PCCP

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/pccp

Towards Physical Interpretation of Substituent Effects: the Case of *meta* and *para*-substituted Anilines

Halina Szatylowicz,[a]* Tomasz Siodla,[b] Olga A. Stasyuk[a] and Tadeusz M. Krygowski[c]*

[a] Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland. Email: halina@ch.pw.edu.pl

[b] Faculty of Chemistry, Adam Mickiewicz University, Umultowska 89b, 61-614 Poznań, Poland

[c] Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland

Abstract

Quantum chemical modeling was used to investigate the electron-donating properties of the amino group in a series of *meta*- and *para*-X-substituted anilines (X = NMe_2, NH_2, OH, OMe, CH_3, H, F, Cl, CF_3, CN, CHO, COMe, $CONH_2$, COOH, NO_2, NO). Different methods (HF, B3LYP, M06-2X) and basis sets (6-31+G(d,p), 6-311++G(d,p), aug-cc-pVDZ) were applied and compared with the MP2 approach. The B3LYP/6-311++G(d,p) method was chosen as the most appropriate one. The substituent properties were described by σ, cSAR(X) and SESE descriptors; the amino group was characterized by structural (d_{CN}, d_{NH} and Σ_{NH2}) and electronic [δ(N) and cSAR(NH_2)] parameters; whereas the transmitting moiety – by aromaticity indices HOMA and NICS, as well as by QTAIM characteristics at the ring critical point. All used parameters were fount to be mutually interrelated with much better correlations for the *para*- than the *meta*-derivatives. It was numerically confirmed that sensitivity of the amino group to the substituent effect was greater by over three times when the substituent was located in the *para*-position. In the case of the *meta*-derivatives, variability of characteristics for both the reaction center and the substituent was small. The reverse substituent effect was clearly shown by comparison of the cSAR(X) characteristics for monosubstituted benzenes, *meta*- and *para*-substituted anilines.

Keywords: substituent effect, aniline derivatives, SESE,

Introduction

Substituents may dramatically change the properties of a given chemical compound. Their effect can be nicely exemplified by benzene derivatives. Benzene is well-known as a toxic, carcinogenic substance,[1] however, its derivatives – benzoic acid and its sodium or calcium salts are known as preservatives with international symbols E210, E211 and E213, respectively.[2] Acetylsalicylic acid has been known for centuries as a medicine, and produced since 1899 under the name of aspirin.[3] Qualitative differences between these substances are self-evident.

Substituent effects (SEs) belong to the most important intramolecular interactions in organic chemistry and related fields. Their description, with the exception of σ_I constants, are mainly based on the characteristics of benzene derivatives.[4] In the late thirties of XX century Louis P. Hammett pioneered the quantitative approach to SEs. He suggested that the SEs on the acid-base equilibrium constants of *meta*- and *para*-substituted benzoic acids[5,6] can be considered as good descriptors of kinetic and equilibria characteristics for similar systems. This was practically realized by the introduction of so-called Hammett substituent constants, (equation 1):

$$\sigma_{p(m)} = \lg K_{p(m)}(X) - \lg K \qquad (1)$$

where K and $K(X)$ are dissociation constants for unsubstituted and *para*- or *meta*-substituted (by X) benzoic acids, respectively.

Then equation (2) can be applied for the equilibrium (K) or rate (k) constants of various reaction series.

$$\lg K[k]_{m,p} = \rho\, \sigma_{p(m)} + \text{const} \qquad (2)$$

where ρ, the regression line slope, is termed as a reaction constant and describes sensitivity of a given reaction to SE.

It is important to note that already in 1940, in the fundamental monograph,[7] the explanatory parameters $\sigma_{p(m)}$ were successfully applied to interpret the data of kinetics and equilibria for 52 reaction series. Since that time, the similarity modeling for describing substituent effects, initiated by Hammett, has accomplished a great success and has become a basic method for the interpretation of the influence of substituents on chemical, and later also physicochemical properties of various organic compounds.[8,9,10,11,12,13,14,15,16] However, even Hammett himself quickly found out[17] that the original constants, σ_p, have failed in some

cases. For this reason, depending on the nature of the reaction sites, many other substituent constants have been introduced in subsequently developed substituent effect theories, for review see Ref. 4,18,19.

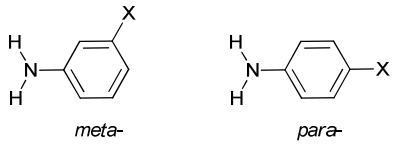
Apart from empirical approaches to the description of SEs by the use of substituent constants, these effect have also been treated by quantum chemistry modeling. *Para*-substituted systems aromatic compounds can be treated here as instructive examples of good correlations between the computationally estimated physicochemical properties and the substituent constants. For example, Gadre and Suresh found successful correlations between molecular electrostatic potential topography of monosubstituted benzene and substituent constants.[20] Indeed, in many cases, the electrostatic potentials at the ring carbon atoms or at atoms of the reaction site correlated well with the substituent constants.[21,22,23] Energy decomposition analysis[24] (EDA) was also successfully applied to confirm that in *meta*- and *para*-substituted benzylic cations and anions the π conjugation strength correlates well with the substituent constants.[25] The energetic characteristics of SE obtained by isodesmic or homodesmotic reactions approach, termed SESE (substituent effect stabilization energy), is also a very important issue.[26,27] In many cases, SESE correlates well with the substituent constants.[28]

It is important to stress that after more than half century the Hammett's idea has come back: "***A substituent produces, in general, different changes in electron density on different carbon atoms in the ring; consequently, its effect differs according to the relative positions of substituent and reaction group***".[17] Although correlations between atomic charges at substituents and substituent constants fail, the idea of using atomic charges can be successful if atomic charges at the substituent are replaced by a **sum of charges at the substituent and the *ipso* carbon atom**. This characteristic named originally as **qSAR** (acronym coming from **q** (charge) of the **Substituent Active Region**)[29,30,31] correlates well with the substituent constants. Recently the name qSAR has been replaced by cSAR to avoid confusion with another acronym – QSAR (Quantitative Structure Reactivity Relationships).[28,32]

The amino group belongs to one of the most important functional groups in organic chemistry and related fields. It constitutes a part of all amino acids - the building blocks of proteins. Three of five nucleic acid bases: cytosine, adenine and guanine contain exocyclic amino groups. In some cases, amino group-containing compounds in which one hydrogen atom is replaced by an additional substituent are biologically active and some of them serve as medicines, e.g. paracetamol,[33] dopamine,[34] adrenaline,[35] amphetamine,[36] *etc*. Recently, NBO

theory has been used to study partial charges at exocyclic nitrogen atoms of 201 known drugs and 50 Ames positive (mutagenic) compounds containing amino and nitro groups attached to the phenyl ring.[37]

In view of this wide occurrence of amino groups in many chemical and biochemical species, the studies of substituent-induced properties changes seem essential. However, an important question must be asked, which of the presently known substituent constants[4] should be used in a given case. The aim of this paper is to present the influence of substituents in *meta*- and *para*-positions of the aniline ring (see Scheme 1) on electron-donating (ED) properties of the amino group and also to show how various substituent characteristics may be successfully applied to describe these type of intramolecular interactions.



Scheme 1. Chemical structure of the studied aniline derivatives, X = NMe_2, NH_2, OH, OMe, CH_3, H, F, Cl, CF_3, CN, CHO, COMe, $CONH_2$, COOH, NO_2, NO.

Methodology

For all studied systems, optimization without any symmetry constraints was performed using the Gaussian09 program.[38] In order to find the optimal level of theory, the calculations for *para*- and *meta*- substituted anilines were carried out at 12 different computational levels: by three methods (HF,[39] DFT with B3LYP[40] and M06-2X[41] functionals, and MP2[42]), with three basis sets each (6-31+G**, 6-311++G**[43] and aug-cc-pVDZ[44]). The vibrational frequencies were calculated at the same level of theory to confirm that all calculated structures correspond to the minima on potential energy surface. In the case of branched substituents, several conformations were taken into account to find the global minimum energy structure for which further analyses were performed.

