REVISION OF THE DUAL-SUBSTITUENT-PARAMETER TREATMENT; REACTION SERIES WITH A DONOR REACTION CENTRE

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Received April 17, 2007
Accepted June 28, 2007

Dedicated to Professor Štefan Toma on the occasion of his 70th birthday.

The dual-substituent-parameter (DSP) treatment was challenged previously as not generally valid. Just in the fundamental reaction, dissociation of 4-substituted benzoic acids and in similar reactions, DPS does not hold for acceptor substituents because the constant reaction centre is itself an acceptor. In this communication, the reverse case was examined, i.e., a reaction series with a donor reaction centre: basicity and acidity of 4-substituted anilines, and acidity of 4-substituted phenols. The reaction energies were calculated for 19 common substituents at the level B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p); the substituents effects were also estimated separately in uncharged molecules and in the ions in terms of isodesmic reaction. DSP is valid and its resonance term is highly significant for molecules with acceptor substituents; donor substituents behave differently and cannot be described by simple resonance constants. Basicity of substituted anilines is more complex since the substituent effects are quite different in the free base and in the protonated form: basicity is controlled by a combination of various effects. It is recommended to use DSP only for acceptor substituents with a donor reaction centre or vice versa; otherwise the accuracy is decreased. All results were obtained with isolated molecules and with resonance constants derived on isolated molecules; however, they retain their validity even with the common constants σ_R determined from the reactions in solution.

Keywords: Aniline derivatives; Isodesmic reactions; Phenol derivatives; Basicity; Acidity; Resonance energy; Substituent effect; DTF calculations.

The dual-substituent-parameter (DSP) treatment[1–4] is probably the most widely used empirical correlation. Equation (*1*) correlates the reaction energies $\Delta_1 E$ in a reaction series (or the corresponding reaction enthalpies or Gibbs energies) with the parameters characterizing the substituent, i.e. inductive constant σ_I and resonance constant σ_R. Parameters ρ_I and ρ_R are

Collect. Czech. Chem. Commun. 2007, Vol. 72, No. 8, pp. 1158–1176
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doi:10.1135/cccc20071158

regression coefficients, $\Delta_1 E°$ equals approximately $\Delta_1 E$ of the unsubstituted compound. In practice, $\Delta_1 E$ was often replaced by pK or in kinetics by log k; the validity of the equation was also extended to various physical properties[5].

$$\Delta_1 E - \Delta_1 E° = \rho_I \sigma_I + \rho_R \sigma_R \qquad (1)$$

The linear form of Eq. (*1*) is only a mathematical approximation[6] (the Taylor expansion); according to the fundamental principle, both inductive and resonance effects are proportional in various reactions. For instance, if Eq. (*1*) is valid for the ionization of 4-substituted benzoic acids (Eq. (*2*), the standard reference reaction), it should be valid for any other reaction, for instance dissociation of anilinium ions, Eq. (*3*), with the same values of σ_I and σ_R, only with altered ρ_I and ρ_R.

$$\text{4-X-}C_6H_4COOH + C_6H_5COO^- \rightleftharpoons \text{4-X-}C_6H_4COO^- + C_6H_5COOH \qquad (2)$$

$$\text{4-X}C_6H_4NH_2 + C_6H_5NH_3^+ \rightleftharpoons \text{4-X}C_6H_4NH_3^+ + C_6H_5NH_2 \qquad (3)$$

However, it has been known for a long time that for many reactions the resonance of some substituents (either donors or acceptors) is not proportional; this is the case just in these two reactions. The problem was resolved[1–4] – in a purely formal way – by constructing alternative sets of constants σ_R (called dual resonance constants), differentiated by a superscript: $\sigma_R°$, σ_R^{Bz}, σ_R^+ and σ_R^-. These sets were chosen in individual reactions according to the strength of resonance as the case might be. This arbitrariness was denoted as an extension of the DSP principle[1–4] but it is merely its failure[7]; another possibility is extending Eq. (*1*) with an additional term[8]. Herein, we will deal only with the simple Eq. (*1*) with constant σ_R.

The DSP theory was also criticized from the statistical point of view: the significance of the second term was rarely proven and the regression coefficients ρ_I and ρ_R were strongly interdependent[9,10]. Further general objections concern a possible dependence of explanatory variables[11] (intercorrelation) or grouping of substituents into clusters[12] but both events seem to occur rarely. More specific criticism concerned the σ_R constants of acceptor substituents, which are small in comparison to great negative σ_R of donors. It was even suggested that they should equal zero[13]. This problem was discussed at length[14,15] but opinions differ even at present[16]. Important progress was reached when the substituent effect was redefined[17] in terms of isodesmic[18] and homodesmic[19] reactions; the distinction of a substituent and functional group was removed, and in ionization reactions the substituent effects could be estimated separately in the ions and in the undissociated species[18]. For instance, the protonation of anilines, Eq. (*3*), can be divided into Eqs (*4*) and (*5*) representing the substituent effect in the unprotonated anilines **1** and in their protonated forms **2**, respectively. Reaction energies of reactions similar to Eq. (*4*) were usually calculated by quantum chemistry[20–24] methods because experimental enthalpies of formation are rarely sufficiently precise[25]. Calculations also enabled the inclusion of more substituents than in the experimental work.

$$\text{4-XC}_6\text{H}_5 + \text{C}_6\text{H}_5\text{NH}_2 = \text{4-XC}_6\text{H}_4\text{NH}_2 + \text{C}_6\text{H}_6 \qquad (4)$$

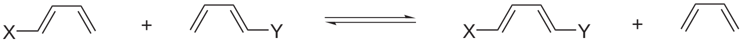
1

$$\text{4-XC}_6\text{H}_5 + \text{C}_6\text{H}_5\text{NH}_3^+ = \text{4-XC}_6\text{H}_4\text{NH}_3^+ + \text{C}_6\text{H}_6 \qquad (5)$$

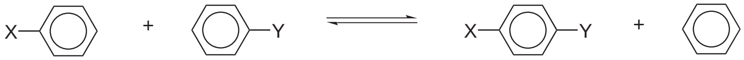
2

Along these lines, the two components of DSP, inductive and resonance, were re-examined, each separately on appropriate model compounds. Numerous results[20–23,26] confirmed that the inductive effect is proportional in various reactions; for exact proportionality, there is a precondition that one of the interacting groups is charged or strongly polar[22,23].

On the contrary, the resonance effect was not found to be proportional in different reactions. In 1,4-disubstituted butadienes[24], Eq. (*6*), as well as 1,4-disubstituted benzenes[24], Eq. (*7*), the resonance effect of variable donors was proportional when they were conjugated with one or another acceptor, and vice versa. However, the interaction of two donors or two acceptors could not be described within this framework, and a unified scale of resonance ability comprising both acceptors and donors could not be generated[24]. Resonance of various substituents was also measured by conjugation in monosubstituted derivatives, for instance in Eq. (*8*); again, a different scale was obtained[27,28].



(*6*)



(7)

$$XCH_3 + C_6H_6 = XC_6H_5 + CH_4 \qquad (8)$$

In the light of these results, the broad acceptance and popularity of the DSP treatment was difficult to understand. Therefore, a detailed analysis was undertaken[29] based mainly on the defining reaction, Eq. (*2*), and using broader sets of substituents and more exact statistical procedures as compared to classical studies[1,3]. DSP was mostly invalid for acceptor substituents, particularly when the effects were divided into those in the ions and unionized molecules (similar to Eqs (*4*) and (*5*)); the main problem is that the functional group in Eq. (*2*) is itself an acceptor and cannot be effectively conjugated with another group of the same character. The reason for the apparent success of DSP in the past was mainly the choice of substituents with very few acceptors, if any[1,3], simple statistical treatment (not testing the significance of the resonance term) and the monotonous choice of reaction series repeating the reaction of Eq. (*2*) at varying conditions[1] for a number of times. As an alternative to traditional DSP, we suggested to restrict the term resonance to the interaction of two different groups, either that of an acceptor reaction centre with donor substituents or that of a donor centre with acceptor substituents. In our first communication[29], we dealt with the former case, which was more common in the literature[1,3] and also more important since it included the standard reference reaction, Eq. (*2*). In this communication, we deal with reactions with a donor group as the reaction centre; standard examples are Eqs (*3*) and (*9*).

$$\text{4-}XC_6H_4OH + C_6H_5O^- = \text{4-}XC_6H_4O^- + C_6H_5OH \qquad (9)$$

3 **4**

Both reactions are well known in correlation analysis; they were used[3] in the definition of dual substituent constants σ_R^- on the basis of pK values in water or in aqueous solvents. Our analysis was based on isolated molecules and the pertinent energies were calculated within the framework of the density functional theory[30] (DFT) using a well established theoretical model[21–25,29]. Calculations enabled us to include more substituents systematically chosen with equal representation of both donors and acceptors. The separation of the effects in the ions and in the unionized parent molecules as in Eqs (*4*) and (*5*) constituted further improvement in comparison with classical treatment[1,3]. In addition, we also improved the statistical treatment and tested the significance of the two terms of Eq. (*1*) by the F-test and by a graphical test used previously[29].

CALCULATIONS

DFT calculations were performed at the B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) level according to the original proposal[30], exploiting the Gaussian 03 program[31]. This level was selected according to previous experience with similar compounds[21–25]. Full energy optimization and vibrational analysis were carried out in all cases, all structures behaved as energy minima. No corrections for the zero-point energy were introduced. The energies of **1a** to **5s** are listed in Table I, some bond lengths in Table II and reaction energies Δ_3E, Δ_4E, Δ_5E, Δ_9E, $\Delta_{12}E$, $\Delta_{13}E$, $\Delta_{14}E$ and $\Delta_{15}E$ of the corresponding isodesmic reactions, Eqs (*3*)–(*15*), are in Table III.

In the case of certain substituted phenols **3** and aniline anions **5** (substituents OH, SH, OCH_3, CHO, COOH and $COOCH_3$), two planar conformations are possible with different mutual position of the two coplanar groups, *sp* and *ap*. In addition, these substituents can sometimes assume a non-coplanar conformation. In the calculations, the coplanarity or any symmetry was never anticipated and the energies given in Table I always refer to the minimum-energy conformation. For some molecules, the DFT energy was calculated for fixed conformation, i.e. with one fixed dihedral angle; in this case all remaining geometry parameters were optimized with internal coordinates.

