Linear Free-Energy Relationships and the Density Functional Theory: An Analog of the Hammett Equation

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Density functional theory has been applied to describe electronic substituent effects, especially in the pursuit of linear relationships similar to those observed from physical organic chemistry experiments. In particular, analogues for the Hammett equation parameters (σ, ρ) have been developed. Theoretical calculations were performed on several series of organic molecules in order to validate our model and for comparison with experimental results. The trends obtained by Hammett-like relations predicted by the model were found to be in qualitative agreement with the experimental data. The results obtained in this study suggest the applicability of similar correlation analysis based on theoretical methodologies that do not make use of empirical fits to experimental data can be useful in the study of substituent effects in organic chemistry.

I. Introduction

For many years, studies in organic physical chemistry have shown that the reactivities of organic compounds usually show linear relationships that involve logarithms of rate (k) or equilibrium (K) constants. An elementary example of such a linear relation comes from the plot of the pK_a of ring-substituted phenylacetic acids versus the pK_a for the corresponding substituted benzoic acids. Such relationships are usually known as linear free-energy relationships (LFER). In the literature, there is extensive material pertaining to this subject.[1−7,13−19] Hansch, Leo, and Taft have written a recent review.[5]

In an abbreviated form, the substituent effects are expressed by

$$\delta_S \Delta\mu_1 = a_{10} \delta_S \Delta\mu_0 \qquad (1)$$

In eq 1, we use the notation of Leffler and Grunwald.[3] $\Delta\mu_1$ and $\Delta\mu_0$ are the changes in chemical potential for two arbitrary organic substrates 1 and 0, respectively. δ_S denotes the change in the chemical potential caused by the substituent S. In addition, the parameter a_{10} is a measure of the sensitivity of the substrate to the molecular change defined by $\delta_{S.}$

Despite the fact that the first LFER was reported by Brønsted and Pedersen[6] in 1924, it was not until the seminal paper by Hammett[1] in 1937 showing the regularities in the changes of reactivities with changes in structures of organic compounds for meta- and para-substituted benzene derivatives that intense work leading to the search for similar correlations and further improvements took place. So much progress has been made that a detailed account of the current breakthroughs in the area would require a series of reviews that are beyond the scope of this work. However, two major advances in the development of LFER are worth mentioning. First, the separation of polar, steric, and resonance effects by Taft,[13−15] which led to an equation applicable to aliphatic systems and ortho-substituted aromatic systems, and second, the development of relationships accounting for the solvent effects.[16,17] More recently, the extension of the correlation analysis for substituent effects to study biological processes via substituent parameters has motivated a renewed interest in this area. The parameters representing the electronic, steric, hydrophilic, hydrophobic, and hydrogen-bonding interactions have been combined to derive quantitative structure−activity relationships (QSAR) for a host of interactions of organic compounds with living systems or parts thereof and for applications in drug design.[18]

The linear plots, represented by the Hammett equation, can be expressed in the form

$$\log\left(\frac{K_S}{K_0}\right) = \rho\sigma \qquad (2)$$

where K_S and K_0 are rate constants or equilibrium constants for the S-substituted and hydrogen-substituted molecules, respectively, σ is the substituent constant, and ρ is a constant depending on the reaction involved. The Hammett equation is one of the most simple and popular linear free-energy relationships currently available, but its interpretation in quantum mechanical terms is by far a challenging task. Jaffé's work[6] was the first successful attempt to explain substituent effects from quantum mechanical principles. However, the traditional methods of quantum chemistry based on wave functions are cumbersome for expressing these ideas. Instead, we propose that density functional theory (DFT) can provide a simple and natural framework.

Density functional theory has been highly successful in the proper description of the electronic structure of atoms, molecules, and solids and especially useful in clarifying the nature of chemical processes. In chemistry, DFT has been used to interpret traditional empirical indexes, such as electronegativity and hardness.[8] In section II of this paper, the theoretical bases of our procedure are discussed. In section III, we compare some theoretical results with corresponding experimental data in order to analyze the model's effectiveness in predicting trends. Despite the empirical character of the inferences resulting from this comparison, we attempt some theoretical explanations based on

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DFT interpretations. Finally, we summarize the results and main perspectives in section IV.