For each studied system, energetic descriptor of substituent effects named Substituent Effect Stabilization Energy (SESE) was evaluated using homodesmotic reaction[45,46,47] (eq. 3):

$$X\text{-}R\text{-}Y + R \rightarrow R\text{-}X + R\text{-}Y \qquad (3)$$

In this model, SESE describes the energetic effect of interaction between substituent **X** and reaction site **Y**, while **R** serves as a transmitting moiety. In our case, **Y** is the amino group

(NH_2), while **R** denotes a benzene ring. The greater value of SESE (see eq 4) means the higher stabilization energy due to the substituent effect.

$$SESE = E(R\text{-}X) + E(R\text{-}Y) - E(X\text{-}R\text{-}Y) - E(R) \quad (4)$$

Based on the best correlation between SESE and Hammett substituent constants, MP2/6-311++G** method was chosen as a reference (Table 1S). Then the results obtained at 11 levels were compared with the reference method using a linear regression analysis. Taking into consideration accuracy, sensitivity and computational costs, the B3LYP/6-311++G** method was chosen for all further calculations.

The next parameter used to describe the SE is cSAR(X) – the substituent active region parameter.[29,30] It can be calculated according to equation (5) by summing up charges of atoms belonging to the substituent X and the *ipso* carbon atom to which the substituent is attached.

$$cSAR(X) = q(X) + q(C_{ipso}) \quad (5)$$

For the atomic charges assessment three different methods were used: Weinhold,[48] Voronoi,[49,50] and Bader.[51] Weinhold's natural population analysis (NPA) was performed using NBO 6.0 program.[52] Voronoi charges were calculated using ADF program,[24] whereas Bader's AIM atomic charges were computed using AIMAll program.[53] Due to good correlations between cSAR(X) values based on these assessments of atomic charges[54] only NBO data were used in this paper. All obtained cSAR values are presented in Table 2S.

Calculations of NICS (nucleus independent chemical shift) index and NMR shielding were carried out using the GIAO/B3LYP/6-311++G** method.[55] NICS was calculated in the center of the ring,[56] NICS(0), and 1 Å above the center, NICS(1).[57]

A geometry-based aromaticity index HOMA (Harmonic Oscillator Model of Aromaticity)[58,59] was used to describe the SE on the transmitting moiety. It is defined as a normalized sum of squared deviations of bond lengths from the values expected for a fully aromatic system. For hydrocarbons, the appropriate expression is given by equation (6).

$$HOMA = 1 - \frac{1}{n}\sum_{i=1}^{n} \alpha\left(R_{opt} - R_i\right)^2 \quad (6)$$

where n is the number of CC bonds taken into consideration, α=257.7 is an empirical normalization constant chosen to give HOMA=0 for non-aromatic system and HOMA=1 for a system where all bonds are equal to R_{opt}=1.388 Å, and R_i are the experimental or computed bond lengths.

The electron density distribution in the ring was also analyzed by Bader's Quantum Theory of Atoms in Molecules (QTAIM).[51] Such parameters as the electron density in the ring critical points (RCPs), ρ_{RCP}, its laplacian, $\nabla^2\rho_{RCP}$, density of the total electron energy in

RCP, H_{BCP}, and its components, potential and kinetic electron energy densities, V_{BCP} and G_{BCP}, were used as the aromaticity characteristics.[60]

Motivation

In general, substituent effect is associated with molecular systems X-R-Y consisting of three parts: fixed group Y in a reaction series, for chemical reactions named as reaction site; varying chemical group X named substituent; and transmitting moiety R. The term substituent effect(s) may be considered in a few different ways:

(i) The first way is that presented already by the Hammett[6] and can be considered as a classical understanding of the substituent effect. The heart of this approach is that the substituent constants, σ, or more generally other characteristics of the substituent X, are able to describe changes observed at group Y. In other words, substituent effects observed in various reaction series are characterized by comparison with those observed in acid-base equilibrium in *meta*- and *para*-substituted benzoic acid derivatives. Quantitatively this is described by a so-called Hammett equation (2), where not only kinetic or equilibrium data can be used but also many physicochemical properties of the group Y. Important to note that the data for *meta*- and *para*-substituted compounds plotted against σ_m and σ_p form a common regression line.

(ii) The next application of the term is focused on the description of the influence of substituents X on the properties of the transmitting moiety R. This may depend also on the nature of Y, but the property taken into consideration is a feature of R moiety.

(iii) The third way of using the SE term is the investigation of interrelation between various properties of group Y, caused by changes of substituents X.

(iv) Finally, reverse substituent effect notion can be introduced[54] when we consider the question how characteristic of the substituent X depends on the rest of a molecule, i.e. on R, Y as well as on R-Y.

Results and Discussion

Different approaches aimed the characterization the effect of substituent X on the properties of *meta*- and *para*-substituted aniline derivatives, mentioned in the Motivation, are presented and discussed below.

To describe the properties of the substituent three different characteristics were used. Apart from classical descriptors introduced by Hammett – σ constants, cSAR(X)[29-31] and

SESE[26,27] were applied. Verification of their mutual correlations revealed that these characteristics are partly interrelated (Fig. 1, Table 1).

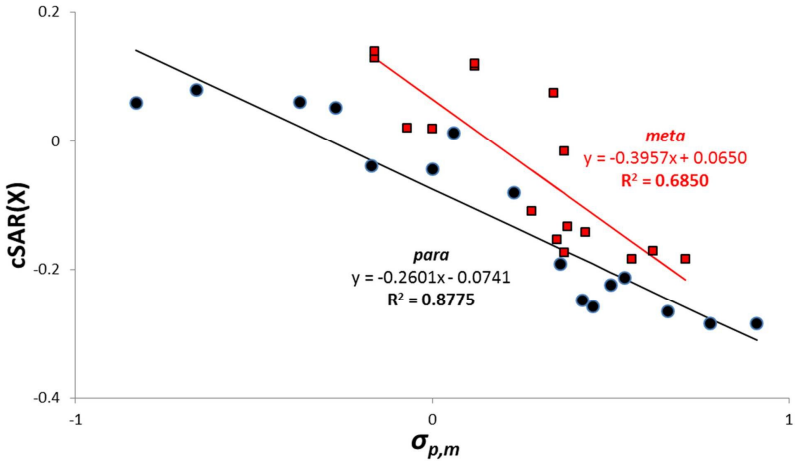


Figure 1. Relationships between cSAR(X) and substituent constants σ for *meta*- and *para*-substituted anilines.

Table 1. Interrelations between characteristics of substituents; the equation $f(x) = a \cdot x + b$, Δ1 and Δ2 denote ranges of variability $f(x)$ and x, respectively.

	R^2	a	b	a_p/a_m	Δ1	$\Delta1_p/\Delta1_m$	Δ2	$\Delta2_p/\Delta2_m$
		SESE = $a \cdot \sigma + b$			SESE		σ	
m	0.758	0.930	0.166	4.55	0.87	7.91	0.87	2.00
p	0.896	4.232	-0.094		6.88		1.74	
m+*p*	0.750	3.433	-0.232					
		cSAR(X) = $a \cdot \sigma + b$			cSAR(X)		σ	
m	0.685	-0.396	0.065	0.66	0.32	1.13	0.87	2.00
p	0.878	-0.260	-0.074		0.37		1.74	
m+*p*	0.632	-0.272	-0.020					
		cSAR(X) = $a \cdot$ SESE + b			cSAR(X)		SESE	
m	0.518	-0.322	0.093	0.19	0.32	1.13	0.87	7.91
p	0.968	-0.061	-0.080		0.37		6.88	
m+*p*	0.591	-0.066	-0.045					

Few interesting feature should be noted regarding the data collected in Table 1. In all three cases, the best correlations are found for *para*-substituted systems with $R^2 > 0.878$, whereas in the case of *meta*-substituted derivatives, R^2 values are between 0.518 – 0.758. The ranges of variation of σ, cSAR(X) and SESE parameters are different for *meta*- and *para*-substituted systems. If the ranges are presented in a unified way the ratios of ranges *para*/*meta* amount to 2.00, 1.13 and 7.91 for σ, cSAR and SESE, respectively. The obtained values show

that the last descriptor of the substituent clearly stands out, most probably because SESE takes into account all kinds of interactions present in the systems in question, whereas it is not the case for two other parameters which are more local.

