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Reassessment of Hammett σ as an effective parameter representing intermolecular interaction energy—links between traditional and modern QSAR approaches

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ABSTRACT

The Hammett σ constant has for a long time been known to be one of most important linear free-energy related parameters that correlate with biological activity. It is a conventionally used electronic parameter in studies of enzymatic quantitative structure–activity relationships (QSAR). However, it is not necessarily obvious why σ represents variations in the free-energy change associated with the complex formation between a congeneric series of ligands with their target protein. So far, several powerful molecular calculations, such as the ab initio fragment molecular orbital (FMO) one, that are directly applicable to ligand–protein complexes have emerged. In this study, we comprehensively reevaluate experimentally derived parameter σ confirming it represents intermolecular interaction energy terms, by applying molecular orbital (MO) calculations to a simple ligand-protein complex model. The current results provide a rational and quantitative basis for bridging the gap between the traditional QSAR approach and 'the modern QSAR one', which involves the molecular calculations to evaluate the overall free-energy change for complex formation.

Hammett σ is one of the most commonly used linear free-energy related parameters in traditional quantitative structure–activity relationship (QSAR) studies.[1] The σ value is experimentally determined from the dissociation constants of substituted benzoic acids as follows[2]: $\sigma = \log (K_X/K_H)$, where K_H is the dissociation constant for benzoic acid in water at 25 °C, and K_X is the corresponding constant for *meta*- and *para*-substituted benzoic acids. Although σ frequently appears to be statistically significant in enzymatic QSAR equations,[3] it is not necessarily obvious why σ represents the variations in the free-energy change accompanying complex formation between a series of ligands with their target protein. To solve the above problem, we previously performed ab initio fragment molecular orbital (FMO) calculations for complexes of HIV-1 protease with a series of cyclic urea inhibitors,[4,5] and ones of carbonic anhydrase with substituted benezensulfonamides,[6,7] and then extracted quantum chemical electronic factors correlated with σ. The results revealed that σ is excellently correlated with the intrinsic binding and solvation energies calculated through FMO[8,9] and generalized Born/surface area (GB/SA)[10] calculations, respectively. We recently proposed linear expression by representative energy terms (LERE)-QSAR analysis involving FMO and GB/SA calculations, and demonstrated that LERE-QSAR can excellently reproduce the observed variations of the free-energy change associated with the complex formation of a series of ligands with a protein.[6,7,11,12] In combination with LERE-QSAR, careful correlation analysis of σ with representative energy terms such as intrinsic and solvation ones sometimes allows a physicochemical and consistent interpretation of the electronic mechanism. