–18** are given in Table II, column 3, as reaction energies  $\Delta_4 E$  of the isodesmic reaction, Eq. (4). Note that they relate exclusively to protonation on the CN group, irrespectively of that the actual protonation of some derivatives may proceed preferentially on the substituent, similarly as observed for certain *para* isomers<sup>18,20</sup>.

The two charged substituents, compounds **17** and **18**, were added only to show how strong the substituent effects could be. They were not included in any correlation since they would affect the results too much (solitary points). The energies  $\Delta_4 E$  of **1–16** were first correlated by the traditional procedure<sup>1,6</sup>, extended dual substituent parameter analysis, Eq. (10), with the parameters  $\sigma_I$ ,  $\sigma_R$  and  $\psi$  expressing the inductive, resonance and steric effect, respectively.

$$\Delta_4 E = \rho_I \sigma_I + \rho_R \sigma_R + \psi \psi + \varepsilon \quad (10)$$

For  $\sigma_R$  several scales are optional, denoted  $\sigma_R^o$ ,  $\sigma_R^+$ ,  $\sigma_R^-$  and  $\sigma_R^{Bz}$ . They are singled out according to the electron demand of the functional group but most often a posteriori. Also the steric effect can be expressed by various scales of constants<sup>6,33</sup>. After many attempts, we obtained the relatively best correlation with  $\sigma_R^-$  and  $B_1$ , the latter giving the smallest dimension of the substituent in the perpendicular direction<sup>33</sup> but the substituents changing conformation (**7**, **8**, **12**, **14**) had to be excluded, Eq. (11). The fit would be still classified<sup>34</sup> as “fair” but the steric term is not significant. Without this term we obtained Eq. (12) but the standard deviation from the regression is too great.

$$\Delta_4 E = (41 \pm 14)\sigma_I + \rho_R(34 \pm 8)\sigma_R^- + (-9 \pm 9)B_1 + 8 \pm 16 \quad (11)$$

$$R = 0.909 \quad s = 10.8 \quad N = 11$$

$$\Delta_4 E = (42 \pm 14)\sigma_I + \rho_R(32 \pm 7)\sigma_R^- - 8 \pm 16 \quad (12)$$

$$R = 0.894 \quad s = 11.0 \quad N = 11$$

Several further correlations with the known reactivity parameters brought no improvement. A qualitative comparison is possible with the acidities of *ortho*-substituted benzoic acids. We used the DFT calculated acidities<sup>2,11</sup> and obtained the graph in Fig. 1, including also the *meta* and *para* derivatives<sup>16a,18</sup>. These display an approximately linear dependence (the Hammett line) with the characteristic deviations of *para* donor substituents<sup>18</sup>. The *ortho* derivatives with these substituents deviate similarly. Several smaller *ortho* substituents (CH<sub>3</sub>, F, Cl, CN, CF<sub>3</sub>) are situated near the Hammett line: their steric effects are small or are similar in benzonitriles as in benzoic acids. The great deviation of 2-OH, 2-SH – and evidently also 2-CHO – is caused by the hydrogen bonds in the anions of 2-substituted benzoic acids<sup>11</sup>. The deviation of *tert*-butyl can be explained in terms of polarizability. The deviation of the NO<sub>2</sub> group must originate in the mentioned interaction in the

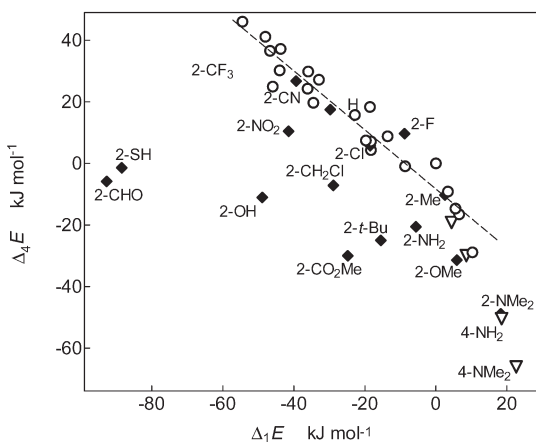


FIG. 1

DFT-calculated basicities of substituted benzonitriles  $\Delta_4 E$  vs the calculated acidities of equally substituted benzoic acids  $\Delta_1 E$ .  $\nabla$  *para* derivatives with strong donor substituents,  $\circ$  other *para* derivatives and all *meta* derivatives,  $\blacklozenge$  *ortho* derivatives; some important substituents are denoted

protonated benzonitrile. Summarizing we can state that the proximity effects in 2-substituted benzonitriles may be weaker than in equally substituted benzoic acids but are not negligible.