II. Theoretical Considerations

In DFT, the ground-state electronic energy is a functional of the density,[9] given by the formula

$$E[n] = F[n] + \int v(\mathbf{r})n(\mathbf{r})\,\mathrm{d}\mathbf{r} \tag{3}$$

Here, ν is the external one-particle potential and $F[n]$ is the sum

$$F[n] = T[n] + V_{ee}[n] \tag{4}$$

where $T[n]$ is the kinetic energy functional, V_{ee} is the energy of electron−electron repulsion, and n is the electron density.

The second Hohenberg−Kohn Theorem[9] ensures the variational character of eq 3 and using the calculus of variations leads to

$$\mu = \frac{\delta F[n]}{\delta n} + v(\mathbf{r}) \tag{5}$$

μ is the electronic chemical potential and is a Lagrange parameter ensuring the constraint $\int n(\mathbf{r})\,\mathrm{d}\mathbf{r} = N$, where N is the number of electrons.

DFT will be used to look for linear relationships among the substituent effects on different substrates from the theoretical point of view. It is not intended to be a “demonstration” or “validation” of the empirical relationships obtained in physical organic chemistry, but a new look at this problem. However, it is possible to link the parameters derived from this approach to the experimental ones. In fact, this paper is an attempt to generalize our results from earlier studies.[10]

To describe the substituent effects on organic substrates, we consider the density, n, of the whole system (substrate plus substituent)

$$n = n_S + n' \tag{6}$$

where n_S is the density of the substrate plus the density of the substituent, except for a small part n' that represents the redistribution of the electron density between the substrate and the substituent in the substituted molecule. The densities are constructed such that n' integrates to N', the number of electrons being transferred between the substituent and substrate. The number of electrons of the whole system is N.

If it is assumed that $n_S \gg n'$ such that eqs 3−5 are approximately valid to n_S and form the Taylor series expansion of $F[n_S + n']$ up to second order around the density n_S

$$F[n_S + n'] = F[n_S] + \int \frac{\delta F}{\delta n_S} n'\,\mathrm{d}\mathbf{r} + \int\int \frac{\delta^2 F}{\delta n_S(\mathbf{1})\,\delta n_S(\mathbf{2})} n'(\mathbf{1})n'(\mathbf{2})\,\mathrm{d}\mathbf{1}\,\mathrm{d}\mathbf{2} \tag{7}$$

From eq 5,

$$\frac{\delta F}{\delta n_S} = \mu_S - \nu_S \tag{8}$$

and

$$\frac{\delta^2 F}{\delta n_S(\mathbf{1})\,\delta n_S(\mathbf{2})} = \eta_S(\mathbf{1}, \mathbf{2}) \tag{9}$$

where **1** and **2** stand for the distance vectors $\mathbf{r}_1$ and $\mathbf{r}_2$; μ_S, ν_S, and $\eta_S(\mathbf{1}, \mathbf{2})$ are, respectively, the electronic chemical potential, the external potential, and the hardness kernel of the molecule. Combining eqs 7, 8, and 9 into eq 3, using $v(\mathbf{r}) = v_S(\mathbf{r}) + v'(\mathbf{r})$ and the electrostatic approximation for the hardness kernel,[20] $\eta_S(\mathbf{1}, \mathbf{2}) \cong 1/|\mathbf{1} - \mathbf{2}|$, we obtain for the energy of the whole system (substituent + substrate)

$$E[n_S + n'] = E[n_S] + \mu_S N' + \int \mathrm{d}\mathbf{r}\,v'(\mathbf{r})n_S(\mathbf{r}) + \int \mathrm{d}\mathbf{r}\,v'(\mathbf{r})n'(\mathbf{r}) + \int\int \mathrm{d}\mathbf{1}\,\mathrm{d}\mathbf{2}\,\frac{n'(\mathbf{1})n'(\mathbf{2})}{|\mathbf{1} - \mathbf{2}|} \tag{10}$$

Here, the potential ν' coming from the electrons transferred from the substituent to the substrate (or vice-versa) is

$$\nu'(\mathbf{r}) = -\int \mathrm{d}\mathbf{2}\frac{n'(\mathbf{2})}{|\mathbf{1} - \mathbf{2}|} \tag{11}$$

The combination of eqs 10−11 gives the change of energy as a consequence of the electronic redistribution for attaching a given substituent to the substrate

$$\Delta E = E[n_S + n'] - E[n_S] = \mu_S N' + \int \mathrm{d}\mathbf{r}\,n_S(\mathbf{r})v'(\mathbf{r}) \tag{12}$$

Equation 12 is the energy change associated with the electron density rearrangement due to the presence of the substituent relative to an ideal state, which has electron density equal to the sum of densities of the substrate and the substituent. We may derive a similar equation using other methods such as an energy perturbation method within the framework of DFT similar to that used by Li and Evans[11] discussing the relationship between frontier molecular orbital (FMO) and hard and soft acids and bases (HSAB) principles.

