

# Classical and Reverse Substituent Effects in Substituted Anthrol Derivatives

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*Dedicated to the memory of Professor Marvin Charton (1932–2012), our friend and outstanding physical organic chemist.*

The substituent effect in 1-, 2-, and 9-anthrols is studied by means of B3LYP/6-311++G(d,p) computation, taking into account substituents (X): NO<sub>2</sub>, CN, OH and NH<sub>2</sub> located in all positions except the adjacent ones. The substituent effect is characterized by approaches based on quantum chemistry: The charge of the substituent active region (cSAR), substituent effect stabilization energy (SESE) and the charge flow index (CFI) describing flow of the charge from X to the fixed group (or vice versa) as well as substituent constants  $\sigma$ . Changes in

properties observed in the fixed group (OH) are described by cSAR(OH). Mutual interdependences are found between these descriptors. The HOMA index is used to describe an effect of a substituent on aromaticity of an anthrol hydrocarbon skeleton and of individual rings. In all cases, the classical (influence of X on the properties of OH) and reverse (influence of OH on the properties of X) substituent effects are studied. The latter is clearly documented by the cSAR approach.

## 1. Introduction

The first quantitative approach in describing the substituent effect was proposed by Louis Plack Hammett.<sup>[1]</sup> For this purpose, the substituent constant, termed  $\sigma$  was introduced. As empirical descriptors of an influence of the X substituent on the Y reaction site in the X–R–Y reaction series they have become a principal and most useful way to characterize substituent effects in organic chemistry and related fields.<sup>[2]</sup> Usually, it is realized by means of the so-called Hammett Equation (1):

$$\log K(k) = \rho \cdot \sigma \quad (1)$$

where the substituent constants  $\sigma$  are defined as in Equation (2):

$$\sigma = \log K(X) - \log K(H) \quad (2)$$

and  $\log K(X)$  and  $\log K(H)$  are dissociation constants of the substituted and unsubstituted benzoic acids, respectively;  $\rho$  is the so-called reaction constants describing sensitivity of the reaction characterized by rate ( $k$ ) or equilibrium ( $K$ ) constants on the impact of the substituents.

The very early Equation (1) has been generalized and other physicochemical properties  $P(X)$  become treated by means of eq. (1).<sup>[2b–d]</sup> The basic assumption of these types of application of eq.(1) is that the substituent effects on properties  $P(X)$  are similar to those observed in *meta*- and *para*- substituted benzoic acids.<sup>[2a,d]</sup> Moreover, Hammett<sup>[1,2a]</sup> also showed that the original substituent constant  $\sigma$  established for benzoic acids does not work properly in *para* substituted phenol derivatives:  $\sigma(\text{NO}_2)$  for benzoic acid series is 0.78 whereas for phenol derivatives equals 1.27. It was the first observation and quantitative documentation that electron donating/accepting properties of the substituents depend not only on the position (e.g. *meta* or *para*) but also on the moiety to which they are attached: X-PhCOOH and X-PhOH. This kind of situations has caused that, depending on the type of moiety, there have appeared many various scales of substituent constants, e.g.  $\sigma$ ,  $\sigma^+$ ,  $\sigma^-$ ,  $\sigma_{\text{R}}$ ,  $\sigma_{\text{I}}$  etc.<sup>[3]</sup> However, the problem arises in the case of a new and unknown molecular system. There is no easy way to judge what kind of substituent constants should be used and what real electron donating/accepting properties have a given substituent in such an unknown situation.

A clear way for solving these problems has come from quantum chemistry modeling. As early as in 1976 there has appeared a concept of homodesmotic reactions<sup>[4]</sup> which have given a possibility to describe quantitatively the substituent effect in an energetic scale. For a virtual Reaction (3) there can be estimated energies for each component of the reaction, and then the difference [Eq. (4)] called substituent effect stabilization energy (SESE) gives the answer for the question: is the substituent X stabilizing or destabilizing the disubstituted system:



$$\text{SESE} = E(\text{products}) - E(\text{substrates}) \quad (4)$$

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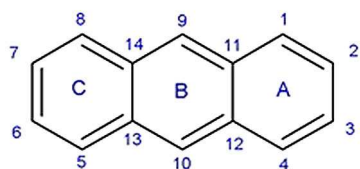
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If  $SESE > 0$  then the  $X\cdots Y$  interactions in the  $X-R-Y$  system are stabilizing ones.

Another step forward has come from a novel consideration of atomic charges. It is well known that, in general, the atomic charges at a substituent,  $q(X)$ , are not correlated with the Hammett substituent constants.<sup>[5]</sup> This is due to a polar character of  $C-X$  bonds. An important step has been given by replacing atomic charges at a substituent  $X$  by so-called "charges of substituent active region", abbreviated by  $cSAR(X)$  (in original paper  $qSAR$ ). This is defined as the sum of atomic charges of  $X$  and the ipso carbon to which it is attached.<sup>[5,6]</sup> The  $cSAR(X)$  values correlate well with the substituent constants and even the values obtained by different methods of atomic charge estimations resulted in good correlations between them.<sup>[7]</sup> The concept of  $cSAR$  has been successfully applied for interpretation of electron properties of  $F^-$  and  $CF_3^-$  groups in *para* substituted benzene derivatives<sup>[8]</sup> as well as for physical interpretation of the Hammett substituent constants.<sup>[9]</sup>

It should be emphasized that substituent effects in the Hammett-type treatments are usually studied for small monocyclic systems. The results of our recent studies document the usefulness of quantum chemistry based  $SESE$  and  $cSAR$  concepts to describe substituent effects in disubstituted derivatives of benzene,<sup>[9,10]</sup> cyclohexa-1,3-diene<sup>[11]</sup> and bicyclo [2.2.2]octane.<sup>[12]</sup> Hence our choice of a larger system – derivatives of anthracene – for testing the suitability of quantum chemistry models and the use of traditional empirical substituent constants to describe the substituent effect.

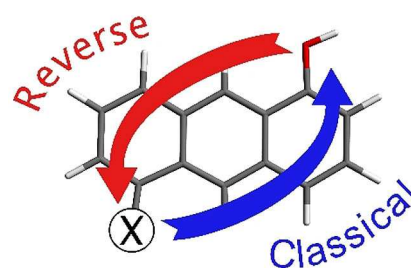
The aim of this report is to present classical and reverse substituent effects. In the first case, a question to be examined is: how substituents, situated in all positions of anthrols, except those in proximity (adjacent) to the OH group, affect properties of the hydroxy group in three different anthracene positions (1, 2 and 9). Secondly, an analysis of the reverse substituent effects on long distances will be discussed. It should be noted that such effects have never been studied. Thus, a variability of electron donating/accepting properties of substituents in dependence on a position in relation to OH positions in anthrols should give a view on the importance of this kind of treatments in fused ring systems. The objects studied are  $X$ -substituted 1-, 2- and 9-anthrol derivatives, where  $X=NO_2$ ,  $CN$ ,  $H$ ,  $OH$ , and  $NH_2$ . The numbering of positions with marked rings naming, in order to consider the individual rings, in anthracene are shown in Scheme 1.