Most important is the comparison of the basicities of *ortho* and *para* derivatives, i.e. of Eqs (4) and (7). One can expect nearly equal substituent effects for the sterically less demanding groups; the deviations of the others may represent the *ortho* effect. Figure 2 reveals that many substituents are arranged near the line  $y = x$  and their *ortho* effect is negligible. The most striking deviations occur for the substituents  $\text{NO}_2$ ,  $\text{CHO}$  and  $\text{CO}_2\text{CH}_3$  and are due to the interaction in the cation as described in the previous section. Deviations of the substituents  $\text{OH}$  and  $\text{SH}$  are negligible since two effects are opposite: a H-bond in the nitrile makes the base weaker, while a change of conformation in the cation makes it stronger. In summary, the linear dependence for the main group of substituents is only approximate and its slope cannot be determined with any reliability. It can be approximately unity as generally assumed but also only 0.8 as estimated previously<sup>2</sup>.

Substituent effects in the unprotonated benzonitriles and in their protonated forms may be defined as reaction energies  $\Delta_5E$  and  $\Delta_6E$  of the reactions of Eqs (5) and (6), respectively, and called generally interaction energies, Table II, columns 4 and 5. In Fig. 3,  $\Delta_5E$  are compared with the interaction energies of corresponding *para* derivatives  $\Delta_8E$ . One could expect

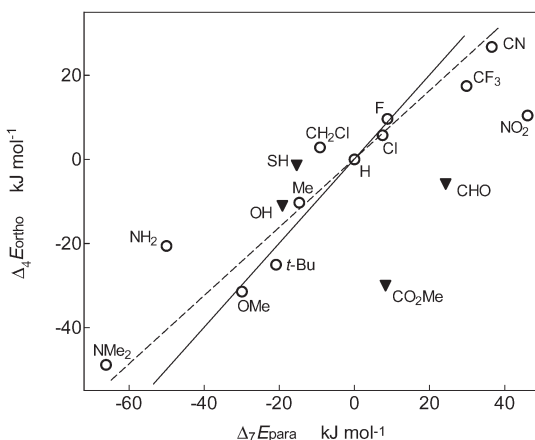


FIG. 2

DFT-calculated basicities of substituted benzonitriles, *ortho* derivatives plotted vs *para* derivatives with the same substituent; ▼ derivatives with different conformation in the protonated form, ○ other derivatives; solid line – unity slope, dashed line – slope 0.81

that the points of smaller substituents would be situated near the line  $y = x$  and all other points will deviate upwards; the deviation should be attributed merely to the steric effect. This is essentially confirmed. Some of the steric effects are relatively great ( $\text{NO}_2$ ,  $t\text{-Bu}$ ) with respect to the small apparent dimensions of the CN group; note particularly the non-negligible interaction of the substituents F-CN, or CN-CN. In Fig. 3 also some substituents were included in their unnatural conformations (points  $\blacktriangle$ ); they do not behave differently from the others. Of course, their steric effects are relatively great.

The substituent effects in the protonated forms are different (Fig. 4). The effects in the *para* position, Eq. (9), are now much greater and the ortho effect is relatively smaller except two cases. One is the group of unnatural conformations (points  $\blacktriangle$ ) with an evident steric effect. The second group of substituents,  $\text{NO}_2$ , CHO and  $\text{CO}_2\text{CH}_3$ , show strongly stabilizing interaction of the lone electron pairs on oxygen and positively charged  $\text{CNH}^+$  group. A general similarity of ortho effects in the uncharged and charged molecules was not observed, it could be found only for certain substituents.