RESULTS AND DISCUSSION

Comparison with Experiments

In our standard approach, the DFT-calculated reaction energies are used as an input into correlation analysis, almost as quasi-experimental data. Therefore, it is always of fundamental importance when these values can be anchored and/or scaled using some dependable experiments. Of the reactions investigated herein, the acidity of substituted anilines, Eq. (*12*), and of substituted phenols, Eq. (*9*), can be compared with the experimental acidity[4] in the gas phase. Basicity of anilines is not suitable for this purpose since protonation in the gas phase proceeds at different sites of the molecule[32,33]. Correlation of calculations and experiments is very close

(Table IV, entries 1 and 2), the standard deviations approximate the experimental uncertainty, which may be estimated to 2 kJ mol^{-1}. However, the regression coefficients differ distinctly from unity: all substituent effects are overestimated. This defect was observed several times[34,25] with the DFT model, although not always. Comparison with other theoretical models was not unambiguous; the poor scaling was sometimes compensated by better standard deviation[25] or better prediction of geometry[35]. Acidity of phenols was calculated several times using more or less sophisticated models[36–39]. We recalculated the agreement with experiments using only the compounds used in this work (Table IV, entries 2a to 2d). Generally, a better fit was observed with higher-level theoretical models but which one of them is the best cannot be decided since the choice of substituents is not

TABLE I
DFT-calculated energies (in a.u.) of substituted anilines and phenols

Compd	X	4-X-$C_6H_4NH_2$ **1**	4-X-$C_6H_4NH_3^+$ **2**	4-X-$C_6H_4NH^-$ **5**	4-X-C_6H_4OH **3**	4-X-$C_6H_4O^-$ **4**
a	CF_3	–624.8398135	–625.1714148	–624.2657683	–644.7092474	–644.1673041
b	CN	–379.9577170	–380.2844426	–379.3914326	–399.8265110	–399.2921471
c	CHO	–401.0499374	–401.3816298	–400.4841079	–420.9186687	–420.3833689
d	CO_2H	–476.3284627	–476.6638657	–475.7582434	–496.1975619	–495.6577897
e	CO_2CH_3	–515.6378308	–515.9770417	–515.0644949	–535.5072612	–534.9642934
f	NO_2	–492.2557597	–492.5785029	–491.7019687	–512.1240076	–511.5997367
g	$SOCH_3$	–800.4253890	–800.7641045	–799.8506033	–820.2956440	–819.7518235
h	SO_2CH_3	–875.6601571	–875.9903017	–875.0945601	–895.5292336	–894.9950319
i	SO_2CF_3	–1173.4602950[a]	–1173.7808130	–1172.9087131	–1193.3280884	–1192.8073326
j	H	–287.6876273	–288.0344197	–287.0902731	–307.5586306	–306.9939822
k	CH_3	–327.0141357	–327.3656212	–326.4146463	–346.8853257	–346.3185517
l	CH_2Cl	–786.6384442	–786.9800797	[b]	–806.5085398	[b]
m	NH_2	–343.0598120	–343.4201874	–342.4566904	–362.9316023	–362.3608528
n	$N(CH_3)_2$	–421.6860271	–422.0514247	–421.0878500	–441.5581497	–440.9915734
o	OH	–362.9316023	–363.2833433	–362.3310794[a]	–382.8028871	–382.2354850[a]
p	OCH_3	–402.2406626	–402.5956844	–401.6413324	–422.1121296	–421.5455610[a]
q	SH	–685.9015917[a]	–686.2478154	–685.3165598[a]	–705.7709608	–705.2190413[a]
r	F	–386.9545844	–387.2963659	–386.3614870	–406.8253422	–406.2661668
s	Cl	–747.3100866	–747.6506325	–746.7232254	–767.1805146	–766.6268801

[a] *E*(DFT) of $C_6H_5SOCH_3$ –745.0478206. [b] No stable molecule was obtained since one chlorine atom was split off.

TABLE II
Calculated bond lengths C2–C3 (in Å) in 4-substituted anilines and phenols

Compd	X	4-X-$C_6H_4NH_2$ **1**	4-X-$C_6H_4NH_3^+$ **2**	4-X-$C_6H_4NH^-$ **5**	4-X-C_6H_4OH **3**	4-X-$C_6H_4O^-$ **4**
a	CF_3	1.387	1.392	1.373	1.387	1.378
		1.387	1.393	1.376	1.391	1.378
b	CN	1.384	1.390	1.370	1.385	1.375
		1.384	1.391	1.373	1.388	1.375
c	CHO	1.381	1.390	1.368	1.383	1.370
		1.385	1.393	1.368	1.390	1.373
d	CO_2H	1.383	1.390	1.368	1.384	1.372
		1.385	1.394	1.370	1.389	1.373
e	CO_2CH_3	1.384	1.390	1.369	1.385	1.373
		1.386	1.394	1.370	1.389	1.374
f	NO_2	1.383	1.391	1.366	1.385	1.370
		1.383	1.393	1.369	1.388	1.370
g	$SOCH_3$	1.389	1.392	1.371	1.393	1.377
		1.389	1.394	1.374	1.393	1.377
h	SO_2CH_3	1.386	1.394	1.370	1.387	1.376
		1.386	1.394	1.373	1.390	1.376
i	SO_2CF_3	1.383	1.392	1.364	1.385	1.370
		1.383	1.392	1.367	1.388	1.370
j	H	1.391	1.393	1.383	1.391	1.388
		1.391	1.395	1.387	1.394	1.388
k	CH_3	1.390	1.390	1.382	1.392	1.39
		1.393	1.399	1.389	1.393	1.387
l	CH_2Cl	1.388	1.391	[a]	1.388	[a]
		1.388	1.393		1.391	
m	NH_2	1.391	1.383	1.384	1.390	1.388
		1.391	1.385	1.388	1.394	1.389
n	$N(CH_3)_2$	1.387	1.383	1.382	1.390	1.387
		1.395	1.384	1.387	1.394	1.388
o	OH	1.390	1.384	1.386	1.388	1.390
		1.394	1.391	1.391	1.397	1.390
p	OCH_3	1.386	1.382	1.385	1.389	1.390
		1.397	1.393	1.389	1.396	1.390
q	SH	1.390	1.388	1.378	1.389	1.383
		1.390	1.389	1.382	1.394	1.383
r	F	1.392	1.392	1.387	1.391	1.392
		1.392	1.392	1.392	1.395	1.392
s	Cl	1.391	1.390	1.383	1.390	1.388
		1.391	1.392	1.387	1.394	1.388

[a] No stable molecule was obtained since the chlorine atom was split off.

the same and is relatively narrow. For the purpose of correlation analysis, our theoretical model is adequate, particularly for the analysis, which deals only with relative values.

Basicity of Substituted Anilines

Let us start with this standard reaction, which has also been used for the definition of the dual constants σ_p^- and σ_R^- devised for the reactions, in which the reaction centre is conjugated as a donor[3]. The relative basicity is expressed by the isodesmic reaction, Eq. (*3*); the corresponding calculated reaction energies Δ_3E are listed in Table III, column 3. The DSP correla-

TABLE III

Calculated energies (in kJ mol^{-1}) of the isodesmic reactions of 4-substituted anilines and phenols

Compd	X	Δ_3E Eq. (*3*)	Δ_4E^a Eq. (*4*)	Δ_5E^a Eq. (*5*)	$\Delta_{12}E^b$ Eq. (*12*)	$\Delta_{13}E^b$ Eq. (*13*)	Δ_9E^b Eq. (*9*)	$\Delta_{14}E^b$ Eq. (*14*)	$\Delta_{15}E^b$ Eq. (*15*)
a	CF_3	39.88	–6.83	33.05	–61.20	–68.03	–59.61	–2.71	–62.33
b	CN	52.69	–9.36	43.32	–81.57	–90.94	–79.51	–3.56	–83.08
c	CHO	39.65	–11.76	27.89	–82.77	–94.53	–77.05	–5.79	–82.85
d	CO_2H	29.90	–10.29	19.61	–71.24	–81.54	–65.31	–5.30	–70.61
e	CO_2CH_3	19.91	–8.76	11.15	–63.06	–71.82	–56.92	–4.63	–61.55
f	NO_2	63.14	–12.50	50.64	–114.38	–126.88	–106.01	–5.27	–111.28
g	$SOCH_3{}^b$	21.21	–3.09	18.11	–59.15	–62.24	–55.27	–0.54	–55.61
h	SO_2CH_3	43.71	–8.84	34.87	–83.38	–92.21	–79.94	–3.78	–83.71
i	SO_2CF_3	68.99	–14.46	54.52	–120.17	–134.64	–115.24	–6.04	–121.28
j	H	0	0	0	0	0	0	0	0
k	CH_3	–12.32	2.71	–9.61	5.61	8.32	5.58	2.22	7.80
l	CH_2Cl	13.54	–3.45	10.09	^{c}	^{c}	^{c}	–1.07	^{c}
m	NH_2	–35.66	11.04	–24.62	15.14	26.18	16.02	8.97	24.99
n	$N(CH_3)_2$	–48.85	11.58	–37.26	2.16	13.75	5.06	8.65	13.71
o	OH	–12.99	8.97	–4.02	8.32	17.29	7.23	8.23	15.46
p	OCH_3	–21.61	8.63	–12.97	5.19	13.82	5.04	7.42	12.46
q	SH	1.49	0.14	1.64	–32.35	–32.21	–33.42	4.43	–28.99
r	F	13.16	5.03	18.19	–11.18	–6.14	–14.37	5.68	–8.69
s	Cl	16.40	1.26	17.66	–27.55	–26.28	–28.92	2.77	–26.14

[a] Calculated with the energies of monosubstituted benzenes taken from ref.[24] [b] Ref.[18] [c] No stable molecule was obtained since the chlorine atom was split off.

