Employment of quantum chemical descriptors for Hammett constants: Revision Suggested for the acetoxy substituent

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ABSTRACT

The Hammett *para* constant (σ_p) of the acetoxy group has been estimated by applying widely available quantum chemical descriptors, such as NPA charges, Wiberg bond indices, electron densities at bond critical points, as well as electrostatic potential at nuclei. The revised σ_p value is predicted to be in the range of $[-0.08, -0.02]$. Direct evaluation of proton transfer free energies between the substituted benzoic acids and the benzoate anion by employing the SMD solvation model resulted in a reasonable linear correlation with the Hammett constants with a prediction of $\sigma_p = -0.02$ for the OAc group.

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1. Introduction

Quantitative structure-activity relationships (QSAR), arisen from the combination of electronic, steric, hydrophobic, hydrophilic and hydrogen-bonding parameters, are widely used even for the description of host interactions of organic compounds with living systems [1]. As the predecessor of most quantitative relationships used in organic chemistry, the mention of the Hammett equation (and its extended forms) is inevitable [2–4]. It has been one of the most widely used means for the study and interpretation of quantitative aspects of organic reactions and that of their mechanisms. The key characteristics of substituents, the values of σ_p or σ_m were defined by Hammett from the ionization constants of *para-* (1) or *meta*-substituted benzoic acids (2), respectively [2].

$$\sigma_p = lgK_p - lgK_H = pK_H - pK_p \tag{1}$$

$$\sigma_m = lgK_m - lgK_H = pK_H - pK_m \tag{2}$$

where K_H is the ionization constant for benzoic acid (in water at 25 °C), K_p or K_m are the corresponding constants of *para-* and *meta*-substituted benzoic acids, respectively.

Due to the wide acceptance and applicability of Hammett substituent constants, extensive lists of σ_p and σ_m have been compiled by McDaniel and Brown [5], Hansch and Leo [6], and Hansch et al. [7]. The efforts to split the electronic effect of a substituent into inductive and resonance components were reviewed by Charton [8].

Recently, several novel attempts have been made in order to refine and complete the existing lists of substituent constants from quantum chemical indices [9,10]. The fundamental model compounds, *meta-* and *para*-substituted benzoic acids, were investigated by DFT introducing relative acidity calculated from isodesmic reactions [11].

Osminski and Dobrowolski divided the substituent effect into σ and π components and employed the sum of natural population [12] of the corresponding ring carbon orbitals as descriptors [13].

Popelier employed a set of QTAIM descriptors denoted as BCP space for the development of quantum topological molecular similarity (QTSM) measures and accurately predicted the Hammett σ_p and σ_m values for benzoic acids [14] and for other carboxylic acids [15]. The method was developed further in order to be applied for the evaluation of a higher range of Hammett constants [16].

A very frequently used electronic property in chemistry for describing substituent effects is the electrostatic potential at nuclei (EPN), which can be calculated using Eq. (3).

$$V_Y \equiv V(R_Y) = \sum_{A \neq Y} \frac{Z_A}{|R_Y - R_A|} - \int \frac{\rho(r\prime)}{|R_Y - r\prime|} dr\prime \tag{3}$$

where Z_A is the nuclear charge of atom A with radius vector R_A and $\rho(r\prime)$ is the electron density of the molecule.

EPN was successfully employed for the evaluation of σ_0 substituent constants for substituted benzenes, which reflects the isolated effect of individual substituents unperturbed by further interactions with a second substituent [17].

So far, most of computational studies aiming the evaluation of Hammett constants are performed on the basis of quantum chemical descriptors, rather than by direct evaluation of relative pK_a values of the respective benzoic acids. Direct calculation of pK_a is

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rather challenging because even small errors can result in large discrepancies.

