

Molecular Quantum Similarity Measures from Fermi Hole Densities: Modeling Hammett Sigma Constants

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A new approach, based on the use of fragment Quantum Self-Similarity Measures (MQS-SM) as descriptors of electronic substituent effect in aromatic series, was proposed. The novelty of this approach consists of the fact that the corresponding MQS-SM are not derived, as usual, from ordinary density functions (DF) but from the so-called domain averaged Fermi holes. This approach was applied to the study of substituent effects on the acidobasic dissociation constants in 6 series of para-substituted aromatic carboxylic acids. It has been shown that MQS-SM calculated for each particular set of acids correlate with the Hammett substituent constants. As a consequence, the corresponding similarity measures can be used as new efficient descriptors of the substituent effect, which hopefully could replace empirical sigma constants in QSAR models.

INTRODUCTION

In the past few years several attempts have been reported to apply the idea of molecular quantum similarity measures (MQSM) to rational drug design.^{1–17} Due to its relevance, this area of chemistry has experienced rapid development. The key concept as well as the mathematical background for this field was developed by Carbó,¹⁸ and since then, several enhancements have been applied not only to basic methodology but also in the formulation of robust computational schemes,^{19–30} which benefit from the exceptional advances in computational architectures and calculation speed, allowing the application of this theory to fields where it was unthinkable few years ago. The basic idea of this similarity approach is to rationalize traditional parameters commonly used in Quantitative Structure–Activity Relationships (QSAR) analysis^{31,32} by selected theoretical descriptors derived from MQSM.

Keeping this idea in mind, the present work reports an attempt to develop a MQSM-based alternative to the classical descriptor for the electronic substituent effects, namely Hammett sigma constants, σ .³³ This study is based on previous works on new theoretical descriptors of various molecular properties such as Molecular Quantum Self-Similarity Measures (MQS-SM)^{5–7} and related momentum space quantities.^{11–13} In these studies it was found that the best description of activities connected with certain functional groups representing the active “reaction center” for a given process requires the corresponding descriptors to be calculated also for the corresponding “active” fragments. This, of course, requires specifying the density functions for these

fragments. Although this procedure might seem simple, the actual situation is a bit more complex. The reason is that the separation of electron density associated with a certain molecular fragment from the density function of the whole molecule is by no means unique, and the straightforward partitioning of density matrices used in previous studies^{6,7} suffer a considerable degree of arbitrariness.

In a previous work,³⁴ another method of calculating the fragment electron densities, which, to considerable extent, eliminates the arbitrariness of previous procedures, was presented. That approach was based on the use of the so-called domain averaged Fermi holes^{35,36} and was tested on a large collection of substituted benzoic acids, and as it was shown, the substituent effect on the acidobasic dissociation constants of the studied series of molecules could be successfully correlated with appropriate fragment self-similarity measures, which were presented as new efficient theoretical descriptors replacing Hammett sigma constants in QSAR models.

Our aim in the present study is to extend the test to 6 different reaction series involving substituted aromatic carboxylic acids, thus proving that the approach is not limited to benzoic acids. As it will be shown, the substituent effect on the acidobasic dissociation constants of the studied series of molecules can indeed be successfully correlated with appropriate fragment self-similarity measures, which can thus be used as new efficient theoretical descriptors replacing Hammett sigma constants in QSAR models.

THEORETICAL FRAMEWORK

Molecular Quantum Similarity Measures. The basic idea of MQSM¹⁸ arises from the inclusion of the intuitive concept of molecular similarity into the framework of quantum mechanics. According to this theory, all information about a molecule can be retrieved from its associated electron distribution, which in turn is obtained from the respective first-order density function (DF), $\rho(\mathbf{r})$. In this way, DF can

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be considered as ultimate molecular descriptors, and the similarity between any pair of molecules can then be characterized by comparing the similarity of their associated density clouds.³⁷ Mathematically, this similarity can quantitatively be measured by the value of the integral

$$Z_{AB}(\Omega) = \int \int \rho_A(\mathbf{r}_1) \Omega(\mathbf{r}_1, \mathbf{r}_2) \rho_B(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2 \quad (1)$$

where $\rho_A(\mathbf{r}_1)$ and $\rho_B(\mathbf{r}_2)$ are the respective first-order DF of molecules *A* and *B*, $\Omega(\mathbf{r}_1, \mathbf{r}_2)$ is a positive definite operator, and $Z_{AB}(\Omega)$ is the resultant value of the measure. One of the most commonly used operators corresponds to $\Omega(\mathbf{r}_1, \mathbf{r}_2) = \delta(\mathbf{r}_1 - \mathbf{r}_2)$, yielding to Overlap similarity measures.

