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Contents

Role of Atomic and Molecular Non-observable Properties in the Understanding and Description of Real Observables of the Chemical Systems. A Review

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Abstract. Chemical species can be characterized by various observable features: mass, enthalpy of formation, charge (ions), dipole moment, magnetic susceptibility, electrical susceptibility, electromagnetic spectra, refraction index, polarizability, electron density distribution etc. But, on the other hand, the understanding of chemical an physical behavior is usually based on specific non-observable features - for example: electronegativity, partial atomic charges, nucleophilicity, atomic and molecular orbitals, aromaticity, hyperconjugation, … All non-observable features generally have no physical unit, and are not amenable to experimental measurements. For that reason the values ascribed to them are strongly dependent on the definition(s). For example, we know (and use) various electronegativity scales: Pauling's, Mulliken's, Alfred-Rochov's [1, 2], Sanderson's, Allen's, and other. They are based on different theoretical assumptions, and produce (on many instances, significantly) different numerical values. On the other hand, all scales follow similar general trend, indicating that the values reflect some intrinsic chemical property.

1 Introduction

Electronegativity, as a concept, is highly powerful for rationalization of atomic and molecular properties and reactivity, and many attempts were made to obtain the scale which will precisely mimic them. The first electronegativity scale was proposed by Pauling [3]. It was based on the fact that the energy, D, of a heteronuclear bond, A&B, is generally higher than the average bond energies of the homonuclear bonds, A&A and B&B. (This is actually the root of idea of *resonance*.)

$$D(AB) = \frac{1}{2}[D(AA) + D(BB)] + \Delta_{AB}$$

The square root of the stabilization term, Δ_{AB}, was found to be proportional to atomic constants that were defined by Pauling as atomic electronegativities,

$$\sqrt{\Delta_{AB}} \propto \chi_A - \chi_B.$$

It was quickly recognized that electronegativity of an atom depends on the other bonds in the molecule (*e.g.* on hybridization).

Another method for definition of electronegativity is well designed for account of mode of bonding. Mulliken electronegativities are defined as a balance between electron attracting and electron releasing ability [4]:

Hence, Mulliken defined the electronegativity of an orbital v (another unobservable) of an atom A as the mean of the correspondent ionization potential (I_{Av}) and electron affinity (E_{Av}),

$$\chi_{Av} = \frac{1}{2}(I_{Av} + E_{Av})$$

Based on Mulliken's definition, a number of 'improved' models emerge [5–9]. Many of them have rather sophisticated computational methodology, but in essence a little improvement was achieved.

Generally, use of Mulliken electronegativities is most popular due the simplicity of the calculation method.

Situation with partial atomic charges (PAC) is even more complicated, because more than 30 different scales are known, and can be divided in four classes, based on the method for defining them.

Concept of partial atomic charges, which is also important term in chemistry, is closely connected to the electronegativity. First definition is known as Coulson's net atomic charges [10].

$$q_A = Z_A - \sum_{\mu \in A} P_{\mu\mu}$$

where q_A is the net atomic charge on A^{th} nucleus, Z_A the charge of Ath nucleus (atomic number), and $P_{\mu\mu}$ the density matrix given by the summation of multiplications of M.O. coefficients (c) over occupied orbitals;

$$P_{\mu\mu} = \sum_{i=1}^{occ} c_{\mu i} c_{v i}$$

Originally it was introduced for the analysis of Hückel molecular orbitals, but quickly is upgraded with Mulliken definition [11] which is better suited for the analysis of all valence orbitals population.

$$q_A = Z_A - \sum_{\mu \in A} \sum_{v \in A} P_{\mu\eta} S_{\mu v}$$

where $S_{\mu v}$ is the overlap matrix. Therefore, the Mulliken's net atomic charges give similar values to the Coulson net atomic charges.

Further variant based on the same (Mulliken's) idea is proposed by Mayer [12, 13] involving much more sophisticated model for interatomic electron density partition. Amount of such variants for the calculation of PAC is very large, but it is hard to pick one which is more reliable than the other.