The main sources of errors in pK_a calculations (in increasing order) are (i) the inaccuracy in gas-phase free energy calculations, (ii) the value employed for the free energy of solvation for **H**$^+$, which is needed explicitly in some of the thermodynamic cycles, and (iii) the treatment of solvation effects, which is particularly challenging for ionic species because of the pronounced electrostatic effects arising from unbalanced localized charges. Some solutes containing concentrated regions of charge density (which is the case for most anions) require a parametrization different from that of most of the neutral solutes. The problem can be overcome by employing monohydrating clusters (that is adding one explicit water to the solute) as demonstrated by Kelly et al. [18] for the calculation of aqueous acid dissociation constants employing the SM6 solvation model combined with DFT methods. They found that for anions concentrating charge on a single heteroatom, augmenting implicit solvent computations with one explicit water molecule significantly improves the accuracy of pK_a calculations. Pliego and Riveros came to the same conclusion when calculated the pK_a for 17 species covering the range from −10 to 50 at MP2 level [19]. Excellent reviews about pK_a calculations have been published recently by Alongi and Shields [20], as well as by Ho and Coote [21].

The regiochemistry of the Diels–Alder reactions of 6-substituted naphthoquinones with *trans*-1-methoxy-3-methyl-1,3-butadiene was studied and the acetoxy substituent acted as a modest electron-donating group [22]. This finding was inconsistent with the Hammett σ constants for the acetoxy group (0.31) [5–7], however, it is in agreement with the analysis of Swain and Lupton which attributes resonance properties to the acetoxy substituent [23].

The aim of this study is the estimation of the Hammett σ_p constant for the OAc substituent by means of simple and widely available computational methods employing quantum chemical descriptors closely related to the original definition of Hammett equations, i.e., the relative acidities of the substituted benzoic acids. Two out of the four descriptors are related to the electron density around the acidic hydrogen atom, whereas the remaining two descriptors refer to the bond strength of the OH group of the carboxylic group. For the assessment 18 *para*-substituted benzoic acids have been selected covering the range of σ_p from almost −1 to 1.

The results obtained by quantum chemical descriptors has been validated by direct evaluation of relative pK_a values in water phase employing cluster continuum model using one explicit water molecule.

2. Computational details

All substituted benzoic acids were fully optimized at the DFT/PBEPBE [24] level of theory with the 6-31G(d,p) basis set [25] employing the Firefly 8.0 program [26]. Harmonic vibrational frequency calculations were also performed to verify that all optimized structures were true minima on the respective potential energy surfaces. Single point calculations were completed on the optimized geometries using the def2-TZVP basis set [27] and the wavefunctions obtained were used for the subsequent electronic structure calculations. Natural bond orbital analyses were carried out by the module NBO 5.G [28] implemented in Firefly. QTAIM (Quantum Theory of Atoms in Molecules) analyses of the wave function were performed with the AIM2000 software [29].

The proton transfer calculations were carried out employing the M06-L [30,31] functional developed by Truhlar and Zhao along with the 6-31+G(d,p) basis set. The M06-L functional was found

to be accurate for main group thermochemistry and it is especially accurate for systems with noncovalent interactions [32].

The effect of the solvent was taken into account by the explicit/implicit solvation model. As such, one molecule of water was added to each benzoic acids and benzoates and full geometry optimization were performed for these clusters utilizing the SMD solvation model [33], introduced by Marenich, Cramer, and Truhlar, with the dielectric constant of $\epsilon = 78.3553$ for water. The SMD method is based on the charge density of a solute molecule interacting with the solvent represented as continuum. The full solute electron density is employed without the definition of partial atomic charges, therefore the "D" stands for "density" in the abbreviation of the model. As in the previous SMx solvation models (x = 1–8) developed by the Minnesota group the solvent is represented as a dielectric medium with surface tension at the solute–solvent boundary. For the water-phase calculations the Gaussian 09 suite of program [34] was used, in which the IEF-PCM algorithm is used with the SMD parameters, namely the intrinsic atomic Coulomb radii and the atomic surface tension coefficients.

3. Results and discussion

3.1. NBO study

The electron donating effect of the acetoxy group can be interpreted within the framework of the NBO methodology [28]. It is reasonable to assume that both lone pairs of the OAc oxygen (i.e. one with σ and one with π symmetry) are involved in the electron donation towards the aromatic ring. Figure 1 depicts the natural localized molecular orbitals (NLMOs) representing the electron pairs originated from the one-center NBOs but extended with so-called 'delocalization tails' which are the results of the interaction of the parent NBO with the appropriate unfilled orbitals. The inspection of these electron pairs show that they are inherited from the lone pairs of σ and π symmetry on the sp^3 oxygen of the acetoxy group but their shapes took place significant distortion via donor–acceptor interactions with the neighboring C = O and aromatic carbon–carbon bonds. Thus, our electronic structure calculations support that the OAc group possesses resonance donating properties.