TABLE IV
Statistics of the correlations

Entry	Response function[a]	Explanatory variables	Regression coefficients[b]		R[c]	d[c]	e[c]	f[d] 1st term	g[d] 2nd term
1	$\Delta_{12}G°_{exp}$	$\Delta_{12}E$	0.769(21)		0.9915	4.1	14		
2	$\Delta_9G°_{exp}$	Δ_9E	0.891(18)		0.9972	3.0	16		
2a	$\Delta_9G°_{exp}$	$\Delta_9G°$ [e]	0.985(11)		0.9995	1.18	9		
2b	$\Delta_9G°_{exp}$	$\Delta_9H°$ [f]	0.974(12)		0.9994	1.31	10		
2c	$\Delta_9G°_{exp}$	$\Delta_9H°$ [g]	1.007(40)		0.9923	4.7	12		
2d	$\Delta_9G°_{exp}$	$\Delta_9H°$ [h]	0.834(15)		0.9989	1.82	9		
3	Δ_3E	$\sigma_I\sigma_R^-$	74(17)	52.1(94)	0.924	13.2	19	0.001	<<0.001
4	Δ_4E	σ_R^-	–21.4(18)		0.944	2.9	19		
5	Δ_5E	σ_I σ_R	64.7(88)	41.0(53)	0.963	7.1	19	<<0.001	<<0.001
6	Δ_3E	σ_I σ_A	48(14)	54(18)	0.972	5.6	10	0.01	0.025
7	Δ_4E	σ_I σ_A	4.9(22)	–28.3(29)	0.983	0.90	10	0.1	<<0.001
8	Δ_5E	σ_I	69.3(83)		0.947	6.0	10		
9	Δ_3E	σ_I $\sigma_{D,A}$	56(10)	49.7(53)	0.982	6.5	19	<0.001	<<0.001
10	Δ_4E	$\sigma_{D,A}$	–19.2(11)		0.972	2.0	19		
11	Δ_5E	σ_I $\sigma_{D,A}$	56(10)	30.7(51)	0.971	6.3	19	0.001	0.001
12	$\Delta_{12}E$	σ_I σ_A	–34(10)	–118(13)	0.989	3.8	10	0.025	<<0.001
13	$\Delta_{13}E$	σ_A	–169(12)		0.982	3.0	10		
14	$\Delta_{12}E$	σ_I $\sigma_{D,A}$	–70(26)	–66(13)	0.944	15.6	18	0.025	0.001
15	$\Delta_{13}E$	σ_I $\sigma_{D,A}$	–71(29)	–85(14)	0.952	17.1	18	0.05	<0.001
16	Δ_9E	σ_I σ_A	–51(12)	–113(16)	0.9907	4.9	10	0.005	<<0.001
17	$\Delta_{14}E$	σ_I σ_A	5.9(15)	–16.6(19)	0.968	0.60	10	0.01	<<0.001
18	$\Delta_{15}E$	σ_I σ_A	–45(12)	–129(16)	0.9910	5.0	10	0.01	<<0.001
19	Δ_9E	σ_I $\sigma_{D,A}$	–84(18)	–54.8(93)	0.967	11.4	18	0.001	<<0.001
20	$\Delta_{14}E$	σ_I $\sigma_{D,A}$	4.0(17)	–13.81(90)	0.982	1.11	18	0.1	<<0.001
21	$\Delta_{15}E$	σ_I $\sigma_{D,A}$	–80(19)	–69(10)	0.970	12.2	18	0.005	<<0.001

[a] The subscript at the reaction energy corresponds to the number of the equation. [b] Standard deviation in parentheses. [c] Correlation coefficient R, standard deviation from the regression d, number of items e. [d] Significance level of each term f and g, respectively (F-test compared to simple regression without this term). [e] Calculated at the level CBS-QB3, ref.[36] [f] Calculated at the level MP2/6-311++G(2df,2pd)//MP2/6-311+G*, ref.[37] [g] Calculated at the level ROMP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d,p), ref.[38] [h] Calculated at the level B3LYP/6-31+G*//B3LYP/6-31+G*, ref.[39]

tion with the most reliable constants[3] σ_I and σ_R^- is rather poor (Table IV, entry 3); it would be classified[40] only as fair; nevertheless, both terms of Eq. (*1*) are highly significant. We attempted to analyze the reasons for this failure by separate correlations of the energies of the uncharged aniline bases and of their protonated forms, Eqs (*4*) and (*5*), respectively; the pertinent data are in Table III, columns 4 and 5. In both cases, the correlation is better. The uncharged particles are controlled only by σ_R^- (Table IV, entry 4), the protonated forms by both σ_I and σ_R since there is no conjugation and no reason for using σ_R^-. The substituent effect on the basicity, Δ_3E, is thus produced as a sum of two incompatible components Δ_4E and Δ_5E, each controlled by different factors. We can confirm this statement by the graphical test representation introduced previously[24,29]: the first right-hand term in Eq. (1) is transferred to the left side and the residuals are plotted vs σ_R^- (Fig. 1). Equation (*1*) would predict a linear dependence with the slope ρ_R. In fact, the scatter is bad but the main defect is a fundamental difference between donor and acceptor substituents; there is a very small dependence on σ_R^- for the latter. There is even a possibility that some constants σ_R^- were estimated[3] with little accuracy, for instance for $N(CH_3)_2$ or $SOCH_3$.