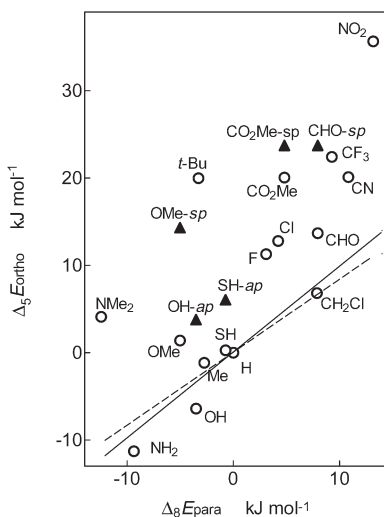


FIG. 3

DFT-calculated interaction energies of the two substituents in substituted benzonitriles, energies  $\Delta_5 E$  of *ortho* derivatives, Eq. (5), plotted vs energies  $\Delta_8 E$  of *para* derivatives with the same substituent, Eq. (8);  $\blacktriangle$  unstable, little populated conformers,  $\circ$  other derivatives; solid line – unity slope, dashed line – slope 0.81

TABLE IV  
DFT-calculated acidities of some 2-substituted benzoic acids

Substituent	Acid conform.	$\Delta E(\text{DFT})$ a.u.	$\Delta_{\text{conf}}E$ $\text{kJ mol}^{-1}$	Anion conform.	$\Delta E(\text{DFT})$ a.u.	$\Delta_{\text{conf}}E$ $\text{kJ mol}^{-1}$	Acidity $\Delta_1E$ $\text{kJ mol}^{-1}$
CHO	<i>sp, sp</i>	-534.2923347 <sup>a</sup>	10.77	<i>sp</i>	-533.7456943	90.85	-92.72
	<i>sp, ap</i>	-534.2964381	0.00	<i>ap</i>	-533.7802974	0.00	
	<i>ap, sp</i>	-534.2952523	3.11				
	<i>ap, ap</i>	-534.2952787	3.04				
CO <sub>2</sub> CH <sub>3</sub>	<i>sp, ac</i> <sup>a</sup>	-648.8822004	0.00	<i>ac</i> <sup>b</sup>	-648.3401989		-24.82
	<i>ap, sp</i>	-648.8814202	2.05				
	<i>ap, ap</i>	-648.8816912	1.34				
SH	<i>sp, sp</i> <sup>c</sup>	-819.1607690	0.00	<i>sp</i> <sup>d</sup>	-818.6429860	0.00	-88.40
	<i>sp, ap</i>	-819.1587561	5.28	<i>ap</i>	-818.6133912	77.70	
	<i>ap, sp</i>	-819.1557585	13.16				
	<i>ap, ap</i>	-819.1561754	12.06				

<sup>a</sup> The CO<sub>2</sub>CH<sub>3</sub> group is rotated out from the ring plane by 127°; the same conformation was obtained when starting from different angles. <sup>b</sup> The CO<sub>2</sub>CH<sub>3</sub> group is rotated out from the ring plane by 114°; the same conformation was obtained when starting from different angles. <sup>c</sup> An intramolecular hydrogen bond. <sup>d</sup> Thiolate anion with an intramolecular hydrogen bond; a tautomeric carboxylate anion could not be obtained.

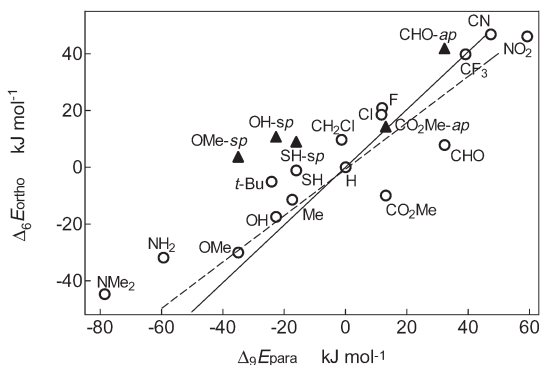


FIG. 4

DFT-calculated interaction energies of the two substituents in the protonated forms of substituted benzonitriles, energies  $\Delta_6E$  of *ortho* derivatives, Eq. (6), plotted vs energies  $\Delta_9E$  of *para* derivatives with the same substituent, Eq. (9);  $\blacktriangle$  unstable, little populated conformers,  $\circ$  other derivatives; solid line – unity slope, dashed line – slope 0.81

*Attempted Separation of Substituent Effects*

In the previous analysis of the ortho effect in 2-substituted benzoic acids<sup>2,11</sup> we attempted to estimate approximately the contribution of its components: hydrogen bond, steric hindrance to resonance, polar effect, steric effect – these all occurring both in the acid molecule and in the anion. Such an analysis will be attempted also here (Table V), although its very approximate character is evident. The present study was undertaken with the assumption that 2-substituted benzonitriles will give a simpler picture since steric hindrance to resonance and hydrogen bonds are excluded. This was not fully confirmed: some H-bonds were revealed but are weak and influence little the total effect. On the other hand, a completely new effect was discovered, change of conformation with protonation (denoted CC in Table V).

TABLE V

Attempted separation of the substituent effects on the basicity of 2-substituted benzonitriles<sup>a</sup>

Compd	Substituent	H-bond	CC <sup>b</sup>	PE	-SE base	SE cation
1	H	0	0	0	0	0
2	CH <sub>3</sub>			-12	-1	3
3	C(CH <sub>3</sub> ) <sub>3</sub>			-17	-23	14
4	CH <sub>2</sub> Cl			-7	0	11
5	CF <sub>3</sub>			24	-15	8
6	CN			30	-11	8
7	CHO <sup>c</sup>		-34	20	-7	16
8	CO <sub>2</sub> CH <sub>3</sub> <sup>c</sup>		-22	7	-16	1
9	NH <sub>2</sub>	7		-41	-3	16
10	N(CH <sub>3</sub> ) <sub>2</sub>			-54	-14	19
11	NO <sub>2</sub>			37	-25	-2
12	OH <sup>c</sup>	11	-28	-16	-7	29
13	OCH <sub>3</sub> <sup>c</sup>			-24	-5	-2
14	SH <sup>c</sup>	6	-10	-12	-7	22
15	F			7	-9	11
16	Cl			6	-9	9

<sup>a</sup> In kJ mol<sup>-1</sup>; the signs have been given in such a way that positive values imply base weakening, negative base strengthening. <sup>b</sup> Effect of change of conformation in the protonation reaction (Eq. (4)). The data relate to the prevailing conformations.

This effect is present only with few substituents and can be assessed rather reliably. The main problem is the polar effect, PE. We do not accept the idea that a part of the substituent effect is "transmitted through the benzene ring" and imagine the polar effect merely as a reference value. It should represent an ideal substituent effect, as it would be if there were no ortho effect, and is approximated by the interaction of the same substituent from the *para* position, multiplied by a factor<sup>2</sup> or not. The uncertainty is in the value of this factor<sup>2,10,22</sup>, but also in the whole concept. In Table V, the values of CC were calculated with the factor 0.81 but using the value 1 would not affect the results so much. The steric effects SE in the base and in the cation may be visualized in Figs 3 and 4: they are the distances of the pertinent points from the line  $y = 0.81x$ . The data of Table V give the right sum equal to  $\Delta_4E$  in Table II; they also would agree with the values of  $\Delta_5E$  and  $\Delta_6E$  when PE were divided into the effects in the uncharged molecule and in the cation.