3.2. Predicting the Hammett constant via quantum chemical descriptors

The NPA (Natural Population Analysis) charges of the acidic hydrogens of *para*-substituted benzoic acids are between
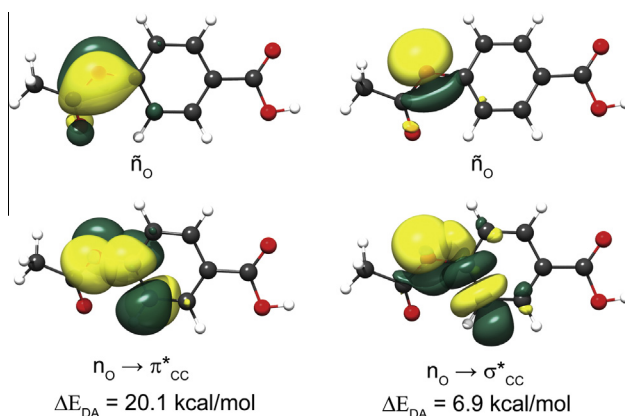

Figure 1. Natural localized molecular orbitals (top) of the electron pairs representing the lone pair of O with π (left) and σ (right) symmetry as well as their donor–acceptor interactions with the corresponding carbon–carbon bonds (bottom).

0.4844 (for the NMe$_2$ group) and 0.4929 (for the NO$_2$ group) revealing a close linear correlation with σ_p, with $r^2 = 0.966$ (Figure 2, top). The charge for the OAc group is 0.4883, almost matches that for the H substituent (Q$_H$ = 0.4884) corresponding to a σ_p of −0.02.

The EPN of the acidic H (denoted as V$_H$) showed a somewhat better linear correlation with σ_p (r^2=0.970) with a range between −0.9741 and −0.9373 (Figure 2, bottom). V$_H$ has a value of −0.9571 for the acetoxy substituent being closest to that of the phenyl group (−0.9581). According to the correlation equation evaluated for V$_H$ a value of −0.04 is proposed for σ_p.

The Wiberg bond indices of the OH bond of the benzoic acids were computed in the natural atomic orbital basis. Unsurprisingly, the bond index was the smallest (0.7337) for the nitro group and the highest (0.7410) for the dimethylamino group. A reasonable linear correlation was established also for the WBI against σ_p with $r^2 = 0.970$ (Figure 3, top). The WBI for the acetoxy substituent is computed to be 0.7376, being closest to those of H, SiMe$_3$, and Ph substituents. Thus, a σ_p of −0.02 is predicted for the OAc group according to the linear equation.

For all the benzoic acids Bader analyses were carried out as well, calculating the bond paths and the bond critical points. The electron density at the bond critical point (ρ_{BCP}) of the acidic OH bond is closely related to its strength, hence its acidity. The computed σ_p has a seemingly narrow range from 0.34273 (for NO$_2$) to 0.34407 (for NMe$_2$), however, ρ_{BCP} reveals close linearity with σ_p with a coefficient of determination of 0.967 (Figure 3, bottom). For the acetoxy group ρ_{BCP} is 0.34345, being very close to that of the phenyl substituent (0.34344). Expression of the expected σ_p from the regression equation results in a value −0.08 for the OAc substituent based on Bader analysis.

Finally, the linear correlation for our set of substituents were also tested for substituted benzenes applying the approach of Galabov et al. [17] A reasonable correlation $r^2 = 0.970$ has been obtained between the σ_p constant and the EPN values of *para* carbon (V$_C$). (See Figure 4.) For the acetoxy substituent V$_C$ = −14.7653 was achieved, being fairly close to that for the phenyl group (V$_C$ = −14.7666). Thus, according to the corresponding linear equation σ_p = −0.02 is predicted for the OAc substituent which is in agreement with those obtained with the σ_p vs. Q$_H$ and σ_p vs. WBI equations for substituted benzoic acids.