The calculation of the integral (1) can, of course, be performed also for the case that molecules *A* and *B* are identical. In this case eq 1 reduces to

$$Z_{AA} = \int \rho_A(\mathbf{r}) \rho_A(\mathbf{r}) d\mathbf{r} \quad (2)$$

and the corresponding quantity is called the molecular quantum self-similarity measure (MQS-SM). These self-similarity measures characterize the distribution of the charge within the molecule, and as we have reported in several previous studies,^{5,38–40} they are just these quantities that can advantageously be used as efficient molecular descriptors for various molecular properties.

Fermi Hole Density Functions. The so-called domain averaged Fermi holes were introduced some time ago^{35,36} as a new powerful means of the interpretation and visualization of molecular structure. The Fermi hole density function (FH DF) associated with the domain θ in the molecule *A* (the so-called domain averaged Fermi hole) is defined by the following formula (3)

$$g_{\theta}^A(\mathbf{r}_1) = N_{\theta} \rho_A(\mathbf{r}_1) - 2 \int_{\theta} \rho_A(\mathbf{r}_1, \mathbf{r}_2) d\mathbf{r}_2 \quad (3)$$

where N_{θ} is the mean number of electrons in the domain θ

$$N_{\theta} = \int_{\theta} \rho_A(\mathbf{r}) d\mathbf{r} \quad (4)$$

and $\rho_A(\mathbf{r}_1, \mathbf{r}_2)$ is the pair density.

For this purpose two basic approximations were used. The first of them concerns the method used for the averaging, namely the integration, over a given domain. Although the most straightforward would certainly be the integration over real domains formed by the union of Bader's atomic domains;⁴² in this study we used another alternative procedure, in which the integration over real domains is replaced by a Mulliken-like approximation according to which the electron is assumed to be in the domain of a certain atom, if it is in the orbital that is localized on that atom. The main reason for using this approximation, which we used also in several previous studies,^{35,36,41,43} is to reduce the considerable computer time required for the integration over real Bader's domains and thus to make the method more efficient for practical applications. The other approximation concerned the pair density. Although again the approach as it is formulated is quite general and can be applied at any level of the theory, we confined ourselves to the AM1 level of approximation at which the pair density can straightforwardly be calculated from first-order density matrix.

The interesting feature of the holes (3), that straightforwardly suggests the possibility of their identification with fragment electron densities, is that they are often surprisingly well localized in the same region θ , as the one, over which the averaging (integration) denoted in eq 3 was performed. In addition to this intuitive parallel, the identification of the holes (3) with the electron density of the fragment θ can be made even more apparent on the basis of the following argument. Imagine, for example, that a given molecule *A* is formally partitioned into an arbitrary number of disjoint regions θ_X in such a way that the union of all these regions fills the whole space. In this case it is possible to show that if we determine the domain averaged Fermi holes associated with each of the regions θ_X , their sum is equal to the total electron density of the whole molecule.

$$\sum_X g_{\theta_X}^A(\mathbf{r}) = \rho_A(\mathbf{r}) \quad (5)$$

Based on this identity, the FH DF (3) can straightforwardly be interpreted as the fragment electron density associated, in a given molecule, with the region θ , characterizing for example a certain functional group. Eq 3 thus in fact represents a new, physically sound, nonarbitrary procedure of partitioning the total electron density of a given molecule into appropriate fragment densities.

MQS-SM Using FH Densities. The fact that FH DF (3) depend, like ordinary electron densities, only on the coordinates of single electron, allows one to incorporate them into the general methodology of MQS-SM. Thus, for example, if total electron densities in eq 2 are substituted by the corresponding Fermi hole density functions (3) averaged over appropriately selected regions θ , the original formula can be rewritten in the form (6)

$$Z_{AA}^{\theta} = \int g_{\theta}^A(\mathbf{r}) g_{\theta}^A(\mathbf{r}) d\mathbf{r} \quad (6)$$

which represents the definition of fragment MQS-SM based on Fermi hole densities, for which a real integration over real space is carried out; and that is why a basis set in terms of Gaussian functions is preferred, as quoted in the following *Molecular Modeling* section, which eases such procedure.

As already stressed in the Introduction, this new class of similarity measures opens the possibility of many novel applications in the field of the rational design of new theoretical QSAR models, and in the following part some examples of the applicability of these new similarity measures will be presented.