Equation 12 can be used to obtain an analogue of the parameter σ for the Hammett equation. Equation 12 is a functional of N’ and ν', $\Delta E = \Delta E[N', v']$, and it can be written for two arbitrary substrates such as 1 and 2 in the form $\Delta E_1 = \Delta E_1[N'_1, v'_1]$ and $\Delta E_2 = \Delta E_2[N'_2, v'_2]$. Now, it is known that two functions $u(x, y, z)$ and $v(x, y, z)$ are related for some function $f(u, v) = 0$ if the vector product of their gradients is null [21]

$$\nabla u \times \nabla v = 0 \tag{13}$$

When the constraint given by eq 13 is applied to these functionals, the necessary condition for obtaining analogues of linear relationships for the substituent effects in the context of DFT is established. Equation 13 is reduced to the Jacobian condition of eq 14 in the case of functions of two variables. Strictly speaking, derivatives involved in eq 14 are functional derivatives.

$$\begin{vmatrix} \dfrac{\partial \Delta E_1}{\partial N'} & \dfrac{\partial \Delta E_1}{\partial v'(\mathbf{r})} \\ \dfrac{\partial \Delta E_2}{\partial N'} & \dfrac{\partial \Delta E_2}{\partial v'(\mathbf{r})} \end{vmatrix} = 0 \tag{14}$$

Then

$$\frac{\mu_1}{N_1 - N'_1} = \frac{\mu_2}{N_2 - N'_2} = \text{constant} \tag{15}$$

When the condition of eq 15 is fulfilled by different molecular substrates with the same substituents, the substituent effects are transferred from series to series in the form of some defined functional correlation. This correlation is not necessarily linear.

We define σ' values for the substituent S within any organic series as

$$\sigma_S' = \Delta E_H - \Delta E_S \tag{16}$$

where the value of ΔE for the S-substituted molecule has been subtracted from the value for the hydrogen-substituted molecule. These σ' values are correlated by some relationship if the condition of eq 15 is satisfied. When the condition of eq 15 is satisfied, a relationship correlating these σ' values exists, whether this relationship is linear or nonlinear is not determined by this condition.

The formalism above avoids the usual rationalizations, based on the law of mass action, that presume the substituent effects are transferred linearly from one reactant to one product and the rest of the reaction species contribute in a constant amount to the total free-energy change. This linear transfer cannot be proven from phenomenological points of view, such as classical thermodynamics. The present formalism also allows us to characterize substituent effects on an isolated substrate without the consideration of a complete chemical reaction system.

Several strategies can be proposed to calculate the energy change given by eq 12 in the exact form. It is only necessary to know the function $n'(\vec{r})$ with sufficient accuracy. For example, because Bader's theory[12] offers a method for rigorously partitioning any quantum system into well-defined subsystems, it can be thought that the zero-flux surface separating substituent and substrate offers a boundary to construct the function $n'(\vec{r})$. For the sake of simplicity, we will use a simpler approximation, and the substrate and substituent densities will be taken as point charges that reside on the A nuclei of the substituent and the B nuclei of the substrate. The density n' will be considered to be generated by net charges, N_i', which reside on the substituent nuclei at distances r_i. Likewise, the density n_S are generated by the net charges, N_j, on the substrate nuclei at the distances r_j. Then

$$n'(\mathbf{r}) = \sum_{i=1}^{A} N_i' \, \delta(\mathbf{r} - r_i) \tag{17a}$$

with

$$N' = \sum_{i=1}^{A} N_i'$$

and

$$n_S(\mathbf{r}) = \sum_{j=1}^{B} N_j \, \delta(\mathbf{r} - \mathbf{r}_j) \tag{17b}$$

This charge discretization can be obtained from a population analysis, such as specified by the Mulliken or Bader analysis.