Scheme 1. Numbering of positions in anthracene (according IUPAC).

## 2. Results and Discussion

The data describing interactions between the hydroxy group and substituents are presented and discussed in four subsections. The first one presents substituent effects (SE) descriptors and interrelations between them. The next subsection shows classical substituent effects of substituents on the hydroxy group, whereas the third one is devoted to the reverse substituent effects: how the hydroxy group (in three different positions: 1, 2 and 9) affects the electron donating/accepting substituent properties in dependence on their position in relation to OH. Scheme 2 presents these two types



Scheme 2. Classical and reverse substituent effects in anthrol derivatives.

of substituent effects. In the final part an impact of a substituent on global and local aromaticity of a transmitting moiety is discussed.

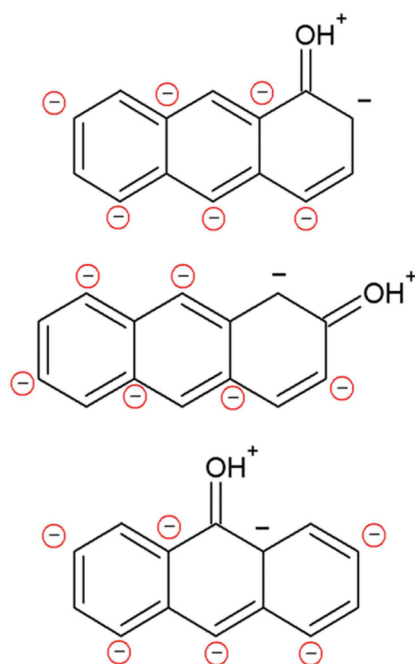
### 2.1. Substituent Effect Descriptors and Interrelations Between Them

As mentioned above, the substituent effects have been the most frequently investigated by using of the Hammett or Hammett-like substituent constants. Since for studied substituents the substituent constants  $\sigma_p^-$ ,  $\sigma_p$  and  $\sigma_m$  are well correlated ( $R^2 \geq 0.88$ ), for further discussion in this section  $\sigma_p$  has been used; all values of the constants (Table S1, Supporting Information) are taken from Ref. [3]. The obtained values of the quantum chemistry descriptors of a substituent:  $SESE$ ,  $cSAR(X)$  and CFI parameters for molecular systems studied in this paper are presented in Tables 1, 2 and S2 (Supporting Information).

The important information resulting from Table 1 is that the ranges of  $SESE$  values for a given substituent may be as large as 2.58 kcal/mol ( $NH_2$  in 9-anthrol) or 2.42 kcal/mol ( $NO_2$  in 2-anthrol). This means that the values of  $SESE$  strongly depend on the position of both the functional group (OH) as well as the substituent. Moreover, taking into account the  $SESE$  ranges for a given position, they can also vary significantly, up to 3.27 kcal/mol for the 4- position in 1-anthrol or 3.25 kcal/mol for the 10- position in 9-anthrol. Interestingly, the greatest ranges for substituted 2-anthrols are for positions 4- and 9- (1.80 and 1.76 kcal/mol, respectively). In general, the greatest ranges of  $SESE$  values are observed for 1- and 9-anthrol derivatives with substituents in the *para* position with respect

**Table 1.** SESE values [kcal/mol] for studied substituted anthrols.

a) 1-anthrol							
No\X	NO <sub>2</sub>	CN	H	OH	NH <sub>2</sub>	Average	Range
3	0.34	0.08	0.00	-1.28	0.53	-0.07	1.81
4	1.61	1.10	0.00	-1.66	0.04	0.22	3.27
5	0.24	0.15	0.00	0.03	-0.05	0.08	0.29
6	0.13	0.14	0.00	-0.64	-0.36	-0.15	0.78
7	0.24	0.20	0.00	-0.91	0.14	-0.07	1.15
8	-0.43	-0.34	0.00	-0.17	-0.12	-0.21	0.43
10	0.20	0.24	0.00	0.02	-0.57	-0.02	0.80
Average	0.33	0.22	0.00	-0.66	-0.06		
Range	2.04	1.44	0.00	1.69	1.10		
b) 2-anthrol							
No\X	NO <sub>2</sub>	CN	H	OH	NH <sub>2</sub>	Average	Range
4	-1.27	-1.00	0.00	0.24	0.53	-0.30	1.80
5	0.23	0.18	0.00	0.15	-0.05	0.10	0.28
6	0.51	0.35	0.00	-0.25	-0.36	0.05	0.86
7	0.16	0.19	0.00	0.14	0.14	0.12	0.19
8	0.56	0.39	0.00	-0.01	-0.12	0.17	0.68
9	1.15	1.19	0.00	0.16	-0.57	0.39	1.76
10	-0.02	-0.11	0.00	0.24	0.04	0.03	0.35
Average	0.19	0.17	0.00	0.10	-0.06		
Range	2.42	2.20	0.00	0.49	1.10		
c) 9-anthrol							
No \ X	NO <sub>2</sub>	CN	H	OH	NH <sub>2</sub>	Average	Range
2	0.37	0.30	0.00	-0.71	-0.10	-0.03	1.08
3	-0.02	0.02	0.00	-0.13	0.32	0.04	0.45
4	0.09	0.21	0.00	0.02	0.45	0.15	0.45
10	0.63	1.12	0.00	-1.54	-2.13	-0.38	3.25
Average	0.27	0.41	0.00	-0.59	-0.36		
Range	0.65	1.09	0.00	1.56	2.58		

**Scheme 3.** Single excited resonance structures of 1-, 2- and 9-anthrols.

to the OH group (3.27 and 3.25 kcal/mol, respectively, Table 1), i.e. in positions with negative charge at canonical structures (see Scheme 3). In addition, the obtained SESE values reveal

both stabilizing (1.61 kcal/mol for 4-NO<sub>2</sub>-1-anthrol) and opposite (-2.13 kcal/mol for 10-NH<sub>2</sub>-9-anthrol) substituent effects.