In order to improve the correlation, we replaced the constants σ_I and σ_R^-, determined from solution reactivity[3], by our parameters determined for isolated molecules. Equation (*1*) is then formally transformed into Eq. (*10*), where both σ_I and σ_A were determined for isolated molecules[21,24] and σ_A is defined only for acceptors if they are conjugated with a donor[24]. (The values of σ_I and σ_A for $SOCH_3$ were now determined by the standard methods[21,24]: $\sigma_I = 0.457$, $\sigma_A = 0.160$.)

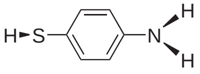
$$\Delta_3E - \Delta_3E^\circ = \rho_I\sigma_I + \rho_A\sigma_A \qquad (10)$$

The correlations obtained (Table IV, entries 6–8) are significantly better than those with σ_I and σ_R^-, (cf. entries 3–5). However, they are restricted to half of the substituents, and the significance of resonance is relatively small in the correlation of basicity (entry 6). The main problem continues to be basicity resulting from two different components: energy of uncharged anilines depends very significantly on resonance (Table IV, entry 7), energy of the protonated forms is controlled, not very precisely, only by the inductive effect (entry 8). Therefore, the basicity can hardly be interpreted in a simple fashion.

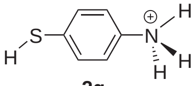
We attempted to extend the above correlation to donor substituents as common in DSP but at variance with our definition of σ_A. For this purpose, Eq. (*10*) was transformed into Eq. (*11*), where the symbol $\sigma_{D,A}$ denotes either σ_A (for acceptors) or σ_D (for donors) as the case may be; ρ is the common proportionality constant.

$$\Delta_3 E - \Delta_3 E^\circ = \rho_I \sigma_I + \rho \sigma_{D,A} \qquad (11)$$

Remarkably, the correlations with Eq. (*11*) are only insignificantly worse than those with Eq. (*10*) (Table IV, entries 9–11 compared with entries 6–8). Lower accuracy is compensated by the extended range and an apparent correlation is observed as if two sets were mixed[12]. In addition, some irregularities of individual substituents were observed, of which that of the SH group is most remarkable. This substituent has a non-coplanar, practically perpendicular conformation in the substituted aniline **1q** but is coplanar in the cation **2q**. Similar changes of conformation with ionization were already observed[37,41] and may disturb any correlation. We calculated the DFT energy of **1q** in the fixed coplanar conformation. It was higher only by 3.6 kJ mol^{-1} but even this deviation may appear in the correlation.



1q



2q

An overview for all substituents may be obtained from a similar graphical test as in Fig. 1. In Fig. 2, we have chosen the reaction of uncharged anilines, Eq. (*4*), but similar results were obtained also for Eq. (*3*) and (*5*). The acceptor and donor substituents behave differently and form two separate groups. Resonance and dependence on σ_A is evident with acceptors, while donors show greater scattering with some apparent deviations as the above mentioned SH group. Nevertheless, the addition of donors may not disturb the correlation since it is in any case improved by extending the range of values[42] and by merging two different sets[12]. In conclusion, the basicity of substituted anilines gives evidence of a reaction controlled by resonance of acceptor substituents with a donor reaction centre but is not the best example since the substituent effects in the protonated form are controlled by other factors; the result is then a combination of different factors. The constants σ_A valid for isolated molecules[24,29] are evidently preferable to common[3] σ_R^-, although some of the latter values could certainly be improved. The following analysis is presented in terms of σ_A; the correlations with σ_R^- were always carried out and were never better.

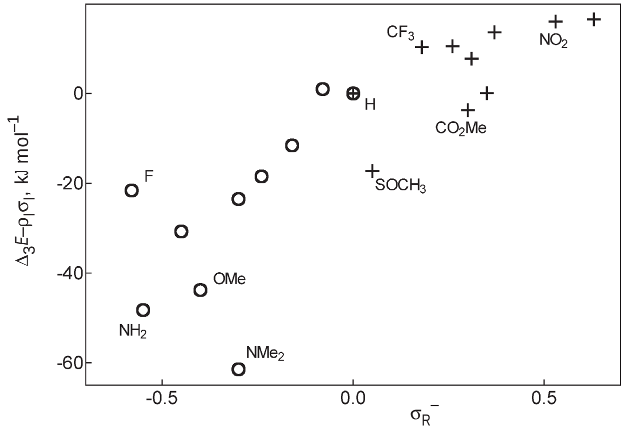


FIG. 1
DSP treatment of substituent effects on the basicity of 4-substituted anilines, Eq. (*3*), specific test of the resonance term: the reaction energies Δ_3E with the inductive term subtracted have been plotted vs the resonance constant σ_R^-; ○ donor substituents, + acceptor substituents. Some typical substituents are denoted