Separation of the substituents effects into  $\Delta_5E$  and  $\Delta_6E$  (Table II) is the reliable part of the analysis, separation into HB, CC, PE and SE (Table V) is the hypothetical part. In spite of all its uncertainty, Table V yields the evidence that the effects of individual substituents are very different in character. For instance, it is evident that the steric effects of  $\text{CH}_3$  are practically zero, those of F, Cl or  $\text{OCH}_3$  are small and almost cancel in the unprotonated and protonated forms. Steric effects of *t*-Bu are strong and cancel only partly. The effects of conformational change are strong (CHO,  $\text{CO}_2\text{CH}_3$ , OH, SH) while those of the H-bonds are minute. The effect of the groups CN,  $\text{CF}_3$  and CHO is mainly polar, since their steric effects partly compensate. The commonly great contribution of the polar effect explains why correlations with  $\sigma_1$  and  $\sigma_R$  were possible<sup>1</sup>, neglecting any steric effect; of course, the selection of substituents was often restricted and the correlations poor. Summarizing, the basicities of *ortho*-substituted benzonitriles are not free from the ortho effects and these effects are not equal in the protonated and unprotonated molecules. This approximation can hold only for a selected group of substituents ( $\text{CH}_3$ , *t*-Bu, F, Cl, CN,  $\text{CF}_3$ , OH,  $\text{OCH}_3$ ) and only very roughly as was seen already from Fig. 2.

## CONCLUSIONS

Basicities of 2-substituted benzonitriles represent a new and interesting model system for studying the ortho effect. DFT calculations yielded rather reliable energies, at least in the relative values. Experimental determination would not be possible for several important derivatives because they would

be protonated at another side of the molecule. An experimental approach could hardly discover the novel substituent effect associated with the change of conformation. On the other hand, the substituted benzonitriles are not a model system without any ortho effect. It is very probable that such a model cannot be found.

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## REFERENCES

1. Charton M.: *Prog. Phys. Org. Chem.* **1971**, *8*, 235.
2. Böhm S., Fiedler P., Exner O.: *New J. Chem.* **2004**, *28*, 67.
3. a) Brown H. C., McDaniel D. H., Häfliger O. in: *Determination of Organic Structures by Physical Methods* (E. A. Braude and F. C. Nachod, Eds), p. 567. Academic Press, New York 1955; b) Hammond G. S. in: *Steric Effects in Organic Chemistry* (M. S. Newman, Ed.), p. 425. Wiley, New York 1956; c) Hine J.: *Structural Effects on Equilibria in Organic Chemistry*, Chaps 3, 4. Wiley, New York 1975.
4. Shorter J. in: *Advances in Linear Free Energy Relationships* (N. B. Chapman and J. Shorter, Eds), p. 71. Plenum Press, London 1972.
5. a) Fujita T., Nishioka T.: *Prog. Phys. Org. Chem.* **1976**, *12*, 49; b) Berg U., Gallo R., Klatt G., Metzger J.: *J. Chem. Soc., Perkin Trans. 2* **1980**, 1350; c) Farthing A. C., Nam B. in: *Steric Effects in Conjugated Systems* (G. W. Gray, Ed.), p. 131. Butterworths, London 1958.
6. Charton M. in: *Similarity Models in Organic Chemistry, Biochemistry and Related Fields* (R. I. Zalewski, T. M. Krygowski and J. Shorter, Eds), p. 629. Elsevier, Amsterdam 1991.
7. Bowden K., Manser G. E.: *Can. J. Chem.* **1968**, *46*, 2941.
8. Charton M.: *Can. J. Chem.* **1960**, *38*, 2493.
9. For instance: a) Nummert V., Piirsalu M., Lepp M., Mäemets V., Koppel I.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 198; b) Nummert V., Piirsalu M., Mäemets V., Koppel I.: *Collect. Czech. Chem. Commun.* **2006**, *71*, 107; c) Bauerová I., Ludwig M.: *Collect. Czech. Chem. Commun.* **2001**, *66*, 770.
10. a) Pytela O., Liška J.: *Collect. Czech. Chem. Commun.* **1994**, *59*, 2005; b) Pytela O., Prusek O.: *Collect. Czech. Chem. Commun.* **1999**, *64*, 1617.
11. Fiedler P., Böhm S., Kulhánek J., Exner O.: *Org. Biomol. Chem.* **2006**, *4*, 2003.
12. a) Pross A., Radom L., Taft R. W.: *J. Org. Chem.* **1980**, *45*, 818; b) Exner O.: *Org. Reactiv.* **1995**, *29*, 1.
13. George P., Trachtman M., Bock C. W., Brett A. M.: *J. Chem. Soc., Perkin Trans. 2* **1976**, 1222.
14. McMahon T. B., Kebarle P.: *J. Am. Chem. Soc.* **1977**, *99*, 2222.
15. Böhm S., Gal J.-F., Maria P.-C., Kulhánek J., Exner O.: *Eur. J. Org. Chem.* **2005**, 2580.
16. a) Exner O., Böhm S.: *J. Org. Chem.* **2002**, *67*, 6320; b) Exner O., Böhm S.: *J. Phys. Org. Chem.* **2004**, *17*, 124; c) Böhm S., Exner O.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 370.
17. Exner O., Böhm S., Decouzon M., Gal J.-F., Maria P.-C.: *J. Chem. Soc., Perkin Trans. 2* **2002**, 168.