Classical Hammett modeling of the substituent effect

Consider now the classical approach – how properties of the amino group or its part(s) [CN bond lengths, d_{CN}, NH bond lengths, d_{NH}, pyramidalization of the NH_2 group, Σ_{NH2}, and NMR shielding at the nitrogen atom, δ(N)] depend on the substituent effect. Appropriate data are presented in Table 2, where linear regressions and relevant statistics of Hammett's constants, cSAR(X) and SESE are gathered in a systematic way.

Table 2. Classical modelling of the substituent effect, the equation $f(x) = a \cdot x + b$ and Δ means the range of variability $f(x)$; d_{CN} and d_{NH} in Å, Σ_{NH2}, in deg and δ(N) in ppm.

	$f(x)$	x	R^2	a	b	a_p/a_m	Δ	Δ_p/Δ_m
	cSAR(NH_2)	σ						
m			0.328	0.028	0.127	3.16	0.044	3.45
p			0.906	0.090	0.122		0.152	
m+*p*			0.759	0.075	0.120			
	d_{CN}	σ						
m			0.851	-0.011	1.398	2.01	0.011	3.14
p			0.915	-0.022	1.397		0.035	
m+*p*			0.800	-0.019	1.398			
	d_{NH}	σ						
m			0.780	-0.0011	1.009	2.05	0.0011	3.27
p			0.918	-0.0022	1.009		0.0036	
m+*p*			0.818	-0.0019	1.009			
	Σ_{NH2}	σ						
m			0.876	4.0635	343.3	2.09	4.10	3.41
p			0.898	8.4942	344.0		14.00	
m+*p*			0.772	7.2384	343.3			
	δ(N)	σ						
m			0.402	-1.6440	186.4	5.16	2.18	6.03
p			0.889	-8.4770	187.3		13.17	
m+*p*			0.742	-6.8811	187.4			
	cSAR(NH_2)	cSAR(X)						
m			0.026	-0.017	0.134	19.68	0.044	3.45
p			0.943	-0.329	0.098		0.152	
m+*p*			0.496	-0.177	0.122			

	d_{CN}	cSAR(X)						
m			0.473	0.017	1.396	4.78	0.011	3.14
p			0.970	0.082	1.403		0.035	
m+*p*			0.680	0.051	1.398			
	d_{NH}	cSAR(X)						
m			0.405	0.0016	1.009	5.02	0.0011	3.27
p			0.963	0.0080	1.010		0.0036	
m+*p*			0.649	0.0049	1.009			
	Σ_{NH2}	cSAR(X)						
m			0.563	-6.8159	344.1	4.63	4.10	3.41
p			0.957	-31.5872	341.7		14.00	
m+*p*			0.689	-19.9945	343.3			
	δ(N)	cSAR(X)						
m			0.056	1.2795	186.0	24.92	2.18	6.03
p			0.969	31.8839	189.7		13.17	
m+*p*			0.517	16.7998	187.3			
	cSAR(NH_2)	SESE	cSAR(NH_2) = *a* · SESE + *b*					
m			0.143	0.018	0.127	1.18	0.044	3.45
p			0.965	0.021	0.124		0.152	
m+*p*			0.906	0.021	0.125			
	d_{CN}	SESE	d_{CN} = *a* · SESE + *b*					
m			0.642	-0.009	1.399	0.58	0.011	3.14
p			0.993	-0.005	1.396		0.035	
m+*p*			0.955	-0.005	1.397			
	d_{NH}	SESE	d_{NH} = *a* · SESE + *b*					
m			0.647	-0.0009	1.009	0.56	0.0011	3.27
p			0.991	-0.0005	1.009		0.0036	
m+*p*			0.957	-0.0005	1.009			
	Σ_{NH2}	SESE	Σ_{NH2} = *a* · SESE + *b*					
m			0.693	3.3832	342.9	0.59	4.10	3.41
p			0.990	1.9951	344.2		14.00	
m+*p*			0.954	2.0297	343.9			
	δ(N)	SESE	δ(N) = *a* · SESE + *b*					
m			0.286	-1.2987	186.5	1.54	2.18	6.03
p			0.989	-1.9996	187.1		13.17	
m+*p*			0.969	-1.9832	187.0			

Let us consider more closely few examples of the obtained dependencies. All structural parameters of the amino group (d_{CN}, d_{NH} and Σ_{NH2}) are sensitive to the substituent

effect, characterizing interaction of the amino group with the substituted moiety. Figure 2 presents an example of the dependence of d_{CN} on the Hammett substituent constants which leads to two regression lines, separately for *para*- and *meta*-substituted derivatives, with determination coefficients R^2=0.915 and R^2=0.851, respectively. Importantly, the obtained slopes are equal to -0.022 and -0.011, indicating *ca* twofold weaker substituent effects from *meta*- than from *para*-positions. The correlation d_{CN} *vs.* σ for *meta*- and *para*-substituted aniline derivatives combined together is worse yielding R^2=0.800. Important to note that the ratio of d_{CN} ranges ($\Delta d_{CN,para}/\Delta d_{CN,meta}$) is 3.14, demonstrating again much weaker communication of the NH_2 group with substituent in *meta*- than in *para*- positions.

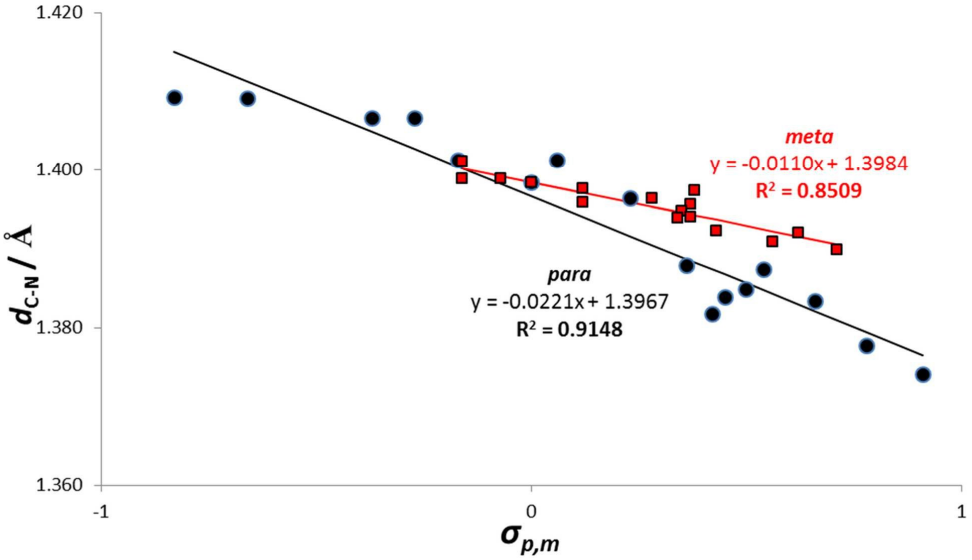


Figure 2. Dependence of d_{CN} on Hammett's substituent constants, σ, separately for *meta*- and *para*-substituted anilines.