By substituting eq 17a,b into eq 12 and solving the integral, which is trivial because of the delta functions under the integral symbol, we obtain

$$\Delta E = \mu_S N' + \sum_{i=1}^{A} \sum_{j=1}^{B} \frac{N_i' N_j}{|r_i - r_j|} \tag{18}$$

The second term of eq 18 is the simplest approximation of the field effect represented by the term under the integral in eq 12. Other approximated equations can be derived by using a different order for the expansion of the respective densities. For example, if the electron density of the substituent is taken as a multipolar expansion and truncated in the second term, then a term resembling a dipole-dependent field effect similar to that of Kirkwood and Westheimer is obtained.[19] Of course, these approaches are not necessary if the integral is solved using the exact densities from ab initio calculations.

Beyond the approximations used above that could leave out some important contributions, it is enough to show substituent effects as consequences of the redistribution of electron density between substituent and substrate. Equation 12 and its approximation (eq 18) quantitatively reflect two more important effects coming from the substituent being qualitatively or semiempirically described in the literature. The first term, on the rhs, represents the contribution to the energy change coming from the income (withdrawal) of electrons in the substrate, and the second term represents the contribution coming from the field effect of the substituent on the substrate.

III. Theoretical Calculations and Discussions

Below, we show some calculations to support our theoretical hypothesis. We do not claim that these calculations are either representative of the wide variety of experimental behaviors or sufficiently systematic that our parameters can be used instead of experimental ones. On the other hand, these comparisons with experimental results should be considered only as a qualitative support for the present procedure. The present correlations, as those from experiment, represent functional relationships of the substituent effects; however, these are different by origin and purpose. What we have tried to validate here is the possibility of expressing the substituent effects by parametric correlations based on DFT theory. In future studies, we will establish parameters that characterize free-energy relationships, solvent effects, and others with theoretical calculations. It is far-reaching to pretend to provide a theoretical basis to the already known experimental relationships, although along this way can be discussed some aspect of them.

Tables 1−5 show the values of HOMO and LUMO energies and electronic chemical potentials in the approximation $\epsilon_{HOMO} + \epsilon_{LUMO}/2$, Mulliken net charges on the substituents, and the values of the field effect (from the second term in the right-hand side of eq 18) for several ring-substituted organic series. These data were obtained from ab initio calculations. The geometry of the derivatives from benzoic acids, phenols, phenylacetic acids, phenylpropenoic acids (trans), and phenylpropanoic acids were optimized at ab initio level using DFT (B3PW91/6-31g*). The absence of imaginary frequencies for each geometry verified that these structures reside at energy minima. Reported data were obtained from single-point calculations at the level B3PW91/6-311++g** using the optimized geometries in all of the molecules.

Using data from Tables 1−5, we calculated the ratios given by eq 15 for each series and tabulated them in Table 6. It is evident that these ratios are practically constants for each substituted molecule with the same substituent on the different substrates. According to the condition of eq 15, a linear relationship exists between the σ' values of any two substrates with the same substituent.

Theoretical σ' values calculated using eqs 16 and 18 and experimental σ values are shown in Table 7. We omit σ' units, but the actual units correspond to energy units. The electronic chemical potential is the negative value of the electronegativity.[8] In analogy with thermodynamics, we interpret the electronic chemical potential as the motive force for determining the

TABLE 1: HOMO and LUMO Energies, Net Charges on the Substituents, Electronic Chemical Potentials, and Field Effect for Benzoic Acids

substituent	E_{HOMO} (eV)	E_{LUMO} (eV)	charge (e)	μ (eV)	field (eV)
p-NO$_2$	−8.369	−3.420	−0.100	5.894	0.074
p-NH$_2$	−6.204	−1.393	0.228	3.798	−0.032
p-CH$_3$	−7.293	−1.849	−0.116	4.571	0.080
p-F	−7.896	−2.306	−0.193	5.101	0.105
p-Cl	−7.441	−2.198	0.569	4.819	−0.138
p-Br	−7.375	−2.247	−0.231	4.811	0.110
H	−7.470	−1.767	0.130	4.618	0.000
m-NO$_2$	−8.313	−3.122	−0.096	5.717	0.084
m-NH$_2$	−6.020	−1.751	0.200	3.885	−0.026
m-CH$_3$	−7.201	−1.919	−0.077	4.560	0.077
m-F	−7.528	−2.251	−0.140	4.889	0.103
m-Cl	−7.346	−2.258	0.546	4.802	−0.150
m-Br	−7.279	−2.273	−0.225	4.776	0.124