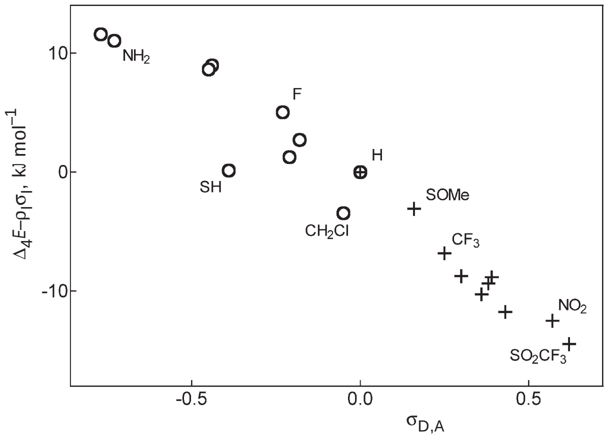


FIG. 2
DSP treatment of substituent effects in 4-substituted anilines **1**, Eq. (*4*), specific test of the resonance term: the reaction energies Δ_4E with the inductive term subtracted have been plotted vs the resonance constant $\sigma_{D,A}$; ○ donor substituents, + acceptor substituents. Some typical substituents are denoted

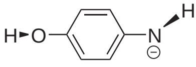
Acidity of Substituted Anilines

The main problem with the basicity of anilines was that the protonated and unprotonated forms were controlled by different factors. The acidity of the same compounds, Eq. (*12*), could be a better example since the substituent effects both in the undissociated anilines **1**, Eq. (*4*), and in their deprotonated forms **5**, Eq. (*13*), should involve strong resonance with the acceptor substituents.

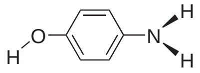
$$\underset{\mathbf{1}}{4\text{-}XC_6H_4NH_2} + C_6H_5NH^- = \underset{\mathbf{5}}{4\text{-}XC_6H_4NH^-} + C_6H_5NH_2 \qquad (12)$$

$$4\text{-}XC_6H_5 + C_6H_5NH^- = 4\text{-}XC_6H_4NH^- + C_6H_6 \qquad (13)$$

The calculated energies of **5** are listed in Table I, column 5, reaction energies pertinent to Eqs (*12*) and (*13*) in Table III, columns 6 and 7. Correlations restricted to acceptor substituents confirm the anticipation since they are controlled essentially by resonance. The energy of anions depends on the resonance constants exclusively and very strongly (Table IV, entry 13), the energy of uncharged anilines approximately six times less (entry 7), the dependence of the acidity is given by difference (entry 12). The dependence on the inductive effect is less important and not regular. It is not equal in entries 7 and 12, since the terms can mutually compensate in the multiple regression.



5o



1o

When the donor substituents are added, the accuracy of regression is lowered, in this case quite dramatically (Table IV, entries 14 and 15, compared with entries 12 and 13). A change of conformation with ionization was observed with OH (in **5o** as compared to **1o**). In addition, there are two possible planar conformations of anions **5** with the substituents OCH_3, CHO, COOH and $COOCH_3$ (and nonplanar conformation with $SOCH_3$), *ap* or *sp* with respect to the N–H bond. However, these conformers differ by less than 1 kJ mol^{-1} and do not influence the results of the correlation. (The data of Table III always relate to the minimum-energy conformer.)

The main reason for the deviations is a different behavior of acceptors and donors in an interaction with another strong donor. In Fig. 3, conjugation of acceptors regularly increasing with the resonance constants can be observed, while the behavior of donors seems to be irregular. In any case, it has little to do with the resonance constants. This picture is a good proof that conjugation of donors and acceptors must be dealt with separately; when they are merged, one try is to describe two different phenomena in one equation.

Acidity of Substituted Phenols

This reaction was also important in correlation analysis and was used for the definition of the dual constants σ_p^- and σ_R^- together with Eq. (*3*), although the results were not always consistent[1–3]. We analyzed this reaction in the same way as the acidity of anilines and the results were similar. The acidity is described by Eq. (*9*) and can be divided into the effects in the phenol molecule, Eq. (*14*), and in the phenolate anion, Eq. (*15*). The pertinent reaction energies are given in Table I, last two columns. Changes of conformation occur more often here: SH, OH and OCH_3 appeared as coplanar in the phenol molecules but in the perpendicular position in the phenolate anions. This was observed with SH but not with OH at a slightly lower level of computation[37]. In addition, two conformations of phenols are possible

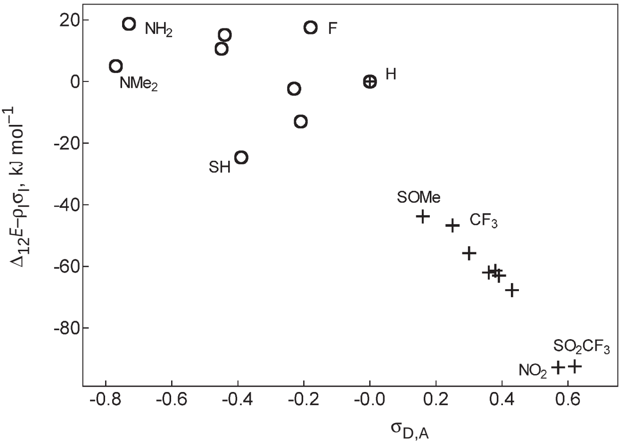


FIG. 3
DSP treatment of substituent effects on the acidity of 4-substituted anilines, Eq. (*12*), the specific test as in Fig. 1

with SH, OH, OCH_3, CHO, COOH, $COOCH_3$ and $SOCH_3$ but the energy differences are unimportant[37]; the data in Table III relate to the minimum-energy conformer.