Other properties characterizing the amino group *i.e.* two structural (d_{NH} and Σ_{NH2}), NMR shielding, δ(N), and finally the cSAR(NH_2), plotted against the σ constants behave in a similar way as observed for d_{CN}. *Para*-substituted systems exhibit the best correlations with $R^2 > 0.889$; those determined for *meta*- ones are always worse. Moreover, if both systems are considered together, R^2 adopts intermediate values. For all considered structural parameters, the ratio of linear equation slopes a_p/a_m is slightly higher than 2 (all correlations with $R^2 > 0.78$). In the case of cSAR(NH_2), this ratio amounts to ~3, whereas for δ(N) it reaches ~5.0, but in both cases, the determination coefficients for *meta*-systems are significantly worse than for *para*-derivatives. For this reason it is rather preferable to discuss the ratio of parameter value ranges (Δ_p/Δ_m). Interestingly, values Δ_p/Δ_m are slightly higher than 3, with an

exception for δ(N) that is ~6.0 (see Table 2), indicating much stronger SE from *para*- than from *meta*-position.

Let us consider now Hammett-like plots where substituent constants are replaced by cSAR(X) values. A good example is the dependence of NMR shielding at the N atom on cSAR(X), presented in Fig. 3. For *para*-derivatives very good correlation is evident (R^2=0.969) whereas almost flat distribution of the data for *meta*-systems is observed, with R^2=0.056. When *meta*- and *para*-substituted species are considered together then R^2=0.517. Similarly as in previous cases, the best correlations is found for *para*-substituted systems, whereas in the case of *meta*-derivatives they are always much worse. When *meta*- and *para*-systems are considered together, the R^2 values exhibit intermediate values. It is also worth noting that for *para*-systems the obtained R^2 values suggest that cSAR(X) is better than σ constants as a substituent descriptor for characterization of properties of the NH_2 group.

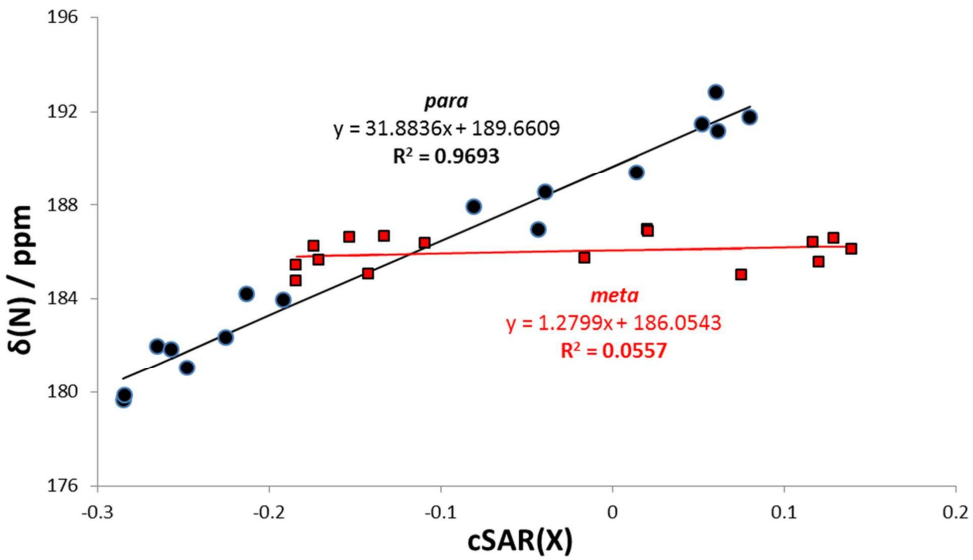


Figure 3. Dependence of NMR shielding at the N atom, δ(N), on cSAR(X) for *meta*- and *para*-substituted anilines.

Application of the Hammett approach to the SE on the "reaction site" (i.e. a fixed group in the reaction series) should yield a linear dependence for jointly treated *meta*- and *para*-derivatives. A common feature of almost all linear regressions presented in Table 2 is that the *meta*-substituted systems do not fit to a common line. Moreover, the variation ranges of the NH_2 properties for the *meta*-substituted systems are usually about three times smaller than those obtained for the *para*-derivatives. In view of these findings, the only exceptions from this rule are the scatter plots with SESE, as an explanatory parameter. Figure 4 may

serve as an example, where the scatter plot of d_{CN} *vs.* SESE is shown. For this relationship good correlations coefficients can be found for both, the regression for *para*-derivatives (R^2=0.993) and for *meta*- and *para*-systems treated together (R^2=0.955). The results obtained for *meta*-derivatives do not follow the linear regression (R^2=0.642), but lie close to the regression line for the *para*-derivatives. Very similar results are obtained when other properties of the amino group are taken into account (Table 2). This can be explained by low variability of characteristics of the reaction center and the substituent in the case of *meta*-derivatives.

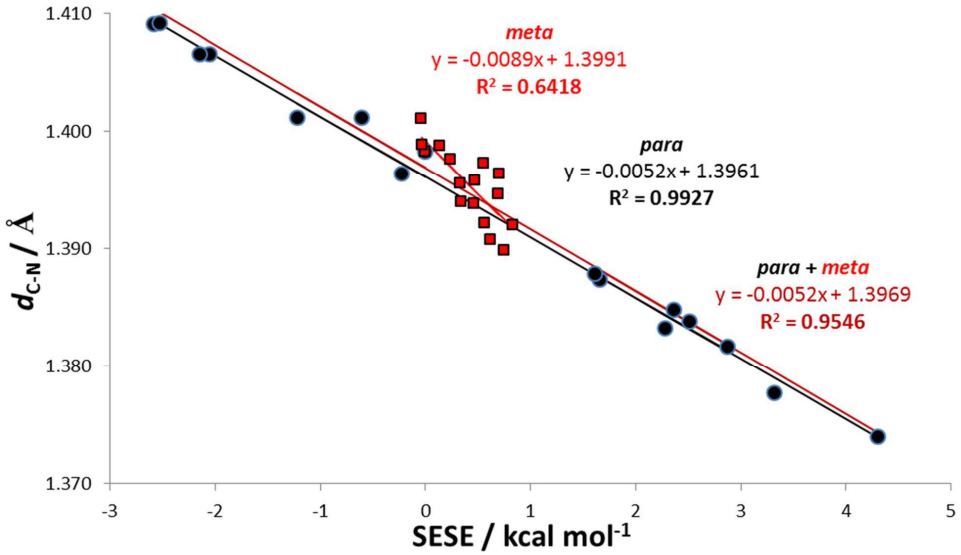


Figure 4. Correlations between d_{CN} and SESE for *meta*- and *para*-substituted aniline derivatives.

A very important observation is that the ranges of the variation of amino group properties for *meta*-substituted systems are between 16.6% and 31.8% of those found for the *para*-ones. This evidently means that the communication between the amino group and the substituents in *meta*-substituted aniline derivatives are dramatically weaker than in the corresponding *para*-systems. In the case of SE descriptors, the range of variation in SESE values for *meta*-derivatives is equal to 12.6% of that found for *para*-systems, whereas for σ constants it amounts to 50.0% and for cSAR(X) values it reaches even 88.5%. Specific data are collected in Table 3S.

Furthermore, it should be stressed that SESE characteristic applied in Hammett-like equations demonstrates the best SE description both for *para*-substituted aniline derivatives (with $R^2 > 0.96$) and for joint *para*- and *meta*-systems.

Values of the ratio of linear equation slopes, a_p/a_m, for the relation between structural parameter of the amino group (d_{CN}, d_{NH} and Σ_{NH2}) and particular descriptor of the substituent are very similar. Since for equations used in the description of *meta*-derivatives R^2 values are rather low, these ratios cannot be considered as sufficiently reliable and in this case the ratio of ranges, Δ_p/Δ_m, is recommended. All obtained results confirm stronger intramolecular interactions in *para*-substituted anilines as compared to the corresponding *meta*-systems.

Substituent effect on the transmitting moiety

The amino group of aniline is known as a strongly electron-donating group, hence its intramolecular interaction with other substituents may exert a substantial influence on π-electron delocalization of the ring.[18,61] HOMA index[58,59] has been used as a quantitative measure of the π-electron delocalization of the ring and was plotted against the Hammett constants, cSAR(X) and SESE. In all cases, no good correlations were found, the best ones are presented in Fig. 5, where for selected substituents (with exclusion of electron-donating NMe_2, NH_2, OMe, OH and NO) the R^2=0.823 for the *para*-derivatives, and R^2=0.004 for the *meta*-ones (with exclusion of NMe_2) have been found.