TABLE 2: HOMO and LUMO Energies, Net Charges on the Substituents, Electronic Chemical Potentials and Field Effect for Phenylacetic Acids

substituent	E_{HOMO} (eV)	E_{LUMO} (eV)	charge (e)	μ (eV)	field (eV)
p-NO$_2$	−7.946	−2.790	−0.118	5.368	0.071
p-NH$_2$	−5.826	−0.673	0.236	3.249	−0.030
p-CH$_3$	−6.712	−0.870	−0.165	3.791	0.084
p-F	−7.015	−1.057	−0.143	4.036	0.080
p-Cl	−6.897	−1.159	0.522	4.028	−0.109
p-Br	−6.868	−1.203	−0.247	4.035	0.102
H	−7.016	−0.825	0.130	3.921	0.000
m-NO$_2$	−7.837	−2.757	−0.108	5.297	0.083
m-NH$_2$	−5.906	−0.844	0.239	3.375	−0.038
m-CH$_3$	−6.829	−0.905	−0.136	3.867	0.093
m-F	−7.142	−1.154	−0.136	4.148	0.095
m-Cl	−6.993	−1.172	0.543	4.082	−0.141
m-Br	−6.943	−1.190	−0.240	4.066	0.123

TABLE 3: HOMO and LUMO Energies, Net Charges on the Substituents, Electronic Chemical Potentials, and Field Effect for Phenylpropenoic Acids

substituent	E_{HOMO} (eV)	E_{LUMO} (eV)	charge (e)	μ (eV)	field (eV)
p-NO$_2$	−7.646	−3.492	−0.158	5.569	0.061
p-NH$_2$	−6.044	−2.064	0.250	4.054	−0.028
p-CH$_3$	−6.722	−2.337	−0.044	4.529	0.036
p-F	−7.011	−2.536	−0.140	4.773	0.058
p-Cl	−6.938	−2.586	0.600	4.762	0.099
p-Br	−6.937	−2.619	−0.230	4.778	0.073
H	−6.868	−2.286	0.122	4.577	0.000
m-NO$_2$	−7.539	−3.166	−0.129	5.353	0.065
m-NH$_2$	−6.047	−2.287	0.210	4.167	−0.023
m-CH$_3$	−6.884	−2.409	−0.207	4.646	−0.022
m-F	−7.196	−2.671	−0.132	4.933	0.066
m-Cl	−7.141	−2.667	0.629	4.904	0.371
m-Br	−7.131	−2.677	−0.206	4.904	0.081

electron flow in a particular direction. Thus, the first term on the right-hand side of eq 18 incorporates the energy change coming from inductive and resonance effects in the σ' values given by eq 16. The second term (rhs) of eq 18 accounts for the energy change produced by the external field effect of the substituent. Our definition of σ' ensures better correspondence between computed σ values and experimental σ' values, as much in magnitudes as in signs, predicting correctly the relative magnitude of the electron-donor or electron-acceptor character of the substituents. This is surprising, because the computed σ' values do not include the solvent effects, temperature, and the statistical mechanical averaging present in the measured σ values. The substituent effects are overestimated for halogen substituents, and in the case of chlorine, the sign is wrong. This is probably due to the use of the point-charge approximation and Mulliken population analysis, and is not a limitation of the method.

TABLE 4: HOMO and LUMO Energies, Net Charges on the Substituents, Electronic Chemical Potentials, and Field Effect for Phenylpropanoic Acids

substituent	E_{HOMO} (eV)	E_{LUMO} (eV)	charge (e)	μ (eV)	field (eV)
p-NO$_2$	−7.877	−2.952	−0.149	5.414	0.062
p-NH$_2$	−5.705	−0.668	0.223	3.186	−0.025
p-CH$_3$	−6.703	−0.720	−0.212	3.711	0.077
p-F	−7.005	−1.036	−0.149	4.020	0.063
p-Cl	−6.888	−1.025	0.544	3.956	−0.092
p-Br	−6.866	−1.149	−0.238	4.007	0.079
H	−6.838	−0.512	0.126	3.675	0.000
m-NO$_2$	−7.764	−2.917	−0.156	5.340	0.094
m-NH$_2$	−5.756	−0.737	0.242	3.246	−0.039
m-CH$_3$	−6.671	−0.764	0.017	3.717	0.036
m-F	−6.978	−0.934	−0.137	3.956	0.088
m-Cl	−6.848	−0.943	0.571	3.895	−0.150
m-Br	−6.811	−0.955	−0.223	3.883	0.117