18. Exner O., Böhm S.: *Phys. Chem. Chem. Phys.* **2004**, *6*, 3864.
19. a) Becke A. D.: *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098; b) Lee C., Yang W., Parr R. G.: *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785; c) Miehlich B., Savin A., Stoll H., Preuss H.: *Chem. Phys. Lett.* **1989**, *157*, 200; d) Becke A. D.: *J. Chem. Phys.* **1993**, *98*, 5648.
20. Castaño O., Notario R., Hori K., Abboud J.-L. M.: *Struct. Chem.* **1996**, *7*, 321.
21. Hunter E. P. L., Lias S. G.: *J. Phys. Chem. Ref. Data* **1998**, *27*, 413.
22. Thompson H. W., Steel G.: *Trans. Faraday Soc.* **1956**, *52*, 1451.
23. Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Montgomery J. A., Jr., Vreven T., Kudin K. N., Burant J. C., Millam J. M., Iyengar S. S., Tomasi J., Barone V., Mennucci B., Cossi M., Scalmani G., Rega N., Petersson G. A., Nakatsuji H., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Klene M., Li X., Knox J. E., Hratchian H. P., Cross J. B., Adamo C., Jaramillo J., Gomperts R., Stratmann R. E., Yazyev O., Austin A. J., Cammi R., Pomelli C., Ochterski J. W., Ayala P. Y., Morokuma K., Voth G. A., Salvador P., Dannenberg J. J., Zakrzewski V. G., Dapprich S., Daniels A. D., Strain M. C., Farkas O., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Ortiz J. V., Cui Q., Baboul A. G., Clifford S., Cioslowski J., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Gonzalez C., Pople J. A.: *Gaussian 03*, Revision B.03. Gaussian, Inc., Pittsburgh (PA) 2003.
24. Exner O., Böhm S.: *Collect. Czech. Chem. Commun.* **2001**, *66*, 1623.
25. Binev Y. I., Georgieva M. K., Daskalova L. I.: *Spectrochim. Acta, Part A* **2004**, *60*, 2601.
26. Seguin J.-P., Guillaume-Vilpert F., Moutiers G., Guével E. L., Villien L., Terrier F.: *J. Chem. Soc., Perkin Trans. 2* **1997**, *7*.
27. Wiberg K. B.: *J. Org. Chem.* **2003**, *68*, 875.
28. Austerheim Å., Gramstad T.: *Acta Chem. Scand., Sect. B* **1985**, *39*, 583.
29. Honda M., Fujii A., Fujimaki E., Ebata T., Mikami N.: *J. Phys. Chem., A* **2003**, *107*, 3678.
30. Yonemoto T., Reynolds W. F.: *Can. J. Chem.* **1965**, *43*, 2668.
31. Pytela O., Otyepka M., Kulhánek J., Otyepková E., Nevěčná T.: *J. Phys. Chem., A* **2003**, *107*, 11489.
32. Grabowski S. J.: *J. Phys. Org. Chem.* **2004**, *17*, 18.
33. Verloop A., Hoogenstraaten W., Tipker J. in: *Drug Design* (E. J. Ariens, Ed.), Vol. VII, p. 165. Academic Press, New York 1976.
34. Jaffé H. H.: *Chem. Rev.* **1953**, *53*, 191.