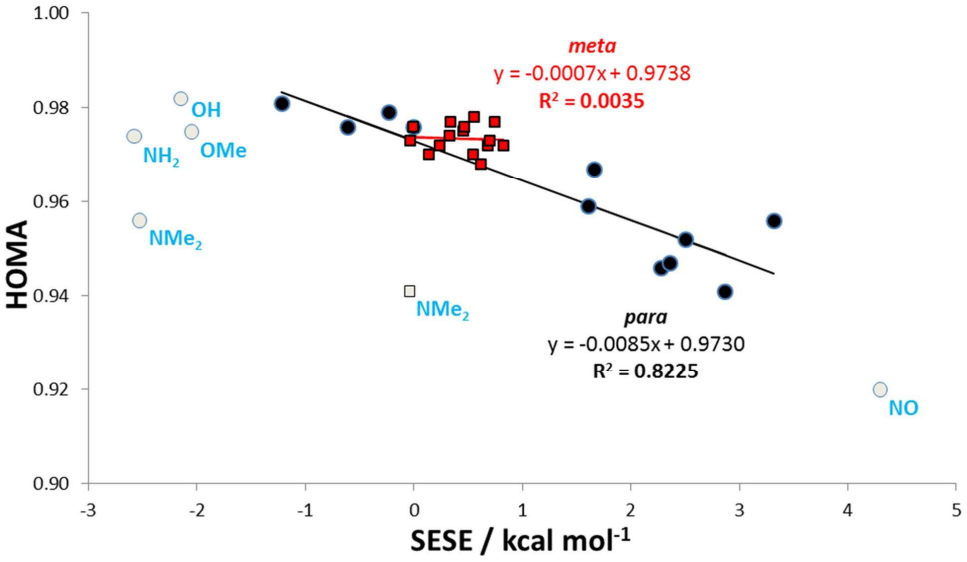


Figure 5. Correlations between HOMA and SESE, separately for *meta*- and *para*-substituted aniline derivatives.

Figure 5 bears a few problems which need clarification. The first question is why electron-donating substituents do not follow the regression line. Obviously, this is a consequence of the fact that the amino group in aniline derivatives does not interact with these

kind of substituents by resonance effect and cannot contribute to formation of quinoid-like structures, which in turn mostly contribute to the aromaticity decrease.[62] This is also the reason of a very small variation of HOMA as well as SESE values for *meta*-derivatives. The reason of strongly outlying points for the NO and OMe groups in *para*-derivatives is probably associated with the angular group-induced bond alternation (AGIBA) effect.[63] It was found that the angular substituents can cause a substantial increase of the bond length alternation. Since HOMA index contains a quadratic function $(R_{opt} - R_i)^2$, thus even small increase of the bond length alternation noticeably decreases the values of the HOMA index. Therefore, the observed changes in bond lengths are not due to a decrease in aromaticity but are caused by a local substituent effect.[64] In the case of the NMe_2 group, it was shown that an increase in the bond lengths alternation is significantly greater in tetramethyl-*p*-phenylenediamine than in simple *p*-phenylenediamine.[65] The optimized geometries indicate an increase in C1C2 and C1C6 bond lengths from 1.403 Å for aniline to 1.412 Å for *N*,*N*-dimethylaniline. This kind of relation is also valid for *p*-aminoaniline and *p*-*N*,*N*-dimethylaminoaniline: 1.400 Å and 1.408 Å, respectively. Thus, the deviations of HOMA values in Fig. 5 seem to be dependent on the geometry changes due to the local substituent effects and do not result from the changes in aromaticity itself.

The above reasoning compel us to apply other aromaticity indices in order to correctly describe the electron delocalization in the ring. In contrast to the HOMA index, the NICS values plotted against the SESE follow a regression line with $R^2 = 0.624$ (Fig. 1S) for all *para*-substituted derivatives. In this case, the effect of local changes in geometry due to the structure of the substituent is inactive.

Both π-electron delocalization indices, HOMA and NICS, show consistent changes in the ring aromaticity. The ranges of HOMA and NICS values for *meta*-derivatives are only 59.7% and 58.7% of that for the *para*-ones, respectively.

Application of QTAIM characteristics at the ring critical point showed no correlations with any substituent descriptor.

Interrelations between some properties of the amino group due to action of the distant substituent X

As it has been already shown, the SE in *meta*- and *para*-substituted aniline derivatives also affects such properties as d_{CN}, d_{NH}, δ(N) and pyramidalization of the NH_2 group. The interrelations between these properties are shown in Figs 6 and 2S as examples, the corresponding data are collected in Table 3.

Table 3. Interrelations between some properties of the amino group; the equation $f(x) = a \cdot x + b$, $\Delta f(x)$ and Δx denote range of variability $f(x)$ and x, respectively; d_{CN} and d_{NH} in Å, Σ_{NH2}, in deg and δ(N) in ppm.

	$f(x)$	x	R^2	a	b	a_p/a_m	$\Delta f(x)$	Δx	$\Delta x_p/\Delta x_m$
	d_{CN}	δ(N)							
m			0.603	0.0036	0.731	0.71	0.01	2.18	3.14
p			0.985	0.0026	0.919		0.04	13.17	
m+*p*			0.939	0.0026	0.915				
	d_{NH}	cSAR(NH_2)							
m			0.430	-0.0159	1.011	1.49	0.0011	0.04	3.27
p			0.960	-0.0236	1.012		0.0036	0.15	
m+*p*			0.913	-0.0231	1.012				
	d_{NH}	δ(N)							
m			0.653	0.0004	0.940	0.67	0.0011	2.18	3.27
p			0.984	0.0002	0.962		0.0036	13.17	
m+*p*			0.950	0.0003	0.962				
	Σ_{NH2}	cSAR(NH_2)							
m			0.368	53.26	337.18	1.74	4.10	0.04	3.41
p			0.951	92.92	332.72		14.00	0.15	
m+*p*			0.889	90.56	332.60				
	δ(N)	cSAR(NH_2)							
m			0.490	-36.69	190.94	2.56	2.18	0.04	6.03
p			0.963	-93.79	198.78		13.17	0.15	
m+*p*			0.927	-89.69	198.14				

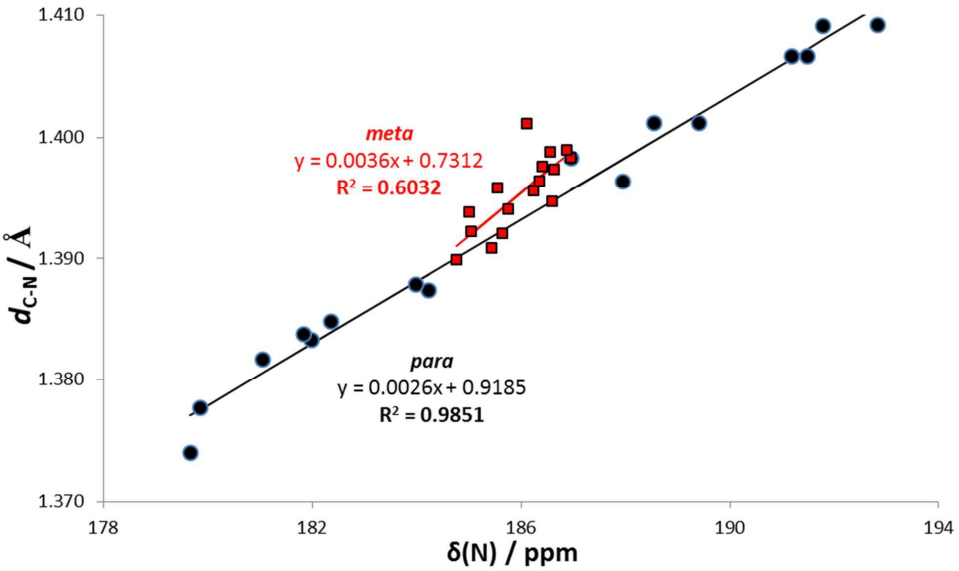


Figure 6. Correlation between CN bond length, d_{CN}, and NMR shielding, δ(N), for *meta*- and *para*-substituted aniline derivatives. R^2=0.939 for joint data.