APPLICATION EXAMPLE: MODELING OF SUBSTITUENT EFFECT IN AROMATIC SERIES

As an example demonstrating the applicability of these similarity measures, we are going to report their use as descriptors of polar substituent effect in aromatic series. Traditionally this effect is being described by Hammett σ constants and as it is shown, these empirical descriptors of substituent effect remarkably well correlate with fragment self-similarity measures based on Fermi hole densities. The applicability of this approach has been tested on the scrutiny of the substituent effect on acidobasic dissociation constants in 6 series of para-substituted aromatic carboxylic, presented in Table 1. In all cases, the $-\text{COOH}$ group has been

Table 1. Studied Reaction Series

I		IV	
II		V	
III		VI	

Table 2. Substituents X, Hammett σ Constants, and Calculated $Z_{AA,X}^\theta$ Values for 6 Studied Series

X	s	I	II	III	IV	V	VI
NO ₂	0.81	5.515	5.499	5.473	5.526	5.542	5.548
CN	0.71	5.524	5.510	5.485	5.532	5.547	5.551
CF ₃	0.53	5.522	5.507	5.482	5.531	5.546	5.551
CCl ₃	0.46	5.525	5.511	5.487	5.533	5.547	5.552
Br	0.22	5.528	5.515	5.492	5.535	5.549	5.553
Cl	0.22	5.530	5.517	5.494	5.536	5.550	5.553
F	0.06	5.532	5.517	5.494	5.537	5.550	5.553
H	0.00	5.535	5.522	5.500	5.539	5.552	5.555
CH ₃	-0.14	5.537	5.523	5.502	5.540	5.553	5.556
CH ₂ CH ₃	-0.13	5.537	5.524	5.503	5.540	5.553	5.556
OCH ₃	-0.28	5.540	5.527	5.504	5.541	5.554	5.556
N(CH ₃) ₂	-0.63	5.548	5.538	5.517	5.547	5.557	5.558

considered the appropriate active fragment θ . Each of the series involved 12 substituted molecules with substituents X specified in Table 2.

Molecular Modeling. The calculation of fragment self-similarity measures was performed in two subsequent steps. In the first step, the geometries of all 72 (12 \times 6) studied molecules have been optimized at the AM1 level of theory using the AMPAC 6.55 software package.⁴⁴ This package, working with Slater functions, was chosen for its computational speed to generate optimized geometries. As, however, the calculation of similarity measures is much more easy with Gaussian functions, the single point calculation with previously optimized geometries have been repeated using Gaussian 98,⁴⁵ again at the AM1 (restricted closed-shell) level, to generate the necessary density functions on the basis of Gaussian orbitals. These density functions have then been used as an input for our self-programmed software,⁴⁶ performing the calculation of Fermi hole densities averaged over the fragment θ .

Similarity Calculations. Based on previously reported FH DF's, the values of MQS-SM were calculated using specific software.⁴⁷ The resulting self-similarity measures for all 6 studied series are summarized, together with the corresponding Hammett σ constants,⁴⁸ in Table 2.

RESULTS AND DISCUSSION

The substituent effect in an aromatic series is traditionally being described by empirical Hammett eq 7, which correlates the logarithm of equilibrium and/or rate constants in a series of substituted derivatives with the product of two parameters. The first of them, the so-called reaction constant ρ , depends on the type of the studied process, and its value characterizes

Table 3. Correlation Results for All 6 Studied Series

series	$Z_{AA}^\theta = a\sigma + b$		r^2	exp ρ/ρ_1	pred ρ/ρ_1
	$a(\cdot 10^{-3})$	b			
I	-20.8	5.534	0.963	1.00 ^a	1.00 ^a
II	-23.3	5.521	0.945	1.13	1.12
III	-27.1	5.500	0.953	1.40	1.30
IV	-12.7	5.538	0.957	0.42	0.61
V	-9.40	5.551	0.944	0.56	0.45
VI	6.40	5.554	0.934	0.21	0.31

^a By definition.

the sensitivity of a given molecular skeleton to transmission of effect of the substituent X to the reaction center. The second parameter is the substituent constant σ_X , and its values quantitatively characterize the "strength" of the polar effect of the substituent X.