A variability of cSAR(X) depends clearly on the type of a substituent (Table 2), in the further part of this work it will be discussed in detail. It results distinctly that property of the substituent dramatically depends on the structural situation (i.e. the position in the anthrol moiety) and is not constant as it could result from the Hammett type approaches. However, it should be noted that for a given position the variability ranges of the cSAR(X) values are comparable.

The effectiveness of a charge transfer from substituent X to the "reaction site", this time OH (or vice versa), is described by CFI. Its value (eq. 6) says how effectively charge flows from one to another part of a molecular system. Positive CFI(X) values mean that the substituent attracts a charge from a fixed group and vice versa for the negative values. The obtained CFI values for substituted anthrols are gathered in Table S2 and, for comparison, for phenol derivatives in Table S3 (their cSAR values are presented in Table S4). It is worth to stress that: (i) for electron accepting substituents (NO<sub>2</sub> and CN) the ranges are significantly greater than for the other cases, this applies to phenol derivatives; (ii) for 1,4 interactions CFI is greater for 1-anthrol than in phenol for both NO<sub>2</sub> and CN substituents; (iii) for 9,10 interactions in 9-anthrol the CFI value for NO<sub>2</sub> group is smaller than in the case of 1,4 interactions in 1-anthrol, and also smaller than for CN group: 0.248 and 0.270, respectively. This may be due to the twist of NO<sub>2</sub> group and hence its smaller charge acceptance ability.<sup>[13]</sup>

**Table 2.** cSAR(X) values in dependence on the kind of substituent and the position in the anthracene moiety.

a) 1-anthrol						
No\X	NO <sub>2</sub>	CN	H	OH	NH <sub>2</sub>	Range
3	-0.159	-0.149	-0.0012	0.041	0.095	0.253
4	-0.173	-0.169	-0.0158	0.044	0.067	0.240
5	-0.142	-0.143	0.0014	0.064	0.094	0.238
6	-0.155	-0.147	-0.0003	0.043	0.099	0.254
7	-0.160	-0.150	-0.0021	0.041	0.096	0.255
8	-0.135	-0.138	0.0052	0.069	0.102	0.240
10	-0.126	-0.148	0.0014	0.058	0.100	0.248
Average	-0.150	-0.149	-0.002	0.051	0.093	-
Range	0.047	0.031	0.021	0.028	0.035	0.017
b) 2-anthrol						
No\X	NO <sub>2</sub>	CN	H	OH	NH <sub>2</sub>	Range
4	-0.123	-0.127	0.0151	0.078	0.111	0.238
5	-0.140	-0.143	-0.0019	0.064	0.095	0.249
6	-0.164	-0.154	-0.0026	0.045	0.092	0.238
7	-0.156	-0.148	-0.0020	0.049	0.098	0.256
8	-0.146	-0.147	-0.0002	0.061	0.090	0.254
9	-0.141	-0.162	-0.0075	0.047	0.084	0.237
10	-0.122	-0.143	0.0035	0.062	0.106	0.246
Average	-0.142	-0.146	0.001	0.058	0.097	-
Range	0.043	0.035	0.023	0.033	0.027	0.019
c) 9-anthrol						
No\X	NO <sub>2</sub>	CN	H	OH	NH <sub>2</sub>	Range
2	-0.162	-0.151	0.000	0.052	0.097	0.259
3	-0.153	-0.145	0.000	0.050	0.101	0.254
4	-0.143	-0.144	0.008	0.074	0.106	0.250
10	-0.153	-0.174	-0.017	0.037	0.074	0.248
Average	-0.153	-0.154	-0.002	0.053	0.095	-
Range	0.019	0.030	0.025	0.036	0.032	0.011

Furthermore, the obtained CFI values (Table S2) are the biggest when X and OH have opposite electron properties. The fixed group (OH) is electron donating, so for the electron-attracting NO<sub>2</sub> substituent the mean CFI(NO<sub>2</sub>) value in all three anthrols is greater than 0.211. In the case of stronger electron-donating substituents than OH, e.g. for NH<sub>2</sub> group, all obtained CFI(NH<sub>2</sub>) values are negative, with mean values between -0.033 (1-anthrol) and -0.052 (2-anthrol). This means that the NH<sub>2</sub> group transfers part of its charge to the OH group. The CFI(X) values ranges for particular substituents are also large, the largest equal to 0.081 (for NO<sub>2</sub> derivative in 1-anthrol) indicating significant differences in the amount of charge transfer due to a way of the transmission and, of course, the nature of the substituent.

The obtained SESE values plotted against the substituent constants lead sometimes to good or even very good linear correlations, as shown in Table 3. In the case of 2-OH anthrols, in all positions the linear regressions are very good ( $R^2 \geq 0.914$ ) except the cases of its 5-X, 7-X and 10-X derivatives. It should be noted that in all these cases (5-X, 7-X and 10-X) there is no charge transfer from OH to these positions in resonance structures (no negative charge at these carbon atoms in anthrol resonance structures, Scheme 3).

In the case of 1-anthrol systems, the acceptable determination coefficient ( $R^2 > 0.8$ ) is found only for series, with substituents in the 5- position. All other regressions are weak or none. In the case of 9-anthrol derivatives, the correlation is

**Table 3.** Dependences of SESE on values of  $\sigma_p$  obtained for substituted anthrol derivatives.

a) 1-anthrol							
	3-X	4-X	5-X	6-X	7-X	8-X	10-X
<i>a</i>	0.296	1.565	0.177	0.459	0.375	-0.210	0.436
<i>b</i>	-0.090	0.088	0.061	-0.183	-0.098	-0.195	-0.058
$R^2$	0.069	0.614	0.869	0.711	0.239	0.583	0.725
b) 2-anthrol							
	4-X	5-X	6-X	7-X	8-X	9-X	10-X
<i>a</i>	-1.245	0.151	0.592	0.033	0.450	1.165	-0.136
<i>b</i>	-0.198	0.090	0.003	0.120	0.128	0.293	0.039
$R^2$	0.977	0.607	0.990	0.083	0.921	0.914	0.443
c) 9-anthrol							
	2-X	3-X	4-X	10-X			
<i>a</i>	0.518	-0.114	-0.096	2.124			
<i>b</i>	-0.071	0.049	0.162	-0.559			
$R^2$	0.578	0.184	0.108	0.913			

**Table 4.** Dependence of cSAR(X) on values of  $\sigma_p$  obtained for substituted anthrol derivatives.

a) 1-anthrol							
	3-X	4-X	5-X	6-X	7-X	8-X	10-X
<i>a</i>	-0.181	-0.181	-0.177	-0.181	-0.181	-0.178	-0.173
<i>b</i>	-0.020	-0.035	-0.011	-0.017	-0.020	-0.005	-0.009
$R^2$	0.990	0.981	0.987	0.991	0.991	0.988	0.978
b) 2-anthrol							
	4-X	5-X	6-X	7-X	8-X	9-X	10-X
<i>a</i>	-0.176	-0.173	-0.177	-0.184	-0.183	-0.178	-0.173
<i>b</i>	0.005	-0.004	-0.010	-0.022	-0.017	-0.014	-0.022
$R^2$	0.988	0.980	0.988	0.990	0.993	0.986	0.975
c) 9-anthrol							
	2-X	3-X	4-X	10-X			
<i>a</i>	-0.187	-0.182	-0.187	-0.176			
<i>b</i>	-0.018	-0.014	-0.005	-0.032			
$R^2$	0.991	0.993	0.987	0.975			

acceptable only for systems with substituents in the 10- position.