In all cases presented in Table 3, very good correlations are observed for *para*-derivatives ($R^2 > 0.95$). When the data for *meta*-derivatives are included, the correlations become slightly worse, $0.89 < R^2 < 0.95$. These results allow to conclude that the changes in the amino group properties are coherent and weakly different for *meta* and *para* derivatives. An important difference is found only for the ranges of variation of the data for the *meta*- and *para*-derivatives of aniline, as mentioned earlier.

Reverse substituent effect

The reverse substituent effect[54] should be considered when one tries to answer the following question: how the characteristics of the substituent X depends on the remaining part of the molecule, *i.e.* on R, Y as well as on R-Y. This problem aroused already in initial studies of the substituent effect. In the original monograph[66] Hammett discussed two values of the substituent constant for the nitro group, one for benzoic acid dissociation and the other one for phenols, $\sigma = 0.778$ and $\sigma = 1.27$, respectively. Thus, the moiety R-Y significantly affects the property of the nitro group as a substituent. Such intramolecular interaction between a fixed functional group (reaction site) and the substituent X is named as the reverse substituent effect.[54]

Application of the cSAR approach allows to estimate how an electronic state of the substituent X depends on the moiety (R-Y) to which this substituent is attached. Table 4 contains data for the cSAR(X) values estimated for *meta*- and *para*-substituted anilines as well as for monosubstituted benzenes. Additionally, differences between cSAR(X) values obtained for X-substituted aniline and X-benzene derivatives (ΔcSAR(X)) are collected. These differences for a given substituent show in a numerical way how far the properties of X as a substituent may vary depending on the chemical nature of R-Y.

At the beginning, let us consider two X-R-Y reaction series, with Y = NH_2 and H. The obtained cSAR values for a given X differ both for *meta*- and *para*-systems in comparison to the case of mono-substituted derivatives (Table 4). This finding confirms the influence of R-Y moiety on the substituent X, that is, the reverse substituent effect.

The data collected in Table 4 provide few important massages. A comparison of the ranges in variation of cSAR(X) values for monosubstituted benzene derivatives and for *para*- and *meta*-substituted anilines reveals that they do not differ too much (0.341, 0.365 and 0.323 for mono-, *para*- and *meta*-substituted systems, respectively). However, cSAR values themselves allow to divide substituents X with respect to their ability to attract [cSAR(X) <0]

and donate [cSAR(X) >0] electrons. Moreover, a comparison of the data obtained for *meta*- and *para*-substituted anilines shows that these properties may differ in a dramatic way. Electron-attracting (EA) power of the nitroso group in *meta*-position is by 0.114 units of cSAR weaker than for the *para*-one (Table 4). Note that it is 0.114/0.365 portion (31.2%) of the total variability of cSAR(X) for *para*-substituted anilines. In a similar way, ED power of the NMe_2 group is by 0.079 units of cSAR stronger for the *meta*-position of NMe_2 as compared to the *para*-one.

Table 4. cSAR(X) values for *para*- and *meta*-X-anilines as well as for X-benzene (mono) derivatives, and the differences between cSAR(X) for *meta*- and *para*-anilives as well as for X-aniline and X-benzene derivatives, ΔcSAR(X).

X	*para* cSAR(X)	*meta* cSAR(X)	$\Delta cSAR(X)_{m-p}$	mono cSAR(X)	*para* ΔcSAR(X)	*meta* ΔcSAR(X)
NO	-0.285	-0.171	0.114	-0.190	-0.095	0.019
NO_2	-0.284	-0.184	0.100	-0.202	-0.082	0.018
CN	-0.265	-0.184	0.081	-0.203	-0.062	0.019
CF_3	-0.213	-0.142	0.071	-0.155	-0.058	0.013
$COCH_3$	-0.225	-0.133	0.092	-0.152	-0.073	0.019
COOH	-0.257	-0.174	0.083	-0.186	-0.071	0.012
CHO	-0.248	-0.153	0.095	-0.172	-0.076	0.019
$CONH_2$	-0.192	-0.109	0.083	-0.123	-0.069	0.014
Cl	-0.081	-0.016	0.065	-0.037	-0.044	0.021
F	0.014	0.075	0.061	0.055	-0.041	0.020
H	-0.043	0.020	0.063	0.000	-0.043	0.020
Me	-0.039	0.021	0.060	0.007	-0.046	0.014
OMe	0.052	0.117	0.065	0.102	-0.050	0.015
OH	0.061	0.120	0.059	0.105	-0.044	0.015
NH_2	0.080	0.129	0.049	0.131	-0.051	-0.002
NMe_2	0.060	0.139	0.079	0.138	-0.078	0.001
				Mean value	-0.061	0.015
				Standard deviation	0.014	0.005

In general, the differences between cSAR(X) values for *meta*- and *para*-substituted positions inform about the ability of the substituent X to interact with other parts of the system ($-C_6H_4-NH_2$). Their small values indicate a weak sensibility of the substituent with respect to its location. However, in the case of EA substituents, the absolute cSAR(X) values for *para*-derivatives are always greater (by ~0.09) than those determined for the *meta*-ones. An opposite trend is observed for ED substituents, where the values of cSAR(X) are always greater for the *meta*- than for the *para*-derivatives by ~0.06. These results support an old

viewpoint,[67,68] for review Ref. 10, that the substituent effects from the *meta*- and *para*-position differ due to a smaller contribution of the resonance effect in *meta*-substituted systems. Hence, the cSAR(X) values for *meta*-derivatives are much closer to those obtained for monosubstituted benzenes than for the *para*-systems, resonance effects in *meta*-derivatives and in monosubstituted benzenes seem to be comparable. The differences ΔcSAR(X) for *meta*- and *para*-derivatives are very symptomatic, their mean values are +0.015 and -0.061, respectively (Table 4), indicating significantly stronger cooperative effects in the *para*-position than in the *meta*-one. Finally, it should be noted that EA abilities of the substituents in monosubstituted benzenes are greater than in *meta*-substituted anilines and their ED abilities are stronger than those in *para*-substituted anilines.

Correlations between cSAR(X) values for *meta*- and *para*-derivatives and the corresponding values for monosubstituted benzenes, presented in Fig. 7, are very instructive.

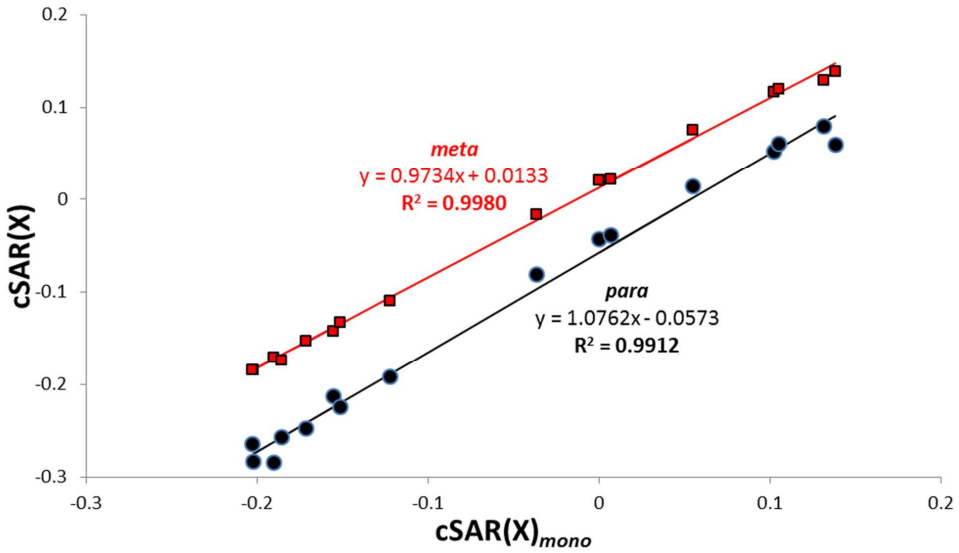


Figure 7. Correlations between cSAR(X) for *meta*- and *para*-substituted anilines and cSAR(X) for monosubstituted benzenes.