Density functional theory is a quantum-chemical method for accurate calculation of electron density distribution. It stems from the basic idea of quantum chemistry, that all molecular properties are derived from the distribution of electron density in molecule(s). Corollary, it justifies the use of partial atomic charges in molecule which reflect the distribution of electron density. Specificity of DFT method(s) is in the inclusion of electron correlation in the calculation of electron distribution in molecule. Besides DFT, many semiempirical methods implicitly include electron correlation in the distribution of electron density calculations. Therefore, they offer a quick computation methodology for the calculation of the distribution of electron density in the molecule.

2   Observables Correlated with Partial Atomic Charges

Partial atomic charges were tested as a reliable method for the calculation of the observable properties of molecules [14].

The observable which is naturally most directly related to PAC, is the **dipole moment** of molecules. In the special case of diatomic molecules, dipole moments can be used for experimental determination of partial atomic charges.

There are number of results on **ESCA and ^{1}H-NMR chemical shifts**, [15–20] dependence on partial atomic charges. PAC values were proven to be important, but chemical shifts in ESCA and NMR are markedly influenced by general electron density distribution.

Many studies were devoted to **Electrostatic effects between molecules**. The models for the prediction of conformations and properties of polymers [21, 22] and proteins [23, 24] are mostly based on electrostatic interactions between partially charged atoms in the neighboring polymer chains. Optimization of these interaction may lead to definition of electrostatic potential surfaces, and from them can be inferred a special scale of partial atomic charges. These charges are very reasonable for the atoms on the surface of molecules, but are quite unreasonable for atoms buried inside the complex molecule.

It was proven that **Electronic polarizability** is strongly coupled with atomic charges, [25, 26] and was mostly applied for the structures in the solid state [27].

Chromatographic retention indices were well correlated with molecular descriptors based on atomic partial charges [28, 29]. Using similar methodology, the odor thresholds were successfully predicted, too.

Surface tension, boiling point, [29, 30] simulation of bulk densities, surface tension, and molecular orientation at liquid/vapor interface of molecular system, [31] hydration free energy estimates, [32] and many other simulations of observables are based on PAC [33–35].

A common chemist's intuition hints that **acid dissociation constants** should be directly related to the partial charge on acidic hydrogen [36]. The acid dissociation constant, K_a, which describes the extent to which the compound dissociates in the gas phase or in the solution, is a fundamental property of many chemical compounds. It is a key feature which governs the chemical reactivity of the substances in any solvent, and the interaction with the solvent itself. In aqueous solution, the pK_a is a proxy for several pharmacokinetic properties. Jointly with integrity, lipophilicity, solubility, and

permeability, pK_a has been considered as one of the five key physico-chemical profiling screens to predict the key properties that affect ADME(T) characteristics [37].

Because no strongly founded method exists for the calculation of partial atomic charges in molecules, we intentionally used a fast semi empirical molecular orbital method, MNDO-PM3 (which by default calculates Mulliken partial atomic charges). This was chosen as one well balanced for hydrogen-bonding interactions. Basic MNDO underestimates hydrogen bonding, and MNDO-AM1 overestimates it [38–40].

The idea was tested on demanding example: the set of unsaturated and epoxy polycarboxylic acids presented in Scheme 1.

a   b

1. $R_1 = H$; $R_2 = H$; $R_3 = COOH$; $R_4 = COOH$

2. $R_1 = H$; $R_2 = COOH$; $R_3 = COOH$; $R_4 = H$

3. $R_1 = CH_3$; $R_2 = H$; $R_3 = COOH$; $R_4 = COOH$

4. $R_1 = CH_3$; $R_2 = COOH$; $R_3 = COOH$; $R_4 = H$

5. $R_1 = H$; $R_2 = H$; $R_3 = COOH$; $R_4 = CH_2COOH$

6. $R_1 = H$; $R_2 = CH_2COOH$; $R_3 = COOH$; $R_4 = COOH$

7. $R_1 = COOH$; $R_2 = CH_2COOH$; $R_3 = H$; $R_4 = COOH$

SCHEME 1

For these 14 acids the 32 dissociation constants were measured [41]. The simple correlation with calculated charge on acidic hydrogen failed (as can be seen on Fig. 1).