When the cSAR(X) values are plotted against  $\sigma_p$  then the correlations are excellent (Table 4), with the worst determination coefficient 0.975. Very similar interrelations were obtained for *meta* and *para* substituted phenol derivatives.<sup>[10b]</sup> It is worth to note that the slopes for differently located substituents, in all three anthrols, are not too much differentiated, they are in the range between -0.173 and -0.187.

As in the case of cSAR(X) relation to  $\sigma_p$ , in all cases CFI(X) values correlate very well with substituent constant ( $\sigma_p$ ), as shown in Table 5. However, interestingly, it turns out that the slopes values are very diverse: for 1-anthrols between 0.235 (position 4-) and 0.181, (position 10-), for 2-anthrols between 0.205 (position 6-) and 0.187 (position 10-) and for 9-anthrols are between 0.226 (position 10-) and 0.193 (position 3-). This means that 2-anthrols as a transmitter is the worst one (see ranges of the *a* values variability in Table 5).

The results of interrelations between quantum chemistry based substituent characteristics – SESE and cSAR(X), are shown in Table 6. For 1-anthrols the acceptable correlation is only for

Table 5. Dependence of CFI on values of $\sigma_p$ obtained for substituted anthrol derivatives.							
a) 1-anthrol							
	3-X	4-X	5-X	6-X	7-X	8-X	10-X
$a$	0.193	0.235	0.184	0.191	0.196	0.193	0.181
$b$	0.096	0.102	0.078	0.084	0.088	0.076	0.081
$R^2$	0.980	0.985	0.985	0.991	0.991	0.988	0.976
b) 2-anthrol							
	4-X	5-X	6-X	7-X	8-X	9-X	10-X
$a$	0.193	0.188	0.205	0.197	0.193	0.200	0.187
$b$	0.047	0.064	0.073	0.069	0.067	0.079	0.058
$R^2$	0.987	0.986	0.988	0.990	0.982	0.971	0.980
c) 9-anthrol							
	2-X	3-X	4-X	10-X	$a$ range = 0.033		
$a$	0.222	0.193	0.201	0.226			
$b$	0.080	0.078	0.069	0.091			
$R^2$	0.992	0.991	0.985	0.980			

Table 6. Dependences of SESE on cSAR(X) for all kinds of substituents obtained for substituted anthrol derivatives.							
a) 1-anthrol							
	3-X	4-X	5-X	6-X	7-X	8-X	10-X
$a$	-1.534	-9.066	-0.982	-2.439	-1.978	1.204	-2.445
$b$	-0.119	-0.231	0.051	-0.224	-0.137	-0.189	-0.079
$R^2$	0.061	0.689	0.851	0.660	0.222	0.610	0.699
b) 2-anthrol							
	4-X	5-X	6-X	7-X	8-X	9-X	10-X
$a$	7.026	-0.820	-3.176	-0.225	-2.512	-6.681	0.822
$b$	-0.235	0.082	-0.066	0.116	0.094	0.148	0.043
$R^2$	0.974	0.569	0.978	0.132	0.923	0.927	0.497
c) 9-anthrol							
	2-X	3-X	4-X	10-X			
$a$	-2.782	0.592	0.360	-11.895			
$b$	-0.121	0.057	0.161	-0.937			
$R^2$	0.587	0.166	0.053	0.907			

substituents in the position 5- ( $R^2=0.851$ ), in 2-anthrols very good correlations are found for X in the positions: 4-, 6-, 8- and 9- ( $R^2 \geq 0.923$ ), whereas for 9-anthrols only in the position 10- ( $R^2=0.907$ ).

Therefore, the SESE relations with cSAR(X) appear to be just as good correlations as were obtained in the series in which SESE was correlated with  $\sigma_p$ . Interestingly, as shown above, for all considered systems the determined cSAR(X) values are well correlated with substituent constants. It should be noted that SESE, like  $\sigma$ , describes the global effect of the substituent, whereas cSAR(X) – rather only its local electron donating/accepting properties. Substituent constants are in principle based on free energy difference between the products and substrates, thus take into account all interactions of these two species and also their interactions with water or other solvents. Concluding this section, we can say that both quantum chemistry based substituent effect characteristics, SESE and cSAR(X), may be considered as equivalent and applied in parallel with the classical substituent constants.

## 2.2. Classical Substituent Effect

The cSAR(OH) values for substituted derivatives of anthrols with the hydroxy group in the positions 1-, 2- and 9- are presented in Figure 1 and Table S5 (Supporting Information). As we can

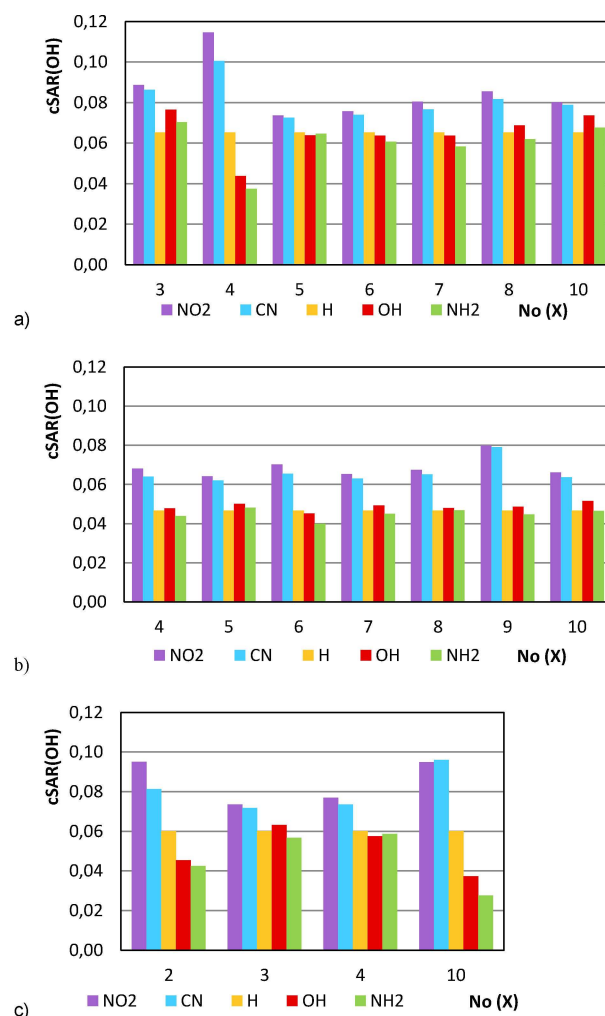


Figure 1. The obtained cSAR(OH) values for substituted (a) 1-anthrol, (b) 2-anthrol and (c) 9-anthrol derivatives.

