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Towards physical interpretation of substituent effects: the case of *meta*- and *para*-substituted anilines†

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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, and NO). Different methods (HF, B3LYP, and M06-2X) and basis sets (6-31+G(d,p), 6-311++G(d,p), and 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, *c*SAR(X) and SESE descriptors; the amino group was characterized by structural (d_{CN}, d_{NH} and Σ_{NH_2}) and electronic [δ(N) and cSAR(NH_2)] parameters; whereas the transmitting moiety was characterized by aromaticity indices HOMA and NICS, as well as by QTAIM characteristics at the ring critical point. All the used parameters were found to be mutually interrelated with much better correlations for the *para*-derivatives 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 *c*SAR(X) characteristics for monosubstituted benzenes, and *meta*- and *para*-substituted anilines.

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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 manufactured 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, is 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 the so-called Hammett substituent constants, (eqn (1)):

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

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

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

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

where ρ, the regression line slope, is termed as a reaction constant and describes the 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 for kinetics and

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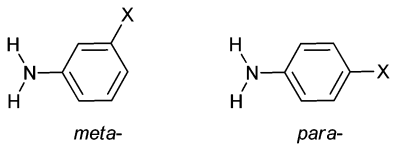
† Electronic supplementary information (ESI) available: SESE values for *para*- and *meta*-substituted anilines obtained at different computational levels (Table S1). cSAR values for *para*- and *meta*-substituted anilines obtained based on different assessments of atomic charges (Table S2). The range of variation in SE descriptors for *para*- and *meta*-substituted anilines (Table S3). Relationships between NICS(0), NICS(1) and SESE values (Fig. S1) and between the NH bond length and NMR shielding (Fig. S2) for *meta*- and *para*-substituted aniline derivatives. The correlation between $cSAR(X)_{meta}$ and $cSAR(X)_{para}$ values for X-substituted aniline derivatives (Fig. S3). See DOI: 10.1039/c5cp06702b

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 properties, and later also on physicochemical properties of various organic compounds.[8–16] 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 and 19.

Apart from empirical approaches to the description of SEs by the use of substituent constants, these effects have also been treated by quantum chemistry modeling. *para*-Substituted systems containing 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 atoms of the reaction site correlated well with the substituent constants.[21–23] Energy decomposition analysis[24] (EDA) was also successfully applied to confirm that in *meta*- and *para*-substituted benzylic cations and anions the strength of π-conjugation correlates well with the substituent constants.[25] The energetic characteristics of SE obtained by isodesmic or homodesmotic reaction 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 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 *q*SAR (acronym coming from *q* (charge) of the Substituent Active Region)[29–31] correlates well with the substituent constants. Recently the name *q*SAR has been replaced by *c*SAR to avoid confusion with another acronym – QSAR (Quantitative Structure-Activity Relationship).[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 medicine, *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]



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, and NO.

In view of this wide occurrence of amino groups in many chemical and biochemical species, the studies of substituent-induced property 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 at *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 types of intramolecular interactions.

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: using 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 the 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, the energetic descriptor of substituent effects named Substituent Effect Stabilization Energy (SESE) was evaluated using a homodesmotic reaction[45–47] (eqn (3)):

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

In this model, SESE describes the energetic effect of interaction between the substituent **X** and the 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 eqn (4)) means the higher stabilization energy due to the substituent effect.

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

Based on the best correlation between SESE and Hammett substituent constants, the MP2/6-311++G** method was chosen as a reference (Table S1, ESI†). Then the results obtained at 11 levels were compared with the reference method using linear

regression analysis. Taking into consideration the 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 *c*SAR(X) – the substituent active region parameter.[29,30] It can be calculated according to eqn (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 assessment of atomic charges three different methods were used: Weinhold,[48] Voronoi,[49,50] and Bader.[51] Weinhold's natural population analysis (NPA) was performed using the NBO 6.0 program.[52] Voronoi charges were calculated using the ADF program,[24] whereas Bader's AIM atomic charges were computed using the AIMAll program.[53] Due to good correlations between *c*SAR(X) values based on these assessments of atomic charges[54] only NBO data were used in this paper. All the obtained *c*SAR values are presented in Table S2 (ESI†).