A logical explanation is that solvation plays important role in the course of the dissociation to ions. When partial charges on all atoms in carboxylic group (-C(=O)OH) are included, the "composite" charge, Q, as a weighted sum of atomic charges, according to the formula (Eq. 1) can be derived:

$$Q = q_H + A \cdot q_{O-} + B \cdot q_C + C \cdot q_{O=} + D \qquad (1)$$

The values of the parameters (after the renormalization) are:

$$-1 \pm 0.0940 \,(\text{for } q\text{H}) \quad A = -0.4931 \pm 0.0235;$$
$$B = -0.0820 \pm 0.0321; \, C = -0.0368 \pm 0.0249;$$
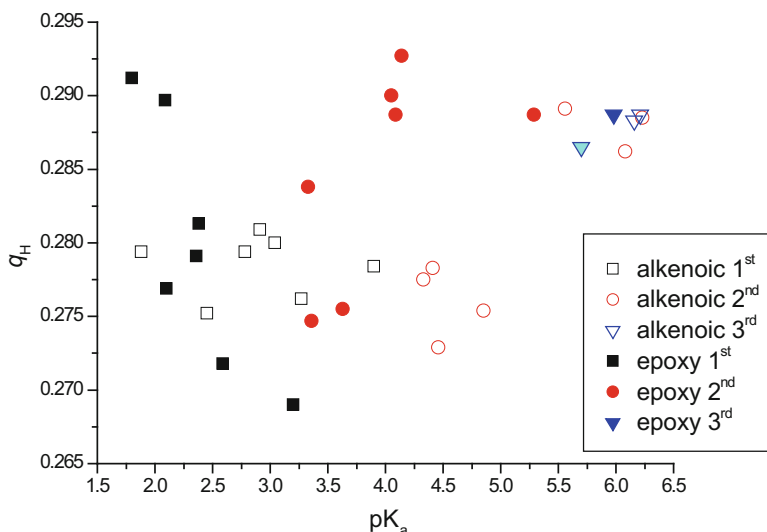$$D = 0.1728 \pm 0.0344; \quad (r = 0.9456, \, n = 32).$$

Fig. 1. Relation between measured pK_a values of β-alkenoic acids (hollow markers) and corresponding epoxy acids (filled markers), and of calculated charges on carboxylic hydrogen for 1st, 2nd, and 3rd dissociation.

This correlation is plotted on Fig. 2.

The magnitude of parameters A-D could give insight into the mechanistic details of reactions involving carboxylic group. The major weight of charges on hydrogen and on hydroxylic oxygen, supports the well-established concept of polarity of O-H bond as a dominant factor determining the efficiency of carboxylic acids dissociation. This is directly confirmed by polylinear correlation including only charges on hydrogen and hydroxylic oxygen. The correlation with charges calculated by the equation:

$$Q' = qH + A \cdot qO- + B \tag{2}$$

is only slightly inferior to that from Eq. (1) $[-1 \pm 0.1070$ (for qH); $A = -0.5480 \pm 0.0267$; $B = 0.1372 \pm 0.0314$; $r = 0.9384$, $n = 32$].

The obvious achievement of this approach is a single basis for the evaluation of all dissociation steps of polycarboxylic acids.

An extensive study is made to find what influences the accuracy of prediction by this approach [42]. In some cases the quality of correlation is slightly improved by addition of the simulation of solvent (medium). When charges are calculated by some *ab initio* method, the use of charges derived from Natural Bonds Analysis (NBO) gives better correlation.