see, the variability ranges of cSAR(OH) are very diverse, both for individual substituents as well as due to the position of the substitution. In the first case, the greatest ones are for 1-OH derivatives (between 0.028 and 0.041) then for 2-OH and 9-OH derivatives they are much smaller: between 0.007 and 0.017 and between 0.022 and 0.031, respectively. For comparison, these data for *meta*- and *para*-substituted phenols (Table 7) are between 0.012 and 0.026. Thus for 1-anthrols the effectiveness of interactions between X and OH is significantly greater than in phenol derivatives. Somewhat similar are the ranges for 9-OH derivatives, and definitely smallest are the ranges for 2-OH derivatives. Considering the position of the substitution, the largest range of cSAR(OH) are observed for systems with a substituent in the *para* position with respect to the OH group

**Table 7.** The obtained cSAR(OH) characteristics for 4- and 3-X-phenol derivatives.

No\X	NO <sub>2</sub>	CN	H	OH	NH <sub>2</sub>	Range
3	0.075	0.071	0.044	0.048	0.040	0.035
4	0.094	0.083	0.044	0.024	0.014	0.080
Range	0.019	0.012	0.000	0.023	0.026	

(0.077 for 4-X and 0.068 for 10-X in 1- and 9-OH series, respectively). These values are close to the ones observed for *para*-X-phenols (0.080).

The obtained cSAR(OH) values may be considered as a characteristics of the substituent effect on the "reaction site" i.e. the OH group. The application of classical substituent constants for a description of the substituent effects is shown in Table S6 (Supporting Information). In these cases, three types of substituent constants ( $\sigma_p$ ,  $\sigma_p^-$  and  $\sigma_m$ ) have been used. In most cases correlations are acceptable, independently of which substituent constants are used. Important to note is that in three cases the plots against  $\sigma_m$  are substantially better than any other: in 1-anthrol  $R^2=0.874$  and  $0.868$  for positions 3- and 10-, respectively, and for 2-anthrol  $R^2=0.943$  for position 5-. These results might suggest that in these positions interactions between OH and substituents resemble those in *meta* substituted phenols.<sup>[10b]</sup>

Another Hammett-like relations are constructed taking cSAR (X) as the substituent effect characteristics and they are presented in Table 8. Again, as above, we find well described linear regressions in almost all cases, with the exceptions of 3- and 10- substituted 1-anthrols ( $R^2=0.691$  and  $0.610$  respectively).

The slopes of Hammett-type equations ( $a=\rho$ ) are very informative. They characterize the sensitivity of the reaction site

**Table 8.** Dependences of cSAR(OH) on cSAR(X) for all kinds of substituents obtained for substituted anthrol and phenol derivatives.

a) 1-anthrol							
	3-X	4-X	5-X	6-X	7-X	8-X	10-X
<i>a</i>	-0.073	-0.294	-0.040	-0.058	-0.080	-0.087	-0.047
<i>b</i>	0.075	0.058	0.067	0.066	0.066	0.071	0.072
$R^2$	0.691	0.980	0.935	0.991	0.983	0.883	0.610
b) 2-anthrol							
	4-X	5-X	6-X	7-X	8-X	9-X	10-X
<i>a</i>	-0.095	-0.067	-0.114	-0.079	-0.088	-0.156	-0.077
<i>b</i>	0.053	0.053	0.049	0.051	0.052	0.054	0.053
$R^2$	0.910	0.819	0.976	0.913	0.898	0.918	0.818
c) 9-anthrol							
	2-X	3-X	4-X	10-X			
<i>a</i>	-0.189	-0.061	-0.075	-0.282			
<i>b</i>	0.059	0.063	0.064	0.050			
$R^2$	0.958	0.908	0.929	0.988			
d) phenol							
	3-X	4-X					
<i>a</i>	-0.147	-0.320					
<i>b</i>	0.052	0.035					
$R^2$	0.925	0.988					

to the substituent effects, and thus describe quantitatively the "strength" of interactions between the fixed group (OH) and substituents X. In some way, for the relationship cSAR(OH) to cSAR(X), they also present the charge exchanged between these two parts of the system. Comparisons of the absolute values of these slopes with those obtained for phenols indicate that they are smaller in anthrols, even if topologically refer to the same situation. The ranges of the slope variability are: 0.254, 0.089 and 0.221 for 1-, 2- and 9-anthrols, respectively, while for phenols it is 0.173, but their average values are:  $-0.097$ ,  $-0.097$ ,  $-0.139$  and  $-0.234$ , respectively. This is also applied to the relationship of cSAR(OH) to substituent constants.

A few important conclusions follow from the above considerations. Firstly, classic substituent constants work well in such a complex system as variously substituted anthrols, although not in all cases. Secondly, the 2-anthrol derivatives differ significantly from the other two ones for all its substituted derivatives. Thirdly, for 1- and 2-anthrols the terminal ring (i.e. C one) is less affected by SE than the 3-X-phenol derivatives.