$$\log \frac{K_X}{K_H} = \rho \sigma_X \quad (7)$$

The main goal of this study is to show that this traditional approach to the study of substituent effect can be complemented by a new alternative protocol based on the use of theoretical molecular descriptors derived from quantum chemical calculations. As already stressed above, an especially efficient class of theoretical molecular descriptors is represented by fragment self-similarity measures (6), associated in any given case, with appropriately selected domain θ . In this context, it is fair to say that the choice of the appropriate domain is a bit arbitrary, and although chemical intuition can be used as a guide, the choice is by no means unique and several alternative fragments can often be considered. Thus, for example, although in our case of the dissociation of the carboxylic acids, the $-\text{COOH}$ fragment is the most evident choice, one can also consider other related fragments, such as the $-\text{OH}$ group. The existence of this ambiguity in the selection of the appropriate fragments is known,^{6,38} and it was found that the quality of correlations based on such alternative fragment similarity measures is often comparable. The reason for the choice of the $-\text{COOH}$ group in our case was that the same group was also considered in previous studies.^{6,13,34}

To demonstrate the possibilities of this new theoretical approach to the description of the substituent effect, we report the existence of simple linear correlations (8) between self-similarity measures $Z_{AA,X}^\theta$ and Hammett σ constants.

$$Z_{AA,X}^\theta = a\sigma_X + b \quad (8)$$

The resulting correlation equations, together with the statistical parameters of the corresponding correlations, are summarized in Table 3.

As it is possible to see in this table, satisfactory correlations are obtained for all the series. As an illustrative example, the correlation of $Z_{AA,X}^\theta$ vs σ_X for substituted benzoic acids is displayed in Figure 1, similar correlations exist also for all remaining series. A more extensive compilation (~ 300 X's) was previously performed,³⁴ dealing only with benzoic acids.

This result is very important since it suggests that fragment self-similarity measures calculated in any given case for appropriately selected domain θ could hopefully be used as

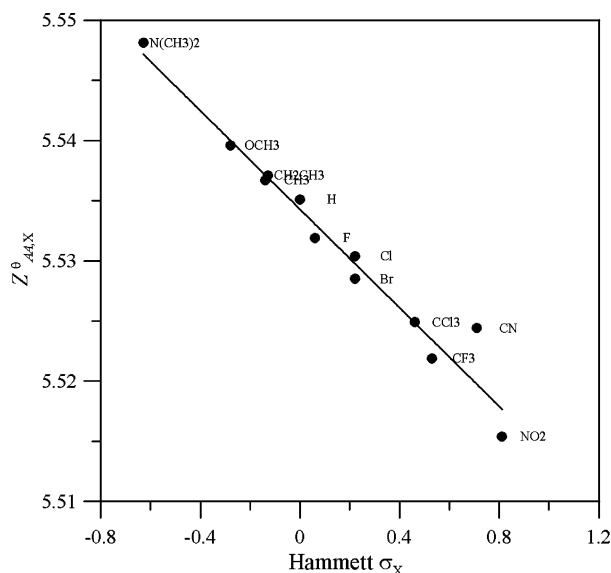


Figure 1. Correlation of $Z_{AA,X}^{\theta}$ vs σ_X for 12 substituted benzoic acids.

Table 4. Comparative Correlations with Previous Studies

series	study I ⁶ , r^2	study II ¹³ , r^2	this study
I	0.939	0.952	0.963
II	0.933	0.927	0.945
III	0.949	0.914	0.953
IV	0.935	0.956	0.957
V	0.923	0.952	0.944
VI	n/a	n/a	0.934

new efficient theoretical descriptors of polar substituent effect able to replace Hammett σ constants in QSAR models. In this connection, it is fair to say that practically the same set of systems (except for series VI) was scrutinized also in our previous studies,^{6,13} and one of the aims of this study is also to compare the results of these studies with the new approach presented here. As presented in Table 4, the results obtained in this study nicely improve those obtained in previous studies^{6,13} for series II and III and give a small improvement for series I, comparable results for series IV, and slightly inferior results for series V.

In addition to this first straightforward conclusion, the existence of the correlations (8) between σ and self-similarity measures (6) opens the possibility to obtain useful qualitative information also about the second empirical parameter of the Hammett equation, namely the reaction constant ρ . This is due to the fact that in contrast to empirical Hammett σ constants that are applicable as “universal” descriptors of the substituent effect in many different aromatic systems, the values of self-similarity measures $Z_{AA,X}^{\theta}$ depend, for any given substituent and the domain θ , also on the type of the skeleton, to which the substituent X is attached. As a consequence, the calculated slopes of the correlations in Table 3 differ from one system to another and one can expect that this variation, reflecting the specificity of each particular skeleton, will somehow be related to the sensitivity of this skeleton to the transmission of the substituent effect. This, however, is exactly what is empirically characterized by the reaction constant ρ and as it will be shown, the expected parallel between the experimental ρ constants and the slopes of the corresponding correlations (8) does indeed hold. Thus, for example, the systematic decrease of experimental ρ