The method is successfully applied for the prediction of pK_a of protonated amines, too. Because here is no carboxylic group, the method is slightly modified [43]. We decided to include in correlation the charge on vicinal nitrogen atom (q_N) along with the partial atomic charge on hydrogen (q_H):

$$pK_{a(calc)} = A \times q_H + B \times q_N + C \times I + D \tag{3}$$
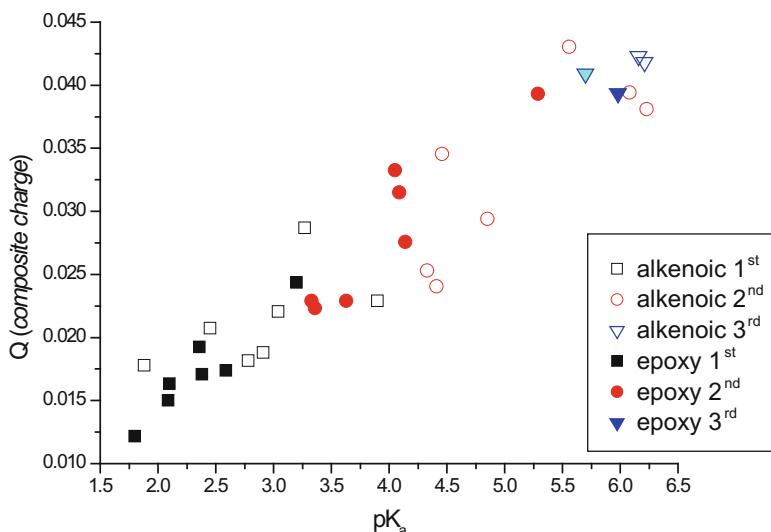
Fig. 2. Relation between measured pK_a values of β-alkenoic (hollow symbols) and corresponding epoxy acids, and of calculated "composite" charges derived from charges of all atoms in carboxyl group.

Here, I is the index variable to distinguish between primary, secondary and tertiary amines. We didn't deeply analyze this variable, but it is clear that it must account for differences in steric hindrance, solvation, and other effectors for acidity of ammonium ions. For this purpose it is set to have integer values. Polylinear regression of data of 57 amines gives the following statistics:

$$A = -140.878; \ B = -11.775; \ C = -1.250; \ D = 52.773$$

$$n = 57; \ r = 0.937; \ sd = 0.604; \ F = 126.306$$

The correlation between pK_a and $pK_{a(calc)}$ of ammonium ions is presented on Fig. 3.

This simple model works equally accurate as various other very sophisticated approaches, and can be valuable aid in estimation of pK_a values of aliphatic amines. In Fig. 3 is obvious that the scattering of data is minimal for primary amines. A likely reason for it is that among secondary and tertiary amines the cyclic amines (with N atom in the ring) are included, which can have markedly reduced steric hindrance. We didn't check quinuclidine, because its peculiar structure (bridgehead tricyclic amine) will set it as outlier.
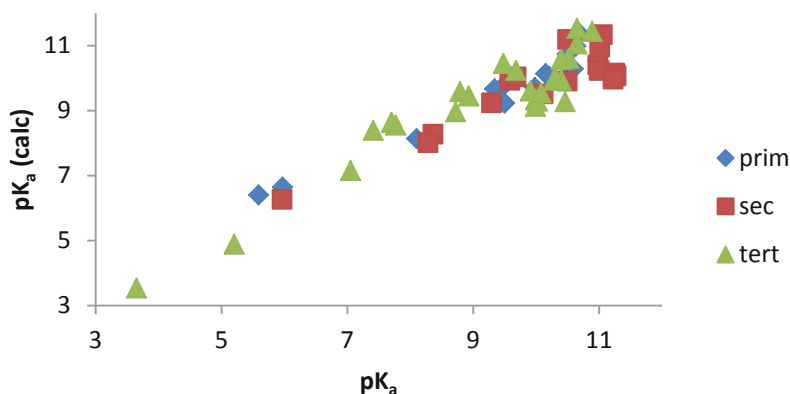
Fig. 3. Correlation of experimental and calculated (Eq. 3) pK_a values for 57 aliphatic amines. Standard deviation of estimate is 0.593.