First, it is important to note that in both cases correlations are very good with R^2 > 0.99. However, even still more important are values of the slopes, 0.973 and 1.076 for *meta*- and *para*- derivatives, respectively, indicating again that the interactions of substituents with the moiety in the case of the *meta*-substituted anilines are weaker than interactions with benzene ring in monosubstituted derivatives, whereas the interactions between the substituents and the moiety in *para*-substituted anilines are stronger. The linear regression between $cSAR(X)_{meta}$ and $cSAR(X)_{para}$ with R^2=0.994 (Fig. 3S) gives the slope equal to 0.899, in line with the former result indicating much stronger interactions between the substituents and the substituted moiety for *para*-derivatives, approximately by ~10%.

The difference in communication mechanism between the substituent and the amino group in *meta*- and *para*-substituted anilines is nicely presented in Fig. 8, showing the regression of cSAR(NH_2) on cSAR(X). Almost a flat distribution of the cSAR(NH_2) data for *meta*-derivatives is observed as result of a very weak communication between X and the amino group. This is additionally corroborated by a comparison of the cSAR(NH_2) variation ranges which for *meta*-derivatives amounts to only 28.9% of that found for *para*-derivatives, whereas in the case of cSAR(X), the variability range for *meta*-derivatives is 88.5% of that found for the *para*-ones. To explain these results additional studies are still required.

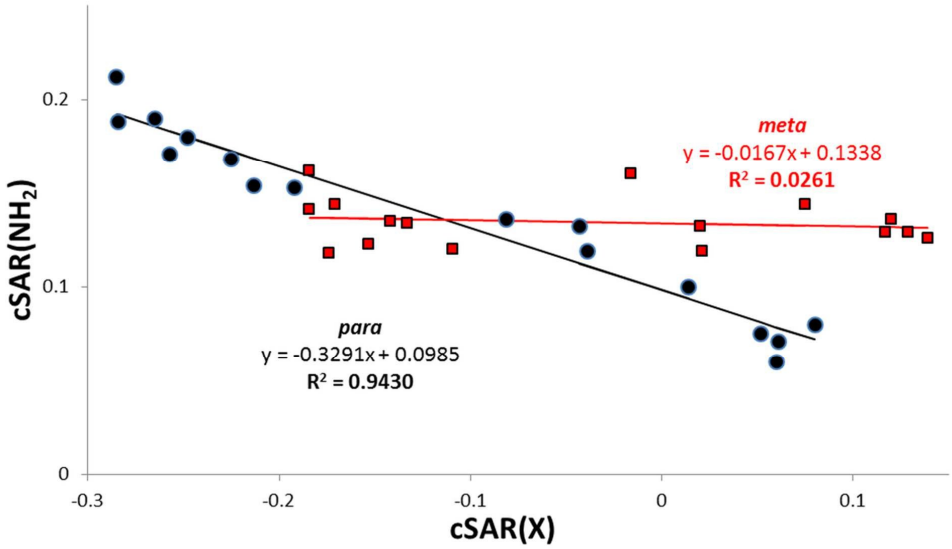


Figure 8. Dependences of cSAR(NH_2) on cSAR(X) for *meta*- and *para*-substituted aniline derivatives.

Conclusions

It is demonstrated that the general term "substituent effect" can be applied to different kinds of the intramolecular interactions in X-R-Y systems, such as: (i) impact of substituent X on the properties of a fixed group Y, known as a classical understanding of the substituent effect, (ii) effect of X on the properties of transmitting moiety R, (iii) interrelations between some properties of Y due to the action of the distant substituent X, and (iv) influence of a fixed group Y or -R-Y on the properties of substituent X, named as the reverse substituent effect. Consideration of the substituent effect from different viewpoints allows us to conclude that:

(i) All studied characteristics of the substituents as well as of the amino group are mutually interrelated, regardless their different nature. The best correlations are always found for the *para*-substituted systems, whereas for the *meta*-substituted derivatives correlations are worse because of small changes in the descriptors. In such cases we

recommend to use the variability ranges of descriptors (Δ) to compare their sensitivity to the SE in *meta*- and *para*-substituted systems.

(ii) The obtained ratio $\Delta_p/\Delta_m \approx 3$ for various parameters of the amino group indicates their similar sensitivity to the substituent effect, except the case of NMR shielding, δ(N), where this ratio amounts to 6. Thus, it can be numerically shown that the intramolecular interaction of the amino group with the substituent in the *para*-position is significantly stronger than in the *meta*- positions. This can also be confirmed by an excellent linear correlation of $cSAR(X)_{meta}$ *vs* $cSAR(X)_{para}$, with the slope equal to 0.899.

(iii) The best correlations between the amino group properties and the substituent descriptors are also found for the *para*-substituted systems. In the case of the *meta*-derivatives, the correlations are worse or even very poor, while for *meta*- and *para*-systems taken together the determination coefficients are found in between. It can be explained by low variability of characteristics for both the reaction center and the substituent in the case of *meta*-derivatives. Only for SESE parameter used as the substituent characteristic the obtained R^2 are always found greater than 0.9.

(iv) The effect of the substituent on π-electron delocalization of the ring in substituted aniline derivatives is not strongly pronounced because of high aromaticity of the ring (for *para*-systems HOMA > 0.92 and NICS < -6.3). The range of HOMA and NICS variability for *meta*-derivatives is only *ca.* 60% of that for the *para*-ones.

(v) The reverse substituent effect has been confirmed. This is manifested by the fact that R-Y moiety in X-R-Y systems (Y = NH_2 and H) affects properties of the substituent X. The obtained cSAR values for a given X differ for both *meta*- and *para*-systems.

(vi) cSAR(X) values for *meta*- and *para*-substituted aniline derivatives are highly correlated with cSAR(X) for monosubstituted benzene derivatives. Their comparison reveals weaker interactions in *meta*-substituted anilines than in monosubstituted benzene derivatives, whereas the interactions in *para*-substituted anilines are significantly stronger.

Acknowledgements

We gratefully acknowledge the Interdisciplinary Center for Mathematical and Computational Modeling (Warsaw, Poland) for providing computer time and facilities. H.S. and T.M.K.

thank the National Science Centre and Ministry of Science and Higher Education of Poland for supporting this work under the grant no. UMO-2013/11/B/ST4/00531.

Electronic Supplementary Information (ESI) available: SESE values for *para*- and *meta*-substituted anilines obtained at different computational level (Table 1S). cSAR values for *para*- and *meta*-substituted anilines obtained basing on different assessments of atomic charges (Table 2S). The range of variation in SE descriptors for *para*- and *meta*-substituted anilines (Table 3S). Relations between NICS(0), NICS(1) and SESE values (Fig. 1S) and between NH bond length and NMR shielding (Fig. 2S) for *meta*- and *para*-substituted aniline derivatives. Correlation between $cSAR(X)_{meta}$ and $cSAR(X)_{para}$ for X-substituted aniline derivatives (Fig. 3S). See DOI:

Notes and references

1. G. De Palma and M. Manno, *Toxicol. Lett.*, 2014, **231**, 194-204.

2. Current EU approved additives and their E Numbers, Food Standards Agency, 2014.

3. P. W. Majerus, *Adv. Biol. Regul.*, 2014, **54**, 231-241.

4. C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165-195.

5. L. P. Hammett, *Chem. Rev.*, 1935, **17**, 125-136.

6. L. P. Hammett, *Physical Organic Chemistry*, McGraw–Hill: New York, 1940, p. 184.

7. L. P. Hammett, *Physical Organic Chemistry*, McGraw–Hill: New York, 1940, p. 189, Table II.

8. H. H. Jaffe, *Chem. Rev*., 1953, **53**, 191-261.

9. P. Zuman, *Substituent Effects in Organic Polarography*, Plenum Press: New York, 1967.

10. O. Exner, Chpt.1 in *Advances in Linear Free Energy Relationships*, Eds N. B. Chapman and J. Shorter, Plenum Press, London, 1972, p.1.