Calculations of the 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 eqn (6).

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

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

The electron density distribution in the ring was also analyzed by Bader's Quantum Theory of Atoms in Molecules (QTAIM).[51] Parameters such as the electron density in the ring critical points (RCPs), ρ_{RCP}, its Laplacian, $\nabla^2\rho_{\mathrm{RCP}}$, the density of total electron energy in RCP, H_{BCP}, and its components, and potential and kinetic electron energy densities, V_{BCP} and G_{BCP}, were used as the aromaticity characteristics.[60]

Motivation

In general, the substituent effect is associated with molecular systems X–R–Y consisting of three parts: a fixed group Y in a reaction series, for chemical reactions named as the reaction site; a varying chemical group X named the substituent; and a 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 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 the 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, eqn (2), where not only the kinetic or equilibrium data but also many physicochemical properties of group Y can be used. It is 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 also depend on the nature of Y, but the property taken into consideration is a feature of the 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, a reverse substituent effect notion can be introduced[54] when we consider the question how characteristic of the substituent X depends on the rest of the molecule, *i.e.* on R and Y as well as on R–Y.

Results and discussion

Different approaches aimed at characterizing 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 – *c*SAR(X)[29–31] and SESE[26,27] were also applied. Verification of their mutual correlations revealed that these characteristics are partly interrelated (Fig. 1 and Table 1).

Few interesting features 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 and 0.758. The ranges of variation of σ, *c*SAR(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

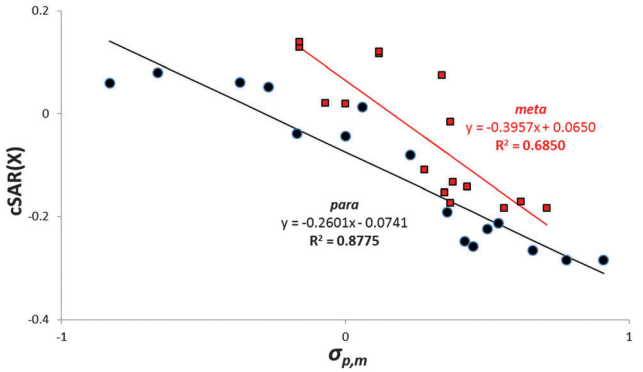


Fig. 1 Relationships between *c*SAR(X) and substituent constants σ for *meta*- and *para*-substituted anilines.

Table 1 Interrelations between characteristics of substituents; the equation $f(x) = a{\cdot}x + b$, $\Delta 1$ and $\Delta 2$ denote ranges of variability $f(x)$ and x, respectively

	R^2	a	b	a_p/a_m	$\Delta 1$	$\Delta 1_p/\Delta 1_m$	$\Delta 2$	$\Delta 2_p/\Delta 2_m$
	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					
	*c*SAR(X) = $a{\cdot}\sigma + b$				*c*SAR(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					
	*c*SAR(X) = $a{\cdot}$SESE + b				*c*SAR(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					

lengths, d_{NH}, pyramidalization of the NH_2 group, Σ_{NH_2}, 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, *c*SAR(X) and SESE are gathered in a systematic way.

Let us consider more closely few examples of the obtained dependencies. All structural parameters of the amino group (d_{CN}, d_{NH} and Σ_{NH_2}) are sensitive to the substituent effect, characterizing the interaction of the amino group with the substituted moiety. Fig. 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.* two-fold weaker substituent effects from *meta*-positions than from *para*-positions. The correlation d_{CN} *vs.* σ for *meta*- and *para*-substituted aniline derivatives when combined together is worse yielding R^2 = 0.800. It is 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 the substituent in *meta*-positions than in *para*-positions.

Other properties characterizing the amino group *i.e.* two structural parameters (d_{NH} and Σ_{NH_2}), 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 *c*SAR(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, the 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 the *para*-position than from the *meta*-position.

Let us consider now Hammett-like plots where substituent constants are replaced by *c*SAR(X) values. A good example is the dependence of NMR shielding at the N atom on *c*SAR(X), presented in Fig. 3. For *para*-derivatives very good correlation is evident (R^2 = 0.969) whereas an 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 are 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 *c*SAR(X) is better than σ constants as a substituent descriptor for characterization of properties of the NH_2 group.

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. Fig. 4 may serve as an example, where the scatter plot of d_{CN} *vs.* SESE is shown. For this relationship good correlation 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.

A very important observation is that the ranges of the variation of amino group properties for *meta*-substituted systems are between

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} are given in Å, Σ_{NH_2} 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_{NH_2}	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_{NH_2}	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						
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						
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						
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_{NH_2}	SESE						
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						
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			

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 is 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 S3 (ESI†).

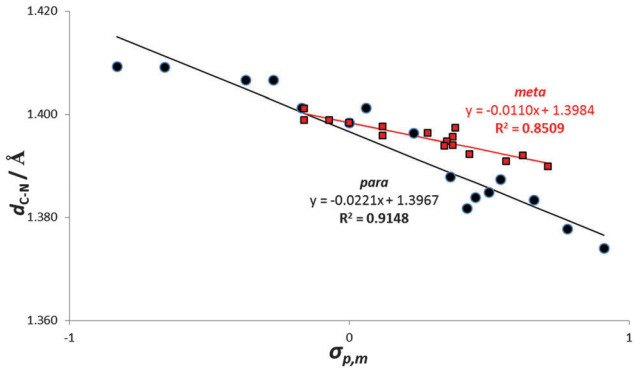


Fig. 2 Dependence of d_{CN} on Hammett's substituent constants, σ, separately for *meta*- and *para*-substituted anilines.

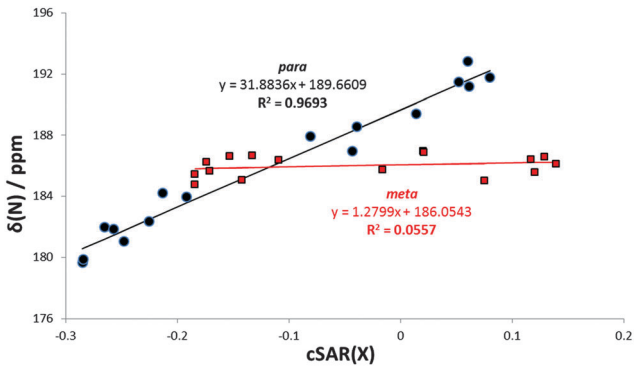


Fig. 3 Dependence of NMR shielding at the N atom, δ(N), on *c*SAR(X) for *meta*- and *para*-substituted anilines.

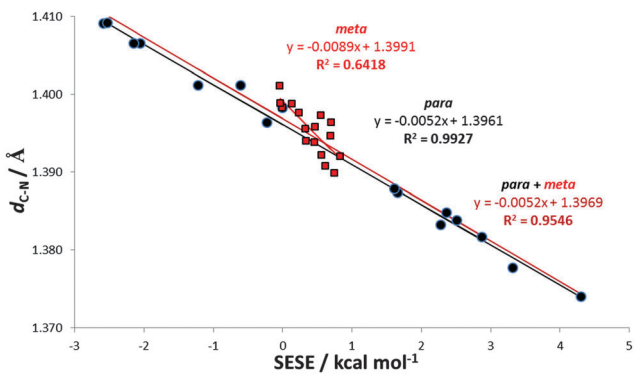


Fig. 4 Correlations between d_{CN} and SESE for *meta*- and *para*-substituted aniline derivatives.

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.

The values of the ratio of linear equation slopes, a_p/a_m, the relationship between structural parameters of the amino group (d_{CN}, d_{NH} and Σ_{NH_2}) and the 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 the 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] The 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, *c*SAR(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) $R^2 = 0.823$ for the *para*-derivatives and $R^2 = 0.004$ for the *meta*-ones (with exclusion of NMe_2) have been found.