3.3. Prediction of the Hammett constant via proton transfer free energies

The strategies aiming at the calculation of pK_a based on thermodynamic cycles usually involve the generation of two ionic species, which increases the uncertainties in the overall solvation energies, potentially resulting in very large errors. More reliable may be the relative pK_a or isodesmic calculations, that is the proton exchange between, for instance, between an acid and a reference base, thereby allowing some cancellation of errors. This concept seems straightforward for the estimation of Hammett constants, because in this case only the evaluation of relative pK_a is needed with respect to benzoic acid. The proton exchange between a substituted benzoic acid and the benzoate anion is depicted in Figure 5.

For the investigation of the proton exchange almost the same training set of benzoic acids have been selected as for the electronic structure calculations. The substituents containing active hydrogens (that is NH$_2$, OH, and COOH groups) have been excluded because in those cases much more complex H-bonding situations are expected. All of the structures (benzoates and benzoic acids)
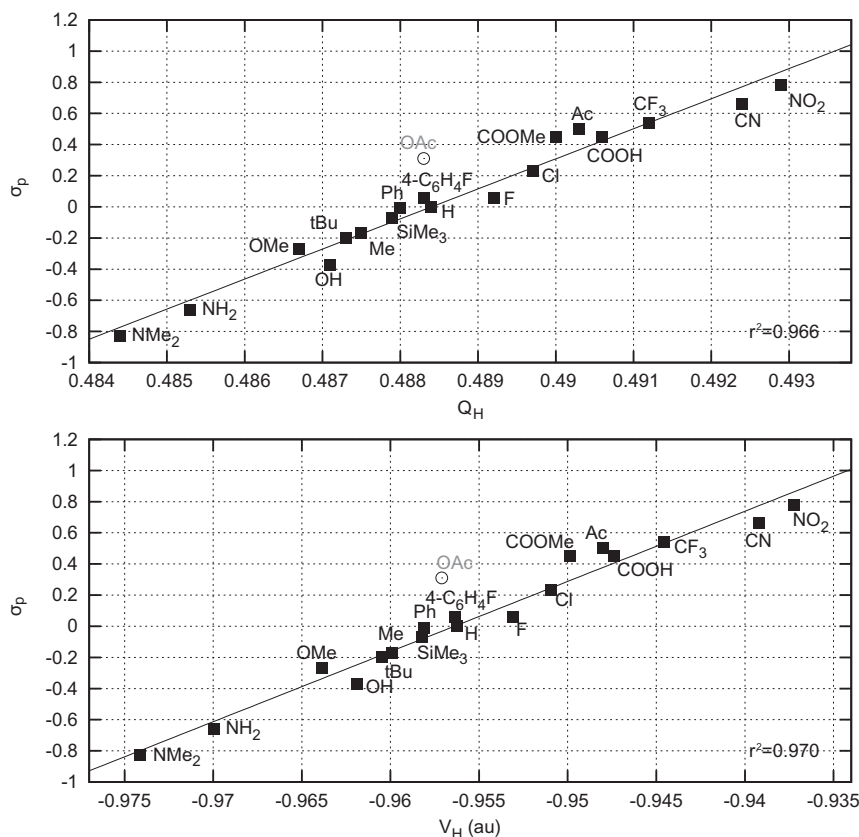