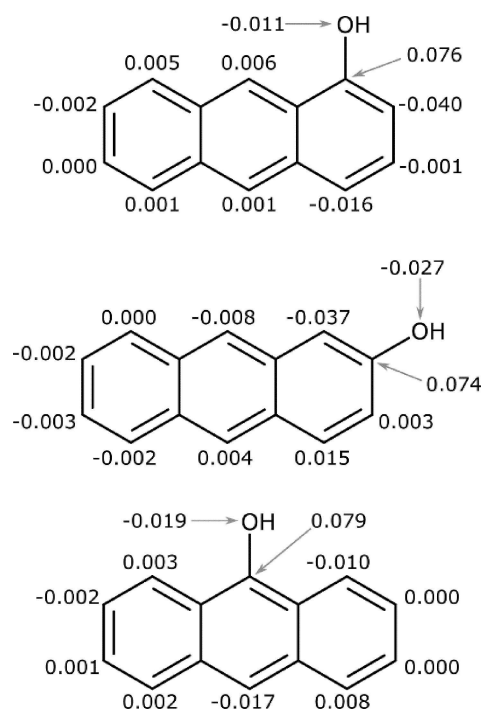
Additional information on the classical substituent effect comes from the relative enthalpy, calculated at 298 K. For variously substituted 1-, 2- and 9-anthrol derivatives, the obtained values (increased by 0.5 kcal to show the presence of the substituent) are presented in the form of diagrams in Figure S1. Two observations seem to be interesting: (i) in almost all cases 9-anthrol derivatives are the least stable, and (ii) the distribution of relative enthalpies in all three anthrol derivatives reveals that diagrams for electron attracting substituted systems are clearly different from those with electron donating ones. It should also be added that in the case of unsubstituted 1-, 2- and 9-anthrols, the values obtained are consistent with previous studies in this field.<sup>[14]</sup>

### 2.3. Reverse Substituent Effect

In basic organic chemistry, many physicochemical properties of molecular systems, with chemical reactivity in particular, are described using a qualitative view of resonance rules.<sup>[15]</sup> In most cases the application of a single excited resonance structure (i.e. with a single separation charge) is sufficient, but in some cases a double excited structure (i.e. double charge separation) are necessary. Typically this is a case of the resonance effect in disubstituted benzene: for *para* substituted species the charge transfer from electron donating substituent to the electron accepting one may be described by the single excited structure. However, to describe this effect in *meta* disubstituted benzene the double excited structure has to be used. This effect was also observed and documented in disubstituted naphthalene derivatives.<sup>[16]</sup> To facilitate further consideration, single excited structures of anthrols are shown in Scheme 3. A comparison of the atomic charges at CH units [cSAR(CH)] (see Scheme 4) with those presented in Scheme 3 shows that in over 75% cases a good agreement of the negative charge prediction is observed. However, for remaining cases the charges are only slightly positive.

Following the ideas of resonance rules, some dependence of  $cSAR(X)_i$  and  $cSAR(CH)_i$  can be expected. These dependences are presented in Figure 2. The linear correlations shown in Figure 2 are acceptable ( $R^2 > 0.8$ ) in 6 of 12 cases and close to the acceptance ( $R^2 = 0.795$ ) in one more case. This indicates that there exist some kind of impact of the OH group in the positions: 1-, 2- and 9- on the electronic properties of (CH)<sub>i</sub> groups in particular positions, which is further transmitted to the substituents in these positions. It should be emphasized that the “worst” substituent is NO<sub>2</sub> group, which depending on the positions in anthrol moiety exhibits various non-coplanar conformations, as presented in Table S7 (Supporting Information). The coplanar conformation of the NO<sub>2</sub> group is observed only in a few cases: in the 3-, 6- and 7- positions in 1-anthrols, 6- and 7- in 2-anthrols, and 2- and 3- in 9-anthrols. In all other positions non-coplanarity, measured by torsion angles, went down to  $\sim 60^\circ$ . Such effects may cause a lower level of linear correlations shown in Figure 2.

A very interesting is a comparison of  $cSAR(X)$  values in a dependence on the type of the substituent and position related to OH group (see Table 2). The result is very important: the variability of the electron accepting/donating property of the substituent estimated by the range of  $cSAR(X)$  values may amount even 31.3% (NO<sub>2</sub>), 20.8% (CN), 54.4% (OH) and 37.5% (NH<sub>2</sub>) of their mean value. This is in contrast with the assumption resulting from the Hammett  $\sigma$  values, implying constant electron accepting/donating properties of a given substituent. Usually, this is overcome by the use of additional types of substituent constants (e.g.  $\sigma^+$ ,  $\sigma^-$ , or others), mainly intuitively selecting which one should be used. This is relatively easy for benzene-like systems but is not available for significantly different structural moieties.



Scheme 4. Charge distribution at the heavy atoms of studied anthrols.

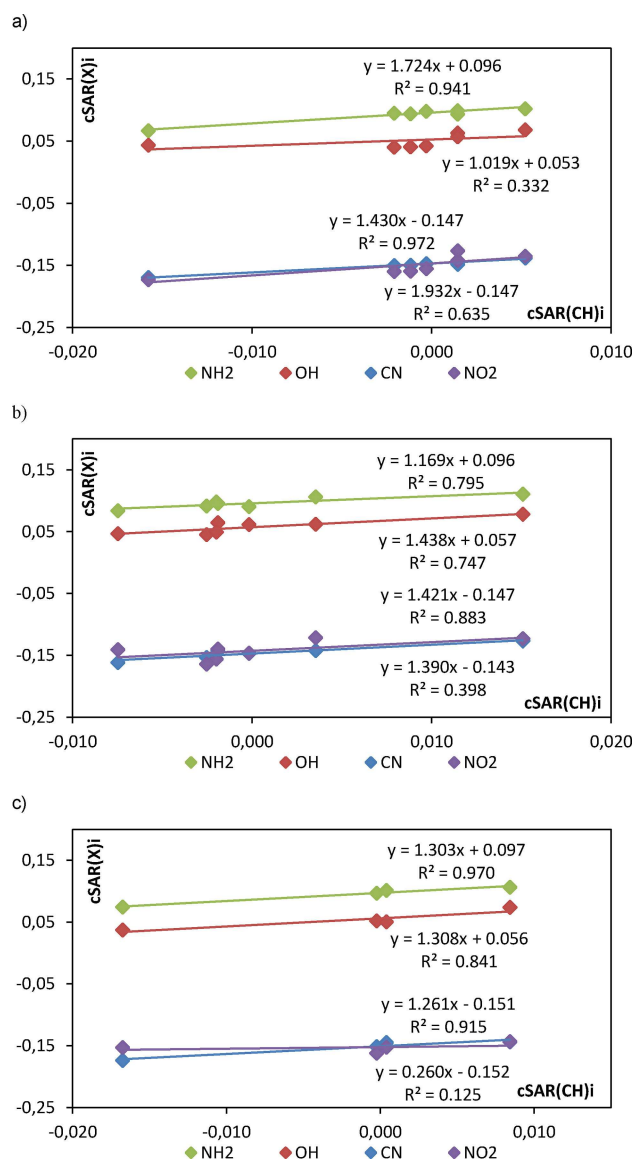


Figure 2. Dependence of  $cSAR(X)_i$  on  $cSAR(CH)_i$  for (a) 1-anthrol, (b) 2-anthrol and (c) 9-anthrol derivatives.

The reverse substituent effect concept is also supported by results gathered the data in Table 9. Changes in the substituent properties due to the position in anthrols and the influence of the OH group on electron property of the substituent X may be well described by the formula:

$$\Delta cSAR(X)_{OH} = cSAR(X)_{X\text{-anthrol}} - cSAR(X)_{X\text{-anthracene}}$$

This presents a change in the electron attracting/donating property of X caused by the introduction of OH to the moiety of anthracene.

The  $\Delta cSAR(X)_{OH}$  values visualize how large is the effect of OH group on substituent X properties in relation to anthracene in dependence on its position related to OH and on the position of OH in anthrol. It is important to notice that the reverse substituent effect is dramatically dependent on the position of

**Table 9.** The  $\Delta\text{cSAR}(X)_{\text{OH}}$  values obtained for substituted anthrol derivatives.

a) 1-anthrol					
No\X	NO <sub>2</sub>	CN	OH	NH <sub>2</sub>	average
3	-0.003	-0.002	-0.001	-0.003	-0.002
4	-0.034	-0.028	-0.022	-0.029	-0.028
5	-0.003	-0.002	-0.002	-0.002	-0.002
6	0.001	0.000	0.000	0.001	0.001
7	-0.004	-0.003	-0.002	-0.002	-0.003
8	0.004	0.004	0.003	0.006	0.004
10	-0.002	-0.003	-0.003	-0.004	-0.003
average	-0.006	-0.005	-0.004	-0.005	
range	0.038	0.031	0.025	0.035	
b) 2-anthrol					
No\X	NO <sub>2</sub>	CN	OH	NH <sub>2</sub>	average
4	0.016	0.015	0.013	0.015	0.015
5	-0.001	-0.001	-0.001	-0.001	-0.001
6	-0.008	-0.006	0.003	-0.006	-0.005
7	0.000	-0.001	0.007	0.000	0.001
8	-0.007	-0.005	-0.004	-0.006	-0.006
9	-0.017	-0.017	-0.014	-0.019	-0.017
10	0.002	0.003	0.001	0.003	0.002
average	-0.002	-0.002	0.001	-0.002	
range	0.033	0.031	0.027	0.034	
c) 9-anthrol					
No\X	NO <sub>2</sub>	CN	OH	NH <sub>2</sub>	average
2	-0.006	-0.004	0.009	-0.001	-0.001
3	0.003	0.003	0.008	0.003	0.004
4	-0.004	-0.003	0.008	0.010	0.003
10	-0.029	-0.029	-0.023	-0.029	-0.027
average	-0.009	-0.008	0.001	-0.004	
range	0.032	0.031	0.033	0.039	

a substituent in relation to the hydroxy group. This effect depends partly on the type of the substituent (the greatest is for strongly electron accepting/donating substituents), but regardless of that, the strongest reverse substituent effects occur for substituents in the position 4- in 1-anthrol, the positions 4- and 9- for 2-anthrols, and in the position 10- in 9-anthrol.

## 2.4. Substituent Effects on Aromaticity

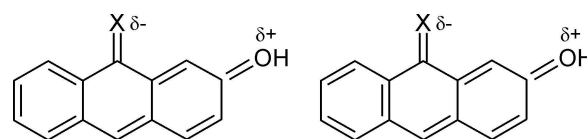
Transmission of the substituent effect through the moiety of anthracene affects its  $\pi$ -electron delocalization, characterized by a geometry based aromaticity index HOMA.<sup>[17]</sup> This should be observed by changes in the local and global aromatic properties, as can be seen from the data in Table S8. The mean values of HOMA estimated for the perimeter of all studied anthrols are almost constant, between 0.778 and 0.788. Their ranges of variability due to different substituted anthrols are also very low (between 0.009 and 0.023). Thus, aromaticity of anthrols understood as delocalization of  $\pi$ -electrons over the perimeter does not depend in any significant way on the substituent attached. Moreover, a comparison with the HOMA value obtained for the perimeter of anthracene (0.785, Table S9) indicates practically no effect of the OH group and substituents in substituted anthrols.

However, this is not the case when the local aromatic character of particular rings is taken into consideration. The variability of the aromatic character of individual rings is much greater than the perimeter characteristics. In the case of all anthrol derivatives the middle ring (B, in Scheme 1) is the most aromatic, just like in anthracene. However, the substituent effect on its aromaticity is not large; the estimated mean values of the HOMA index are in the ranges: 0.713:0.733, 0.703:0.722 and 0.694:0.715 for 1-, 2- and 9-anthrols, respectively; in each case, the lower value refers to 10-X substituted derivatives. In contrast, for substituted 1-anthrols the ranges of the mean HOMA values between the most and the least aromatic ring are almost always greater than 0.1, with the exception for 10-X system. The same is true for 4-, 5- and 8-X substituted derivatives of 2-anthrol, while in the case of 9-anthrols it is equal to (4-X derivatives) or less than the value found for anthracene (0.091).

The outer rings of substituted anthrols (A and C) are rather more sensitive to the substituent effect than the middle one (B). For 1-anthrol changes of HOMA values are between 0.569 (ring A of the molecule 4-NH<sub>2</sub>) and 0.678 (ring C of the derivative 10-CN). The largest range of HOMA values (0.052) is found for ring A of the 4-X substituted derivatives.

For 2-anthrols changes of HOMA values are between 0.585 (ring A of the system 4-NH<sub>2</sub>) and 0.689 (ring C of the derivative 9-CN). The most sensitive to the substituent effects is the ring C of the 9-X derivatives, range of their HOMA values is 0.090. In addition, for all 2-anthrols series, the largest ranges of HOMA values are observed for the ring C, with the exception of 4-X derivatives (0.074 for ring A and 0.065 for ring C). Thus, we observe a long distance substituent effect: the fixed group is in the ring A, the substituent is attached to the ring B and the most sensitive on  $\pi$ -electron delocalization is the C ring. This seems to be a slightly unexpected result. From a typical resonance structure with the electron-accepting substituent X (Scheme 5) the  $\pi$ -electron delocalization of the ring C should be least perturbed by the substituent effect. However, strongly accepting substituents increase the contribution of this resonance structures, resulting in the greater aromaticity of the C-ring in relation to the A-ring (see Table S8b).

In 9-anthrol, changes in HOMA values are between 0.596, (ring A for the 4-NH<sub>2</sub> derivative) and 0.683 (ring C of the 2-NO<sub>2</sub> and 4-NH<sub>2</sub> systems), whereas the largest range of HOMA values (0.055) is observed for the ring A of 4-X derivatives. It should be also noted that all rings in the 10-X systems are similarly sensitive to the substituent effects; their range of the obtained HOMA values are 0.048, 0.051 and 0.052 for A, B and C rings, respectively.