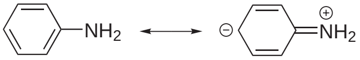
$$4\text{-}XC_6H_5 + C_6H_5OH = 4\text{-}XC_6H_4OH + C_6H_6 \qquad (14)$$

$$4\text{-}XC_6H_5 + C_6H_5O^- = 4\text{-}XC_6H_4O^- + C_6H_6 \qquad (15)$$

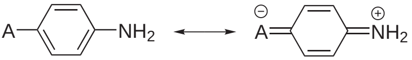
Correlations restricted to acceptor substituents (Table IV, entries 16–18) are good if they are dominated by a strong resonance in the phenolate anions (entry 18). Resonance in the phenol molecules is eight times weaker (entry 17); its effect on the acidity is given by difference (entry 16). This all is the same picture as in the acidity of anilines, the main, not very important difference is the lower importance or even statistical insignificance of the inductive term in the aniline derivatives. The graphical test for the acidity of phenols is very similar to the acidity of anilines (Fig. 3) and is not reproduced.

Evidence of Resonance from the Bond Lengths

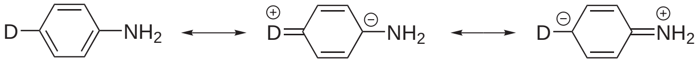
Different character of substituent effects of donors and acceptors can be supported by the calculated bond lengths. The resonance in aniline **1A** ↔ **1B** is evident from shorter bond lengths C2–C3 and C5–C6. Resonance should be stronger and the bonds shorter in the presence of acceptors (through-resonance **1D**). Donors can be conjugated only with the benzene ring (**1F**) and their conjugation competes with the conjugation of the amino group itself (**1G**) – crossed conjugation.



1A **1B**



1C **1D**



1E **1F** **1G**

Similar formulae can be drawn for the conjugation with OH, O^- and NH^- in **3**, **4** and **5**, respectively. The bond lengths C2–C3 and C5–C6 were slightly different, particularly in **3** and **5** because of the Krygowski AGIBA effect[43]; the average of the two values was correlated with the resonance constants. Figure 4 is a significant example (compounds **5**), but for **1**, **3** and **4** the graphs are very similar. In the case of acceptor substituents, the C2–C3 bond lengths decrease steadily with increasing resonance constant σ_A. For donors, no dependence on σ_D is observed. Interaction of two donors and interaction donor–acceptor appear as dissimilar phenomena.

CONCLUSIONS

Interaction of two functional groups connected by an unsaturated system has always been described in terms of resonance. We have good proofs that this term has been applied too broadly, and its use should be restricted according to the character of the interacting groups. When one group is a donor and the other an acceptor (as in the formulae **1C** ↔ **1D**), resonance is a proper formal description. The formula **1D** predicts well some observable quantities such as bond lengths (Fig. 4 and ref.[29]) and enhanced dipole moment[44]. The interaction energy is stabilizing and can be expressed by the DSP equation, Eqs (*1*) and (*10*); these equations may be given some physical meaning. The DSP treatment, however, has been commonly applied to all

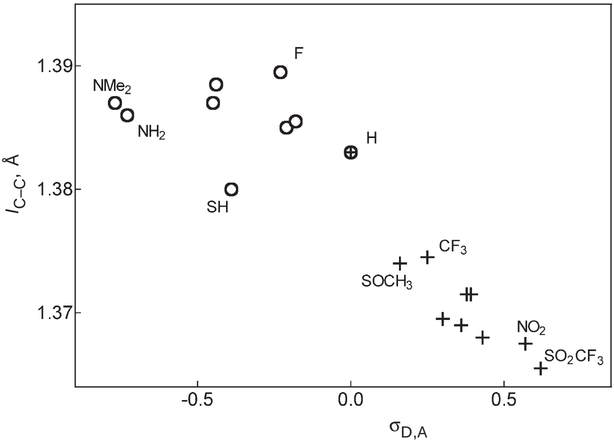


FIG. 4

Calculated bond lengths C2–C3 in the deprotonated forms of 4-substituted anilines **5** plotted vs the resonance constants σ_A and σ_D

substituents without distinction. It has been shown that acceptor substituents deviate when the functional group itself is an acceptor[29]. The same behavior was observed with donor substituents when the functional group was a donor (see Fig. 3 in particular). Most correlations described in the past were seeming and were made possible by unsymmetrical choice of substituents. Interaction of two donors as in **1F** ↔ **1G**, or a similar interaction of two acceptors can be classified as crossed conjugation but it can hardly be described by an empirical equation with resonance constants[24]. Nevertheless, with this restriction, resonance remains a simple tool for appropriate description of a number of substituent effects.

This work was carried out within the framework of the research project Z4 055 0506 of the Academy of Sciences of the Czech Republic.

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