11. M. Charton, *Progr. Phys. Org. Chem*, 1973, **10**, 81-204.

12. C. D. Johnson, *The Hammett Equation*, Cambridge University Press, 1973.

13. A. R. Katritzky and R. D. Topsom, *Chem. Rev*., 1977, **77**, 639-658.

14. O. Exner, Chpt 10 in *Correlation Analysis of Chemical Data*, Eds N. B. Chapman and J. Shorter, Plenum Press: New York, 1988, p. 439ff.

15. J. Shorter, Chpt. 2 in *Similarity Models in Organic Chemistry, Biochemistry and Related Fields*, Eds R. I. Zalewski, T. M. Krygowski and J. Shorter, Elsevier: Amsterdam, 1991, p. 77.

16. O. Exner and T. M. Krygowski, *Chem. Soc. Rev*., 1996, 71-75.

17. L. P. Hammett, *Physical Organic Chemistry*, McGraw–Hill: New York, 1940, p. 196.

18. T. M. Krygowski and B. T. Stepien, *Chem. Rev*., 2005, **105**, 3482-3512.

19. O. Exner and S. Bohm, *Current Organic Chemistry*, 2006, **10**, 763-778.

20. S. R. Gadre and C. H. Suresh, *J. Org. Chem*., 1997, **62**, 2625-2627.

21. B. Galabov, S. Ilieva and H. F. Schaefer III, *J. Org. Chem.*, 2006, **71**, 6382-6387.

22. B. Galabov, S. Ilieva, B. Hadijeva, Y. Atanasov and H. F. Schaefer III, *J. Phys. Chem*., 2008, **112**, 6700-6708.

23. N. Sadlej-Sosnowska, *J. Phys. Chem. A*, 2007, **111**, 11134-11140.

24. G. te Velde, F. M. Bickelhaupt, E. J. Baerends, S. J. A. van Gisbergen, C. Fonseca Guerra, J. G. Snijders and T. Ziegler, *J. Comput. Chem*., 2001**, 22**, 931-967.

25. I. Fernandez and G. Frenking, *J. Org. Chem.*, 2006, **71**, 2251-2256.

26. A. Pross, L. Radom W. R. Taft, *J. Org. Chem*., 1980, **45**, 818-823.

27. W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, John Wiley & Sons, New York, 1986.

28. T. Siodla, W. P. Oziminski, M. Hoffmann, H. Koroniak and T. M. Krygowski, *J. Org. Chem.*, 2014, **79**, 7321-7331.

29. N. Sadlej-Sosnowska, *Polish J. Chem.*, 2007, **81**, 1123-1134.

30. N. Sadlej-Sosnowska, *Chem. Phys. Lett*., 2007, **447**, 192-196.

31. T. M. Krygowski and N. Sadlej-Sosnowska, *Struct. Chem*., 2011, **22**, 17-22.

32. T. M. Krygowski and W. P. Oziminski, *J. Mol. Model*., 2014, **20**, 2352.

33. L. F. Prescott, *Am. J. Ther*., 2000, **7**, 143-148.

34. J. Meiser, D. Weindl and K. Hiller, *Cell Commun. Signal*., 2013, **11**, 34.

35. J. L. Alonso, M. E. Sanz, J. C. Lopez and V. Cortijo, *J. Am. Chem. Soc*., 2009, **131**, 4320-4326.

36. H. H. Sitte and M. Freissmuth, *Trends Pharmacol. Sci*., 2015, **36**, 41-50.

37. E. J. Kim, A. M. Matuszek, B. Yu and J. Reynisson, *Austr. J. Chem*., 2011, **64**, 910-915.

38. Gaussian 09, Revision **D.01**, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L.

Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

39. V. Fock, *Z. Phys*., 1930, **61**, 126-148.

40. A. D. Becke, *J. Chem. Phys*., 1993, **98**, 5648-5652.] [C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785-789.

41. Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc*., 2008, **120**, 215-241.

42. M. Head-Gordon, J. A. Pople and M. J. Frisch, *Chem. Phys. Lett*., 1988, **153**, 503-506.

43. R. Ditchfield, W. J. Hehre and J. A. Pople, *J. Chem. Phys*., 1971, **54**, 724-728.

44. T. H. Dunning Jr., *J. Chem. Phys*., 1989, **90**, 1007-1023.

45. W. J. Hehre, R. Ditchfield, L. Radom and J. A. Pople, *J. Am. Chem. Soc*., 1970, **92**, 4796-4801.

46. P. George, M. Trachtman, C. W. Bock and A. M. Brett, *J. Chem. Soc. Perkin Trans. 2*, 1976, 1222-1227.

47. W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, John Wiley & Sons, New York, 1986.

48. F. Weinhold and C. R. Landis, *Valency and Bonding. A Natural Bond Orbital Donor-Acceptor Perspective*. Cambridge University Press, Cambridge, UK, 2005.

49. F. M. Bickelhaupt, N. J. R. van Eikema Hommes, C. Fonseca Guerra and E. J. Baerends, *Organometallics*, 1996, **15**, 2923-2931.

50. C. Fonseca Guerra, J.-W. Handgraaf, E. J. Baerends and F. M. Bickelhaupt, *J. Comput. Chem*., 2004, **25**, 189-210.

51. R. W. F. Bader, *Atoms in Molecules: A Quantum Theory*. Clarendon Press, Oxford UK, 1990.

52. NBO 6.0. E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, C. R. Landis, and F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, 2013.

53. T. A. Keith, AIMAll (Version 12.06.03), TK Gristmill Software, Overland Park KS, USA, (aim.tkgristmill.com), 2013.

54. O. A. Stasyuk, H. Szatylowicz, C. Fonseca Guerra and T. M. Krygowski, *Struct. Chem*., 2015, **26**, 905-913.

55. J. R. Cheeseman, G. W. Trucks, T. A. Keith and M. J. Frisch, *J. Chem. Phys*., 1996, **104**, 5497-509.

56. P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao and N. J. R. v. E. Hommes, *J. Am. Chem. Soc*., 1996, **118**, 6317-6318.

57. P. v. R. Schleyer, M. Manoharan, Z. X. Wang, B. Kiran, H. Jiao, R. Puchta and N. J. R. v. E. Hommes, *Org. Lett*., 2001, **3**, 2465-2468.

58. Kruszewski J., Krygowski T. M., *Tetr. Lett.*, **1972,** 3839.

59. T. M. Krygowski, *J. Chem. Inf. Comput. Sci*., 1993, **33**, 70-78.

60. M. Palusiak and T. M. Krygowski, *Chem. Eur. J*., 2007, **13**, 7996-8006.

61. T. M. Krygowski, J. E. Zachara and H. Szatylowicz, *J. Phys. Org. Chem*., 2005, **18**, 110-114.

62. T. M. Krygowski and M. K. Cyrański, *Chem. Rev.*, 2001, **101**, 1385-1419.

63. T. M. Krygowski, M. Wisiorowski, S. T. Howard and L. Z. Stolarczyk, *Tetrahedron*, 1997, **53**, 13027-13036.

64. T. M. Krygowski and M. K. Cyranski, *Synlett*, 2003, 922.

65. J. Maurin and T. M. Krygowski, *J. Mol. Struct*., 1988, **172**, 413-421.

66. L. P. Hammett, *Physical Organic Chemistry*, McGraw–Hill: New York, 1940, p. 188.

67. R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc*.**,** 1958, **80**, 2436-2443.

68. R. W. Taft, *J. Phys. Chem*., 1960, **64**, 1805-1815.