Figure 2. Relationship between the NPA charge (top) or the electrostatic potential (bottom) of the acidic hydrogen of *para*-substituted benzoic acids and the Hammett σ_p constants. Correlation equations: σ_p = 193.02 (±8.61) · Q$_H$ − 94.27 (±4.21); σ_p = 45.05 (±1.97) · V$_H$ + 43.08 (±1.88) Points for the OAc substituent with the original σ_p = 0.31 are indicated in grey.
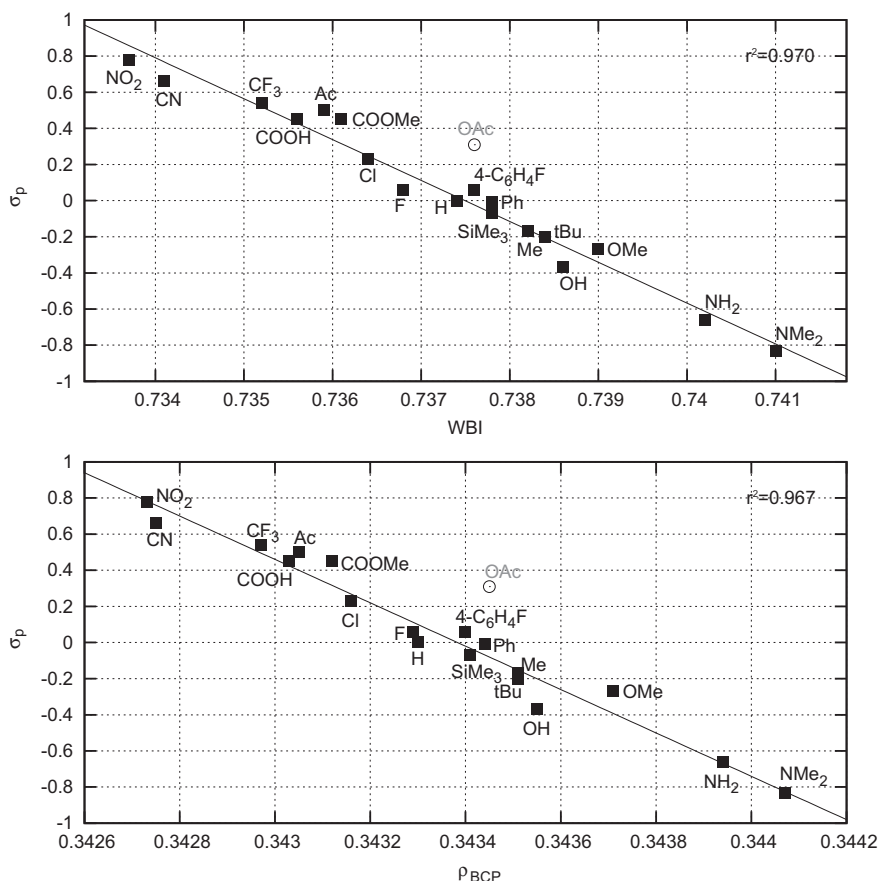
Figure 3. Relationship between the Wiberg bond indices (top) or the electron densities at the bond critical points (bottom) of the carboxylic OH bond of *para*-substituted benzoic acids and the Hammett σ_p constants. Correlation equations: $\sigma_p = -226.36\,(9.88) \cdot \text{WBI} + 166.94\,(7.28)$; $\sigma_p = -1200.61(55.64) \cdot \rho_{BCP} + 412.27\,(19.10)$. Points for the OAc substituent with the original $\sigma_p = 0.31$ are indicated in grey.
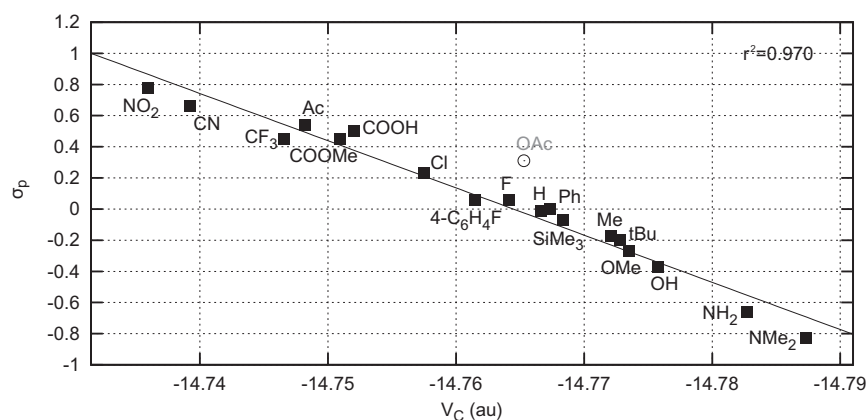