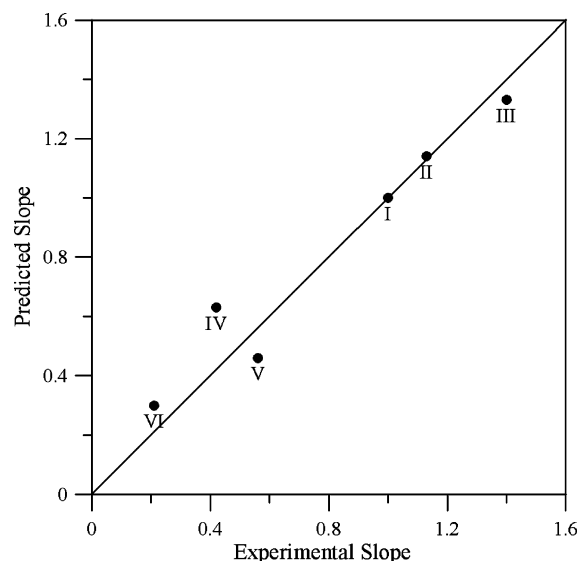


Figure 2. Predicted vs experimental ρ constants for the dissociation of the studied series of substituted aromatic acids I–VI.

constants for the dissociation of the series of carboxylic acids I, V, VI, that reflects the anticipated attenuation of substituent effect with the elongation of the chain over which the substituent effect has to be transmitted, is qualitatively reproduced by the analogous variation of the slopes of the corresponding correlation equations (8). Here it is, however, necessary to realize that while the original Hammett eq 7 describes the substituent induced variation of real experimental data, the empirical eq 8 correlates the calculated self-similarity descriptors $Z_{AA,X}^{\theta}$ that are only proportional to experimental data. As a consequence, the calculated slopes of the observed $Z_{AA,X}^{\theta}$ vs σ_X correlations (Table 3) cannot coincide with the values of the corresponding ρ constants directly, but only the relative values within a certain series of structurally related skeletons can be expected to be reproduced. Thus, for example, taking the calculated value of the slope of $Z_{AA,X}^{\theta}$ vs σ_X correlation for the dissociation of benzoic acid as the standard, the “theoretical” values of ρ constants for the remaining series of acids (II–VI) can be calculated as the ratio of the corresponding slopes. The comparison of experimental vs predicted “theoretical” ρ constants for the dissociation of substituted aromatic carboxylic acids (series I–VI) is given in Table 3, and, as it is possible to see also from Figure 2, the agreement between experimental and theoretically calculated ρ constants is indeed very satisfactory.

In this connection it is perhaps interesting to note that the possibility of theoretical calculation of Hammett ρ constants was for the first time addressed in the study,⁴⁹ but this original approach was based on the simple HMO perturbation theory, which could only be properly applied to reaction series involving only conjugated skeletons. In contrast to this original study the approaches proposed here and in ref 6 and 13 are much more general and, as such, can be applied also to other systems (like the reaction series V and VI) containing aliphatic side chains.

As a final note, connected to an earlier discussion on the fragment choice, it is fair so mention that excellent correlations can be obtained between σ and simpler parameters derived from other fragments, such as Mulliken charges on $-\text{COOH}$ or the even smaller acidic $-\text{OH}$ groups. These

charge-derived values do also sensibly correlate with those derived from the proposed quantum similarity based measures; however, when comparing the correlations with the experimental vs predicted ρ , it was found that those predicted by the proposed approach were of higher quality than those derived from simpler descriptors. This fact can be associated to a tighter relationship between the chosen fragment and the rest of the molecule in the proposed approach, as compared to a simpler charge-based description, as even the FH DF is mostly defined on the selected fragment, it is still expressed in the rest of the molecule, thus having an overall influence on the following similarity measure, which in turn provides a better capture of the electronic effects.

CONCLUSIONS

A new approach to theoretical modeling of electronic substituent effect is proposed. The approach is based on the use of Quantum Self-Similarity Measures derived from the so-called domain averaged Fermi holes. This new approach has been applied to the description of substituent effect on the acidobasic dissociation equilibria in 6 reaction series involving para-substituted aromatic carboxylic acids. It has been found that self-similarity measures associated in each particular case with the appropriate functional group responsible for the observed acidobasic properties (COOH in the case of carboxylic acids) successfully correlate with Hammett substituent constants. In addition to this primary result, which clearly suggests the possibility of using self-similarity measures as a new theoretical descriptor of the substituent effect, the application of the proposed similarity approach also opens, at least in the series of structurally related skeletons, the possibility of theoretical prediction Hammett reaction constant ρ .

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