The analogous approach was successfully applied for the correlation of the rate constants for the esterification of substituted pyrimidine acids with diazo diphenyl methane (DDM) [44] (Table 1).
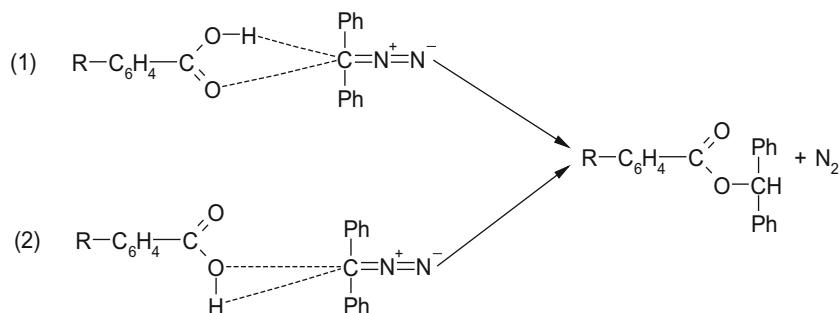
Transition states
SCHEME 2.

The reaction kinetics is compatible with either transition state shown on Scheme 2: Concerted five (1) and three (2) membered transition states for the esterification of carboxylic acids with DDM.

A straightforward correlation of log k_2 rate constants with charges on the carboxylic hydrogen (q_H) was satisfactory having regression coefficient r = 0.9708 (Fig. 4, Left). n = 11, s = 0.001.

An analysis is done on the contribution of the partial charges on every atom of the carboxylic group of each acid to the composite charge Q, obtained according to Eq. (1), as shown in Fig. 4, Right (r = 0.9911).

The calculated parameters are as follows: q_H = 1.00 ± 0.23, A = 0.06 ± 0.19, B = 0.32 ± 0.14 C = 1.44 ± 0.10, denoting the relative contribution of the atomic charges to the overall charge expression of the carboxylic group.

Table 1. Various 2,6-disubstituted-4-pyrimidine carboxylic acids subjected to calculation by AM1 semiempirical MO method, including solvation effects of DMF.

	N (1)	N (3)	X	Y
1			-SCH$_3$	-OH
2			-H	-OH
3			-H	-H
4			-Cl	-CH$_3$
5			-OH	-CH$_3$
6	-CH$_3$	-H	=O	=O
7			-OH	-OH
8	-CH$_3$	-CH$_3$	=O	=O
9			-SH	-OH
10			-Cl	-Cl
11			-CH$_3$	-OH
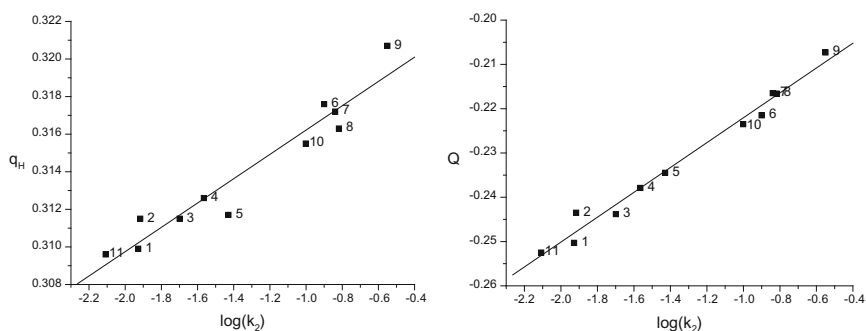
Fig. 4. Left: Correlation of the log (k$_2$) values with calculated charges on carboxylic hydrogen (q$_H$): Right: the same correlation of log k$_2$ with derived charges (Q) according to the Eq. (1).

Among most probable transition states for this reaction, the first one on the Scheme 2, above, is compatible with the values of parameters obtained by polylinear regression of Eq. 1. In other words, high value of parameter C shows the dominant role of carbonyl oxygen interaction with DDM in the transition state of the reaction.

In these calculations, only the most stable conformations of molecules were considered. Preliminary results show that for conformationally mobile molecules, the distribution among various conformations markedly influence the reactivity. A weighted contribution of most stable conformations of the same acid could give more accurate description of reactivity.

3 Conclusion

In this short review is shown that calculated partial atomic charges (the easily obtainable non-observable property) can be used for relatively accurate estimation of (observable) pK_a values of carboxylic acids and of protonated amines. Similar approach can enable to decide on most probable mechanism for the reaction with carbene precursors, too.

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