

Structure–property relationships and momentum space quantities: Hammett σ -constants[†]

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Correlations are established between Hammett σ constants and momentum–space expectation values ($\langle p^2 \rangle$). Momentum–space quantities, which have generally been neglected by chemists, are shown to be valuable for such problems, which suggests they may be useful more widely as suitable molecular descriptors for quantitative structure–property studies.

Empirical quantitative structure–activity (QSAR) and structure–property (QSPR) relationships continue to be widely used in chemistry, in particular in the design of pharmaceutically active compounds. These approaches rely broadly on the intuitive concept of similarity, i.e. a similar structural change in a series of structurally related compounds will usually result in a similar effect on the properties or reactivity of each. In recent years there has been considerable effort devoted to the introduction and application of quantitative measures of molecular similarity using *ab initio* wavefunctions or electron densities [1, 2]. Graham Richards has been a pioneer in this field [3]. In contrast there has also traditionally been little attention paid to the use of momentum–space quantities in chemistry and in this field in particular. Nevertheless, we have previously shown how momentum–space (p -space) electron densities may be used in QSAR studies and have established, for example, useful relationships between momentum–space similarity indices and the activity of some anti-HIV phospholipids [4]. For a survey of p -space applications see [5, 6].

For molecular systems the most straightforward route to momentum–space quantities is to obtain first the

position–space wavefunction $\Psi(\mathbf{r})$ and then to transform it analytically to momentum space as described in [7]. The Fourier transform that relates $\Psi(\mathbf{r})$ to $\Psi(\mathbf{p})$,

$$\Psi(\mathbf{p}) = \frac{1}{(2\pi)^{3/2}} \int \Psi(\mathbf{r}) \exp(-i\mathbf{p}\cdot\mathbf{r}) \, d\mathbf{r}, \quad (1)$$

preserves the form of the wavefunction so that the electron density, individual orbitals, basis functions and wavefunction are related to each other in p -space exactly as they are in r -space. In momentum space all explicit information concerning the coordinates of nucleus α are contained in ‘phase factor’ terms of the form $\exp(-i\mathbf{p}\cdot\mathbf{R}_\alpha)$. Momentum–space expectation values $\langle p^n \rangle$, the moments of momentum, are defined according to

$$\langle p^n \rangle = \int p^n \rho(\mathbf{p}) \, d\mathbf{p}, \quad (2)$$

and are calculated conveniently by numerical integration of $\rho(\mathbf{p})$. $\langle p^2 \rangle$ ($n = 2$) is twice the kinetic energy and $\langle p^0 \rangle$ simply the number of electrons. Decreasing values of n place increasing emphasis on the slower moving valence electrons.

In this paper we present results using momentum–space ideas for an admittedly well-studied problem: linear free-energy relationships and the rationalization and prediction of Hammett σ -parameters. The incentive

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for this work was that of Ponec *et al.* [8] who show how position (*r*-space) quantum similarity measures correlate with σ , and demonstrate the use of such measures as theoretical descriptors in QSPR and as replacements for empirical constants such as σ .

The starting point in [8] is the calculation of the widely used molecular quantum similarity measure, Z_{AB} , introduced by Carbó-Dorca and co-workers [1, 2], where

$$Z_{A,B}(\Theta) = \int \int \rho_A(\mathbf{r}_1)\Theta(\mathbf{r}_1, \mathbf{r}_2)\rho_B(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2 \quad (3)$$

and ρ_A and ρ_B are electron densities associated with molecules or fragments A and B, respectively. In the present work, the positive definite operator $\Theta(\mathbf{r}_1, \mathbf{r}_2)$ is set equal to $\delta(\mathbf{r}_1 - \mathbf{r}_2)$, so that 'overlap' quantum molecular similarity measures are evaluated. Ponec *et al.* [8] examine the dissociation equilibrium of several sets of substituted carboxylic acids. They consider the electron density, ρ_{COOH} associated with the -COOH group, the active part of the molecule, and evaluate the *self*-similarity measure by using equation (1) and putting $\rho_A = \rho_B = \rho_{\text{COOH}}$. Reasonable correlations between this self-similarity and Hammett constant σ were then established.