Figure 4. Relationship between the electrostatic potential of the *para* carbon of substituted benzenes and the Hammett σ_p constants. Correlation equation: $\sigma_p = 30.32\,(1.32)$ $V_C + 447.72\,(19.55)$ Point for the OAc substituent with the original $\sigma_p = 0.31$ is indicated in grey.
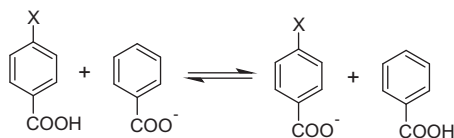

Figure 5. Proton exchange equation between the substituted and unsubstituted benzoic acids.

have been recalculated at the M06-L/6-31+G(d,p) level of theory, invoking the SMD solvation model, including one water molecule. As example, the structures of AcO-C_6H_4-COOH, AcO-C_6H_4-COO$^-$, as well as those of the unsubstituted benzoic acid and benzoate anions are shown in Figure 6, clustered with one H_2O molecule each.

The inspection of bond lengths reveals only very subtle changes in comparison of the unsubstituted and substituted pair of species. Notable is, however, the elongation of H-O bond in water, which
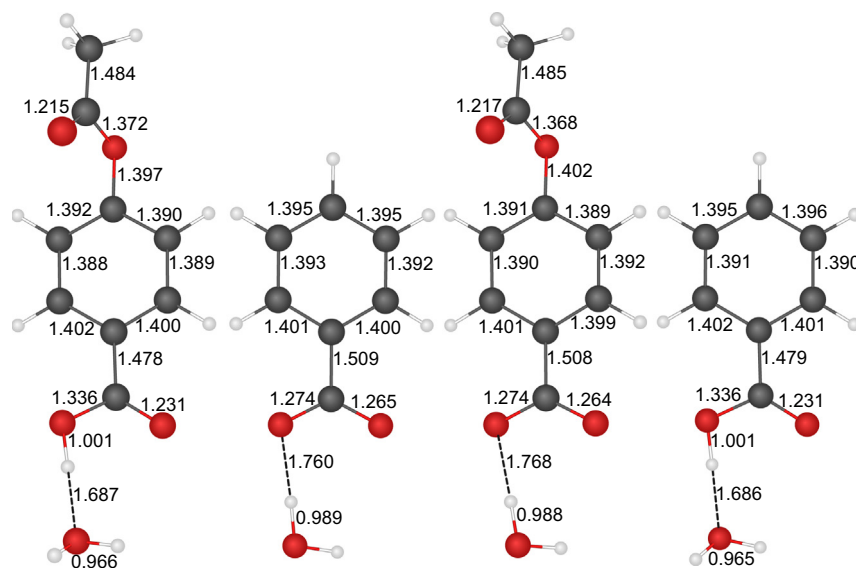
Figure 6. Computed structure of AcO-C_6H_4-COOH, C_6H_5-COO$^-$, AcO-C_6H_4-COO$^-$, and C_6H_5-COOH. Bond lengths are given in Å.
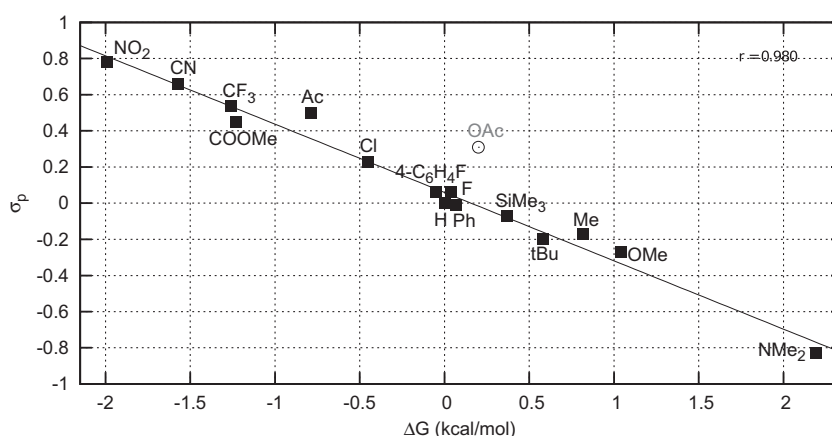

Figure 7. Relationship between the relative free energy of proton transfer. Correlation equation: $\sigma_p = -0.378\ (0.0148)\ \Delta G + 0.05915\ (0.01597)$ Point for the OAc substituent with the original $\sigma_p = 0.31$ is indicated in grey.

participates in the hydrogen bonding with the oxygen of the carboxylate group. This emphasizes the importance of the explicit water being involved in accurate water-phase proton exchange calculations. Moreover, the length of the H-bonds in benzoic acids is somewhat short in comparison to that in water dimer (1.848 Å) computed at the same level of theory.