Fig. 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 the resonance effect and cannot contribute to the formation of quinoid-like structures, which in turn mostly contribute to the aromaticity decrease.[62] This is also the reason for a very small variation of HOMA as well as SESE values for *meta*-derivatives. The reason for 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 the HOMA index contains a quadratic function $(R_{opt} - R_i)^2$, even a 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 length 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

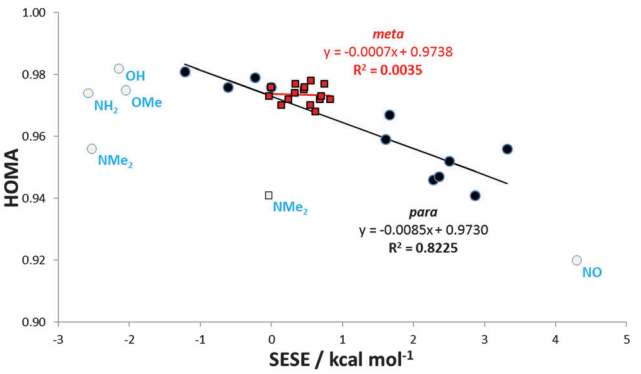


Fig. 5 Correlations between HOMA and SESE, separately for *meta*- and *para*-substituted aniline derivatives.

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 compels 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. S1, ESI†) 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 those found for the *para*-ones, respectively.

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

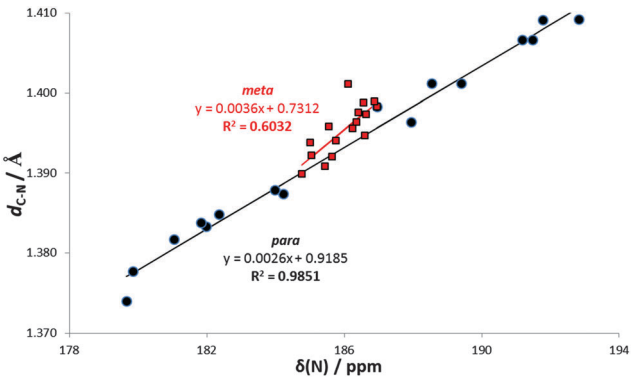


Fig. 6 Correlation between the CN bond length, d_{CN}, and NMR shielding, δ(N), for *meta*- and *para*-substituted aniline derivatives. $R^2 = 0.939$ for joint data.

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

As it has already been shown, the SE in *meta*- and *para*-substituted aniline derivatives also affects properties such as d_{CN}, d_{NH}, δ(N) and pyramidalization of the NH_2 group. The interrelations between these properties are shown in Fig. 6 and Fig. S2 (ESI†) as examples, the corresponding data are collected in Table 3.

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 us 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 depend on the remaining part of the molecule, *i.e.* on R and Y as well as on R–Y. This problem already arose 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 R–Y moiety significantly affects the properties of the nitro group as a substituent. Such intramolecular interactions 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 us 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 *c*SAR(X) values estimated for *meta*- and *para*-substituted anilines as well as for monosubstituted benzenes.

Table 3 Interrelations between some properties of the amino group; the equation $f(x) = a \cdot x + b$, $\Delta f(x)$ and Δx denote the range of variability $f(x)$ and x, respectively; d_{CN} and d_{NH} are given in Å, Σ_{NH_2} in deg and δ(N) in ppm

	$f(x)$	x	R^2	a	b	a_p/a_m	$\Delta f(x)$	Δx	$\Delta f(x)_p/\Delta f(x)_m$
	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_{NH_2}	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				

Table 4 *c*SAR(X) values for *para*- and *meta*-X-anilines as well as for X-benzene (mono)derivatives, and the differences between *c*SAR(X) values for *meta*- and *para*-anilines as well as for X-aniline and X-benzene derivatives, Δ*c*SAR(X)

X	*para* *c*SAR(X)	*meta* *c*SAR(X)	$!\Delta cSAR(X)_{m-p}$	Mono *c*SAR(X)	*para* Δ*c*SAR(X)	*meta* Δ*c*SAR(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

Additionally, differences between *c*SAR(X) values obtained for X-substituted aniline and X-benzene derivatives (Δ*c*SAR(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 *c*SAR 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 the 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 *c*SAR(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, *c*SAR values themselves allow one to divide substituents X with respect to their ability to attract [*c*SAR(X) < 0] and donate [*c*SAR(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 the *meta*-position is by 0.114 units of *c*SAR weaker than for the *para*-one (Table 4). Note that it is 0.114/0.365 portion (31.2%) of the total variability of *c*SAR(X) for *para*-substituted anilines. In a similar way, ED power of the NMe_2 group is by 0.079 units of *c*SAR stronger for the *meta*-position of NMe_2 as compared to the *para*-one.