**Scheme 5.** Single excited resonance structures of 2-anthrol.



An interesting question is how far OH group and substituents in anthrols modify aromaticity of particular rings in comparison to the reference, i.e. the appropriate substituted anthracene. Table S9 presents HOMA values for monosubstituted anthracenes, whereas Table S10 – the  $\Delta$ HOMA values defined as [Eq. (5)]:

$$\Delta\text{HOMA} = \text{HOMA}(\text{X-anthrol}) - \text{HOMA}(\text{X-anthracene}) \quad (5)$$

A positive value of  $\Delta$ HOMA means the greater aromaticity of the ring in anthrol compared to the monosubstituted anthracene.

Given X-anthracene derivatives as reference systems (Table S10), for 1-anthrols changes of  $\Delta$ HOMA are between  $-0.048$  (ring C of the 8-NH<sub>2</sub> molecule) and  $0.050$  (ring A of the 8-NH<sub>2</sub> molecule). Thus, the largest range of  $\Delta$ HOMA ( $0.059$ ) is found for rings A and C of the 8-X substituted derivatives.

In the case of 2-anthrols changes  $\Delta$ HOMA values are between  $-0.031$  and  $0.029$  for rings C and A, respectively, of 2-anthrol, whereas the largest range of  $\Delta$ HOMA is  $0.058$  for the ring C of 9-X derivatives.

For 9-anthrols, changes in  $\Delta$ HOMA values are between  $-0.018$  (the ring A of the derivative 2-OH) and  $0.048$  (the ring C of the 2-NO<sub>2</sub> molecule), whereas the largest range of  $\Delta$ HOMA ( $0.056$ ) is observed for the ring A of 2-X derivatives.

It can be stated that for the studied anthrols, the influence of substituents on the aromaticity of individual rings is negligible. Only for substituents attached to the 4-, 9- and 10-positions of 2-anthrol changes in the HOMA index in relation to its average values are greater than 10% (the ring A – 12%, the ring C – 14 and 11%, in 4-, 9- and 10- positions, respectively). Therefore, the greatest aromaticity changes refer to less aromatic anthracene rings. In the case of *meta* and *para* substituted phenol derivatives<sup>[10b]</sup> the corresponding deviation is ~2% of the average HOMA value of the benzene ring. These results are in line with an observation found for monosubstituted benzene<sup>[18]</sup> supporting the assumption of a resistance of aromatic system on the perturbation realized by substituents introduction.

### 3. Conclusions

Quantum chemistry based descriptors of the substituent effect (cSAR and SESE) were used to characterize influence of the substituent (NO<sub>2</sub>, CN, H, OH or NH<sub>2</sub>) on electronic properties of 1-, 2- and 9-anthrols. Usually, the acceptable correlations of the cSAR and SESE characteristics with substituent constants document that they may be considered as equivalent and applied parallelly with the classical substituent constants.

However, in contrast to the classical substituent constants, the cSAR(X) values clearly indicate that changes of electron accepting/donating properties of X depend on the position of the substituent (X) in anthrols moieties. Thus, the reverse substituent effect is documented.

In addition, the cSAR approach allows an easy comparison of the sensitivity of the reaction site to the substituent effect,

characterized by slopes of Hammett-like relations – the classical substituent effect. According to the cSAR(OH) relationship to cSAR(X), the absolute values of the obtained slopes for anthrols are smaller than those for phenols, even if topologically they refer to the same situation. The most sensitive to the substituent effect are: 4-X-anthracen-1-ol, 9-X-anthracen-2-ol and 2-X- and 10-X-anthracen-9-ol derivatives, in line with the rule that odd number of bonds between substituted carbon atoms (by X and OH) generates stronger intramolecular interactions by the substituent effect.

The effect of substituent on the aromaticity of anthrol moiety resemble that found for anthracene. The greatest aromaticity changes refer to less aromatic anthracene rings. The global aromaticity of anthrols – delocalization of  $\pi$ -electrons over the perimeter does not depend on the substituent effect.

### Computational Details

For each studied system an optimization without any symmetry constraints was performed using the Gaussian09 program.<sup>[19]</sup> The B3LYP/6-311++G(d,p) method was used for all calculations as the one which was proven to give fine results.<sup>[10a]</sup> 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.

The substituent properties were characterized by SESE (substituent effect stabilization energy), cSAR (charge of the substituent active region) and CFI (charge flow index) descriptors, whereas transmitting moieties by the HOMA index.

According to equations (3) and (4) SESE descriptors were calculated as the energy of the homodesmotic reaction.<sup>[4b]</sup> For substituted anthrols SESE values are defined by the reaction as Eq. (6).



The cSAR descriptor was calculated as a sum of charges at all atoms of the substituent X or OH and the charge at the ipso carbon atom.<sup>[5,6]</sup> Following the earlier studies<sup>[10b,12]</sup> the Hirshfeld method was applied to calculate all cSAR values.<sup>[20]</sup>

As a result of intramolecular interactions between substituents X and the “reaction site” (the fixed group) Y, a charge transfer from the electron donating (ED) group to the electron attracting (EA) one is observed. Quantitatively this process is described by a Charge Flow Index (CFI), defined as Equation (7):

$$\text{CFI}(\text{X},\text{Y}) = \text{cSAR}(\text{Y}) - \text{cSAR}(\text{X}) \quad (7)$$

In the case of studied systems Y=OH and therefore this index is denoted CFI(X).

The effect of a substituent on  $\pi$ -electron delocalization of a transmitting moiety was characterized by a geometry-based aromaticity index HOMA (Harmonic Oscillator Model of Aromaticity).<sup>[17]</sup> HOMA is defined as a normalized sum of squared deviations of bond lengths from the values for a system assumed to be fully aromatic. The appropriate expression is given by Equation (8):

$$\text{HOMA} = 1 - \frac{1}{n} \sum_{i=1}^n \alpha (d_{\text{opt}} - d_i)^2 \quad (8)$$

where  $n$  is the number of CC bonds taken into consideration,  $\alpha = 257.7$  is an empirical normalization constant chosen to give  $\text{HOMA} = 0$  for non-aromatic system and  $\text{HOMA} = 1$  for a system where all bonds are equal to  $d_{\text{opt}} = 1.388 \text{ \AA}$ , and  $d_i$  are the bond lengths.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** anthrol · aromaticity · computational chemistry · reverse substituent effects · substituent effects

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