TABLE 5: HOMO and LUMO Energies, Net Charges on the Substituents, Electronic Chemical Potentials, and Field Effect for Phenols

substituent	E_{HOMO} (eV)	E_{LUMO} (eV)	charge (e)	μ (eV)	field (eV)
p-NO$_2$	−7.362	−2.569	−0.153	4.965	0.092
p-NH$_2$	−5.150	−0.402	0.158	2.776	−0.009
p-CH$_3$	−6.102	−0.568	−0.205	3.335	0.108
p-F	−6.414	−0.914	−0.156	3.664	0.094
p-Cl	−6.367	−0.935	0.391	3.651	−0.082
p-Br	−6.383	−0.952	−0.249	3.667	0.115
H	−6.353	−0.478	0.128	3.415	0.000
m-NO$_2$	−7.225	−2.769	−0.140	5.069	0.101
m-NH$_2$	−5.599	−0.151	0.184	2.875	−0.021
m-CH$_3$	−6.306	−0.530	−0.149	3.418	0.105
m-F	−6.688	−0.775	−0.145	3.731	0.106
m-Cl	−6.655	−0.899	0.465	3.777	−0.123
m-Br	−6.491	−0.897	−0.189	3.694	0.115

TABLE 6: Theoretical Ratios (from eq 15)

	Substrates				
substituent	benzoic A.	Ph-acetic A.	phenol	Ph-propenoic A.	Ph-propanoic A.
p-NO$_2$	−0.136	−0.134	−0.137	−0.131	−0.128
p-NH$_2$	−0.095	−0.091	−0.096	−0.094	−0.094
p-CH$_3$	−0.106	−0.099	−0.104	−0.105	−0.105
p-F	−0.111	−0.108	−0.115	−0.110	−0.110
p-Cl	−0.111	−0.099	−0.101	−0.101	−0.101
p-Br	−0.085	−0.076	−0.087	−0.085	−0.086
H	−0.120	−0.121	−0.126	−0.121	−0.121
m-NO$_2$	−0.132	−0.128	−0.132	−0.128	−0.128
m-NH$_2$	−0.100	−0.095	−0.099	−0.097	−0.097
m-CH$_3$	−0.126	−0.097	−0.117	−0.108	−0.108
m-F	−0.115	−0.109	−0.118	−0.114	−0.114
m-Cl	−0.110	−0.099	−0.110	−0.105	−0.105
m-Br	−0.088	−0.077	−0.088	−0.088	−0.088

The correlation analysis shows excellent linear relationships ($r^2 > 0.96$ with confidence interval of 99%) for the plot of σ' values for a series of substrates versus σ' values of benzoic acids, the reference substrate. An example of such a relationship is shown in Figure 1, in which σ' values for the ring-substituted phenylpropenoic acids are plotted against σ' values for the corresponding substituted benzoic acids. This type of plot will be referred to as a σ' plot and its slope as the ρ' parameter. In this case, slopes of the 'best straight lines' of σ' plots are similar to the corresponding Hammett ρ-values, indicating the sensitivity of the substrate to substituents.

Table 8 shows computed ρ' values and experimental ρ values for the studied substrates. These data support the proposal that our theoretical parameters account for contributions relevant to the experimental parameters. In fact, in Table 8, we observe that all calculated ρ-values are positive corresponding to a reaction that is facilitated by reducing the electron density at

TABLE 7: Experimental σ Values (from ref 1) and σ' Values Calculated from Eqs 16 and 18

substituent	σ	σ' benzoic acid	σ' Ph-acetic acid	σ' Ph-propenoic acid	σ' Ph-propanoic acid	σ' phenol
p-NO_2	0.78	1.136	1.043	1.342	1.073	1.051
p-NH_2	−0.66	−0.485	−0.446	−0.613	−0.381	−0.112
p-CH_3	−0.17	1.216	1.241	0.795	1.119	1.246
p-F	0.06	1.596	1.150	1.257	1.074	1.065
p-Cl	0.23	−2.165	−1.646	−2.089	−1.629	−0.981
p-Br	0.23	1.777	1.580	1.684	1.417	1.404
m-NO_2	0.71	1.128	1.016	1.213	1.131	1.017
m-NH_2	−0.16	−0.349	−0.466	−0.425	−0.466	−0.212
m-CH_3	−0.07	1.033	1.136	0.411	0.437	1.051
m-F	0.34	1.350	1.138	1.229	1.055	1.038
m-Cl	0.34	−2.071	−1.761	−1.949	−1.786	−1.274
m-Br	0.39	1.7641	1.574	1.583	1.400	1.198