The self-similarity measure Z_{II} is thus simply given by

$$Z_{II} = \int \rho_I^2(\mathbf{r}) d\mathbf{r}. \quad (4)$$

In free-electron gas theory, the simplest version of density functional theory, integrals such as equation (4), which involve only powers of the *r*-space electron density, are related directly to momentum space quantities via

$$\langle p^n \rangle = \frac{3(3\pi^2)^{m/3}}{m+3} \int \rho^{(3+n)/3}(\mathbf{r}) d\mathbf{r}. \quad (5)$$

Allan and Cooper [9] have shown previously that even in small molecules, where free-electron theory performs poorly, $\langle p^n \rangle$ remains proportional $\int \rho^{(3+n)/3}(\mathbf{r}) d\mathbf{r}$ to a surprisingly good approximation even though the constant of proportionality is not that for the free-electron gas. The work of Ponec *et al.* [8], together with equation (5), suggests that it is worthwhile to investigate correlations between $\langle p^n \rangle$ and the Hammett constants.

In this short paper we investigate correlations between $\langle p^2 \rangle$ and σ . The five sets of acids chosen are shown in figure 1: the (classical) series of *p*-substituted benzoic acids (I), 5-substituted thiophen (II) and furan-2-carboxylic acids (III), *p*-substituted trans-cinnamic

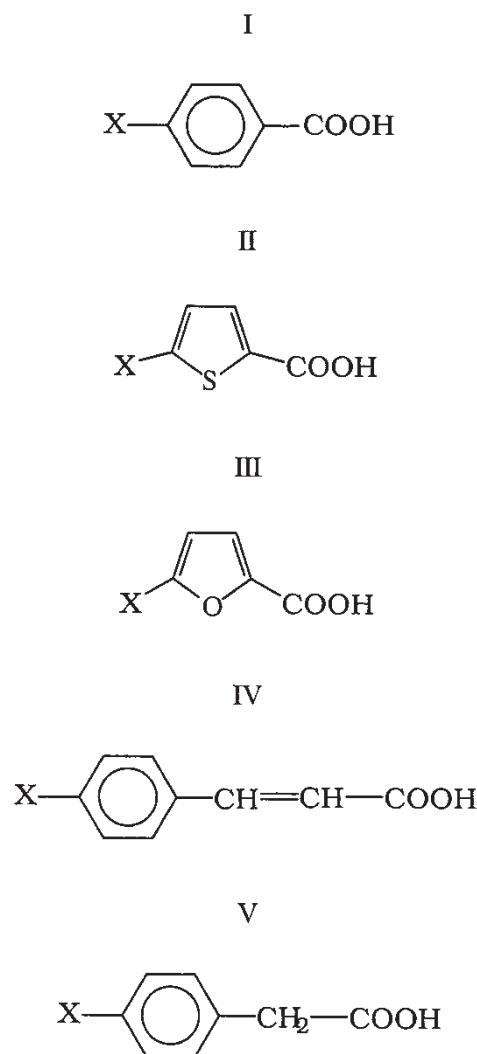


Figure 1. The five series of substituted carboxylic acids studied: I, benzoic acid; II, thiophen-2-carboxylic acid; III, furan-2-carboxylic acid; IV, trans-cinnamic acid; V, phenylacetic acid.

(IV) and phenylacetic acids (V). Substituents X include both electron-donating and withdrawing groups. Wavefunctions and optimized geometries were calculated for all molecules using the MOPAC program [10] and the AM1 parameterized Hamiltonian [11]. Values of $\langle p^2 \rangle$ were calculated for the -COOH fragment via equations (1) and (2) using only basis functions centred on atoms within this group.

All the results of our study are shown graphically in figure 2, in which $\langle p^2 \rangle$ is plotted against σ for each set of acids I-V. In general the larger the value of σ , the lower the value of $\langle p^2 \rangle$. In each case the correlation coefficient exceeds 0.95, which is at least comparable to those reported previously for self-similarities in [8]. Momentum-space quantities such as $\langle p^2 \rangle$ can thus