In Figure 7 the Hammett *para* substituent constants for the training set of 15 benzoic acids are shown as the function of water-phase reaction free energies of proton exchange according to Figure 5. A reasonable linear correlation has been established with $r^2 = 0.980$ with a slope of -0.378. For the acetoxy group $\sigma_p = -0.02$ was predicted with $\Delta G = 0.20$ kcal/mol as proton exchange free energy.

For the two extrema of the σ_p scale in our dataset, reaction free energies of 2.19 and -1.99 kcal/mol were obtained for NMe_2 and NO_2, respectively in accord with the significantly smaller slope with respect to the expected experimental slope of -1. The computed ΔG values are compiled in Table 1. The low slope of the experimental pK_a-scale versus the calculated free energy of dissociation has been reported frequently by several authors. Kelly et al. reported a slope of 0.87/RT ln(10) when plotted the experimental pK_a-values of 57 acids against the acid dissociation free energies

Table 1
Water-phase reaction free energies (in kcal/mol) of proton exchange between *para*-substituted benzoic acids and the benzoate anion.

Substituent	σ_p	ΔG_{solv}
NMe_2	−0.83	2.19
OMe	−0.27	1.04
tBu	−0.20	0.56
CH_3	−0.17	0.82
$SiMe_3$	−0.07	0.37
Ph	−0.01	0.07
F	0.06	0.04
4-C_6H_4F	0.06	−0.05
Cl	0.23	−0.45
COOMe	0.45	−1.23
Ac	0.50	−0.79
CF_3	0.54	−1.26
CN	0.66	−1.57
NO_2	0.78	−1.99

employing the SM6 model. [18] Chipman evaluated acid dissociation free energies in water for 6 different acids utilizing an implicit solvation model and reported a slope of 0.51/RT ln(10) [35]. Kicić and coworkers computed dissociation free energies for a data set

containing 121 acids with a slope of 0.53/RT ln(10). Klamt et al. determined the pK_a of 64 organic and inorganic acids using the COSMO–RS method and obtained a slope of 0.58/RT ln(10). They came to the conclusion that the commonly achieved low slope is not due the weaknesses of the calculation methods, but rather the experimental pK_a-scale depends differently on the free energy of dissociation than generally assumed [36,37]. The experimental pK_a scale probably does not correspond to the free energy of dissociation in infinite dilution of an acid in pure water, which is the case for most theoretical pK_a calculations.

4. Conclusion

In this letter, a simple approach for the description of Hammett *para* substituent constant has been discussed. As a part of it, a corrected Hammett *para* constant for the acetoxy substituent has been determined. It is expected to be in the range of [−0.08, −0.02], which is somewhat more negative in comparison to that of the Ph group. The more positive σ_p of OAc, with respect to that of OMe (0.27), may be the consequence of the strong group electronegativity[38] of the former with pronounced field/inductive effect, which mostly compensates its resonance donating properties.

The results obtained by quantum chemical descriptors have been validated by invoking water-phase calculations utilizing the SMD solvation model. For the representative dataset of *para*-substituted benzoic acid high linear correlation ($r^2 = 0.98$) has been obtained with a slope of −0.378. The proposed Hammett constants for the OAc group has been evaluated by fitting the free energy of proton exchange between AcO-C_6H_4-COOH and the unsubstituted benzoate anion; which has been found to be −0.20 kcal/mol. As a result, $\sigma_p = -0.02$ has been estimated, which is in the range achieved by electronic structure calculations. Thus, according to computational data, the σ_p of the acetoxy substituent known from the literature [5,7] needs to be revised.

Acknowledgment

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cplett.2013.10.017.

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