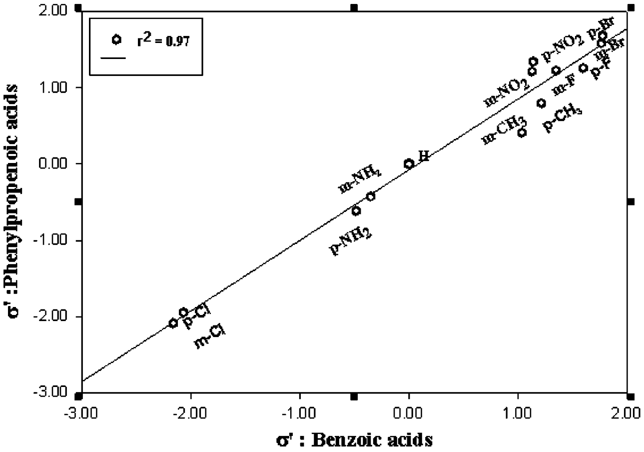

Figure 1. σ' plot for acid dissociation of phenylpropenoic acids: phenylpropenoic acids σ' values vs benzoic acids σ' values.

TABLE 8: Theoretical ρ' Values and Experimental ρ Values (from ref 1)

substrate	ρ' (theoretical)	ρ (experimental)
benzoic a.	1.00	1.00
Ph-acetic a.	0.85	0.49
Ph-propenoic a.	0.90	0.47
Ph-propanoic a.	0.80	0.27
phenol	0.65	2.11

the reaction center. In agreement with experimental observation, the magnitude of ρ' is greater for the substrates that are more susceptible to polar effects. It has been observed experimentally that some reaction series (e.g., acid dissociation of phenols) show marked deviations from the Hammett equation due to "cross-conjugation" and require a different set of parameters (e.g., σ^+, σ^-). In our theoretical approach, the phenol series has the lowest value of ρ', suggesting a marked difference from the rest of the substrates. Of course, the numerical value of ρ' is also affected for the σ' value overestimation for halogen substituents.

Although the present treatment is incomplete, our procedure appears to account for the most important factors affecting substrates. The correspondence exhibited among σ' and σ values suggests that these parameters are affected by the intramolecular interaction between substituent and substrate and are almost insensitive to environmental effects. A comparison of the ρ and ρ' values is less clear, because is impossible to ignore the actual impact of effects such as temperature or solvation.

It would be naïve to attribute more significance to this relation between the theoretical parameters and experimental ones. What is actually possible is to improve the theoretical method from an effective partition of the density in eq 6 and solve the integral term in eq 12 in order to get better numerical results. Effects coming from the environment, ignored in the present formulation, such as solvent or temperature could be incorporated into a more general approach to this problem within finite temperature DFT formalism. We insist that our approximation is an attempt to describe substituent effects with a pure theoretical basis and is only from this point of view without any particular relation to the vast experimental results in this area.

IV. Conclusion

This work is an attempt to look for a new route to obtain parameters characterizing substituent effects using theoretical calculations. It has been shown that first principles of DFT are fairly appropriate for recovery of the most important features of the linear free-energy relationships that are described in physical organic chemistry literature.

Preliminary DFT equations have been developed for interpretation of the substituent effects from a purely theoretical point of view. In particular, we found an equation that resembles the fact that the change of net charge on the substrate and the field effect on it as a consequence of attaching a substituent are the fundamental contributions to a theoretical analogue of the σ parameter of Hammett.

These theoretical σ' values were calculated for different ring-substituted benzene derivates, and it was possible to establish linear relationships among them resembling the linear relationships of the Hammett analysis. At the same time, the slopes of these plots were proportional to the susceptibility of the substrate to the polar effects of the substituents, that is, the experimental ρ parameter. Effects such as entropy changes, temperature dependence, solvent effect, and so on, can be very relevant to the values of the ρ parameters and have been ignored in the present formulation.

We hope this point of view offers a new tool for development of a new correlation analysis for organic chemistry using ab initio calculations. Also, it opens a new direction to explore more about the origin and pursuit of the linear free-energy relationships. The substituent effects are a complex problem, and the use of DFT would be useful to contrast with the experimental behavior in order to investigate the relative importance of the different effects contributing to reactivity, the deviations of the linear behavior, the diversity of parameters, and so on.

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