In general, the differences between *c*SAR(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 *c*SAR(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 *c*SAR(X) are always greater for the *meta*-derivatives than for the *para*-derivatives by ∼0.06. These results support an old viewpoint,[67,68] for review see ref. 10, that the substituent effects from the *meta*- and *para*-positions differ due to a smaller contribution of the resonance effect in *meta*-substituted systems. Hence, the *c*SAR(X) values for *meta*-derivatives are much closer to those obtained for monosubstituted benzenes than for the *para*-systems, the resonance effects in *meta*-derivatives and monosubstituted benzenes seem to be comparable. The differences Δ*c*SAR(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 *c*SAR(X) values for *meta*- and *para*-derivatives and the corresponding values for monosubstituted benzenes, presented in Fig. 7, are very instructive.

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 the 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. S3, ESI†) 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, by ∼10%.

The difference in the communication mechanism between the substituent and the amino group in *meta*- and *para*-substituted anilines is nicely presented in Fig. 8, showing the

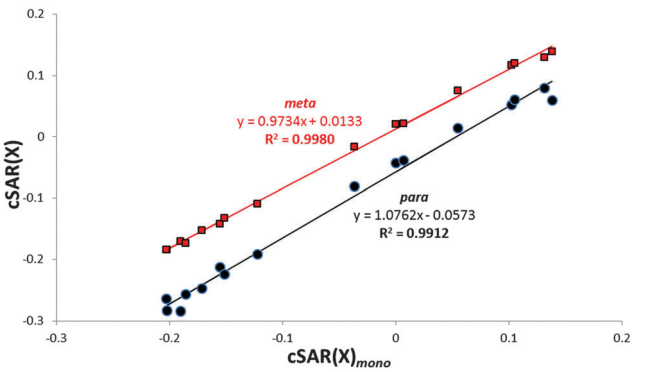


Fig. 7 Correlations between *c*SAR(X) for *meta*- and *para*-substituted anilines and *c*SAR(X) for monosubstituted benzenes.

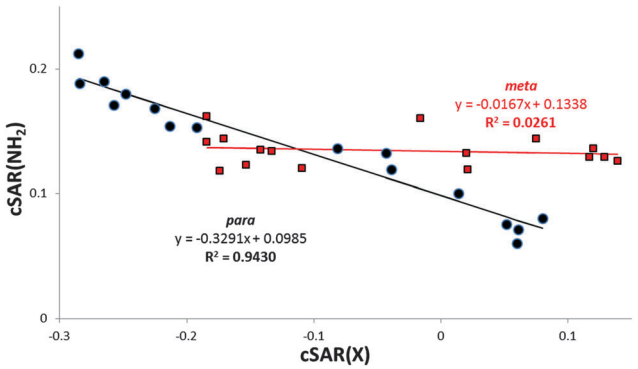


Fig. 8 Dependences of cSAR(NH_2) on *c*SAR(X) for *meta*- and *para*-substituted aniline derivatives.

regression of *c*SAR(NH_2) on *c*SAR(X). Almost a flat distribution of the *c*SAR(NH_2) data for *meta*-derivatives is observed as a 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 *c*SAR(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.

Conclusions

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

All studied characteristics of the substituents as well as of the amino group are mutually interrelated, regardless of 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.

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 for 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*- position. This can also be confirmed by an excellent linear correlation of $c\mathrm{SAR(X)}_{meta}$ *vs* $c\mathrm{SAR(X)}_{para}$, with the slope equal to 0.899.

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 the low variability of characteristics for both the reaction center and the substituent in the case of *meta*-derivatives. Only for the SESE parameter used as the substituent characteristic the obtained R^2 are always found to be greater than 0.9.

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 found for the *para*-ones.

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

The *c*SAR(X) values for *meta*- and *para*-substituted aniline derivatives are highly correlated with *c*SAR(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.

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