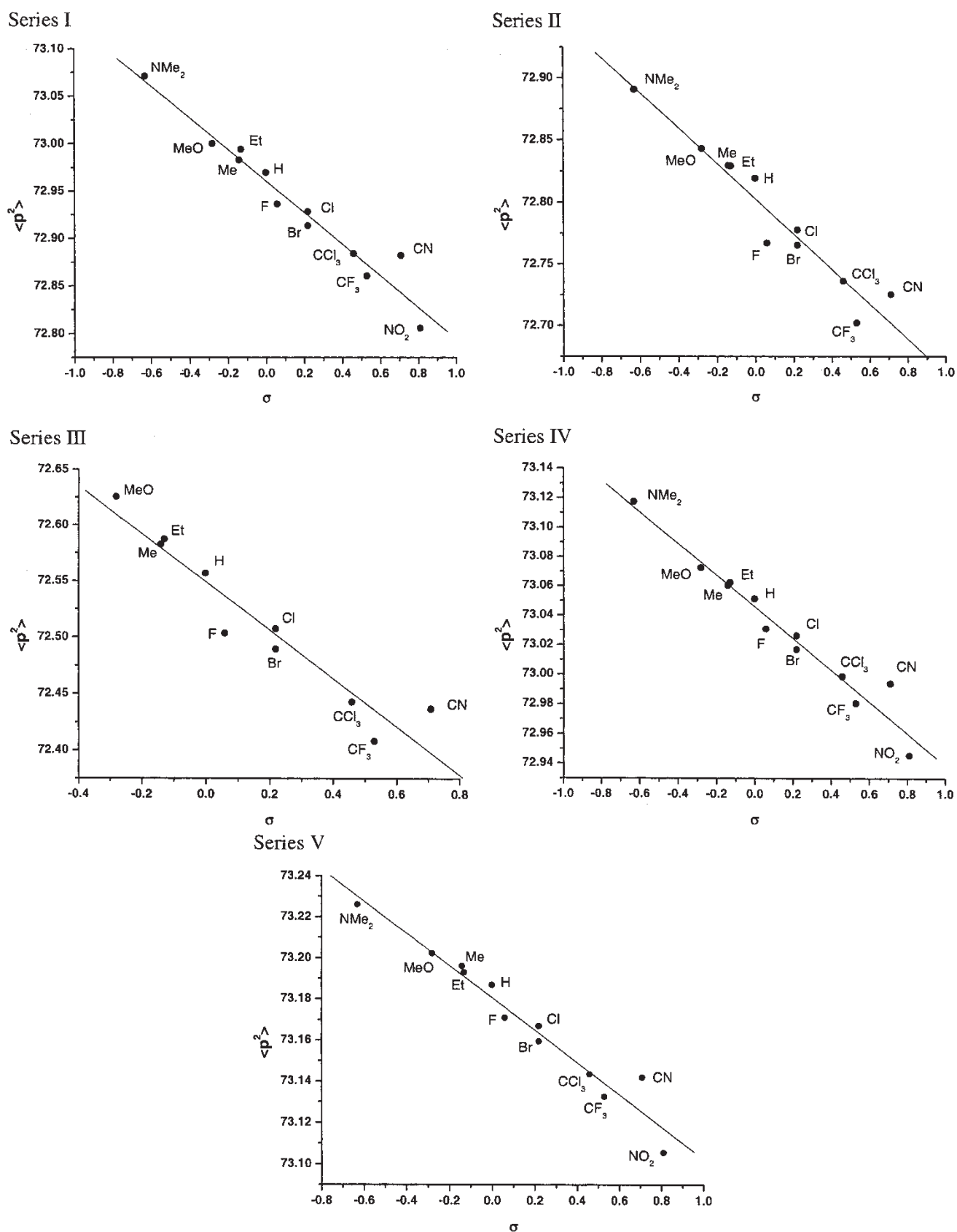


Figure 2. $\langle p^2 \rangle$ versus σ for each of the series I–V. Correlation coefficients are 0.976, 0.963, 0.956, 0.978 and 0.976, respectively.

represent good theoretical descriptors of substituent effects. As with the self-similarities [8], the slopes of the lines in figure 2 can be used to obtain satisfactory estimates of the Hammett constant ρ for each series and there is also a satisfactory correlation between $\langle p^2 \rangle$ for the non-substituted acids and the corresponding pKa values. The possible advantage of correlations such as those in figure 2 over conventional approaches using perturbation theory [12] is that in principle there is no restriction to conjugated aromatic systems.

In summary, we have established useful correlations between Hammett σ constants and momentum-space expectation values. These complement previous structure-activity relationships relating either position-space similarity measures or p -space quantities to biological activity. We are now investigating the use of such quantities to predict molecular properties such as partition coefficients and biological activities that are often determined primarily by the values of such coefficients.

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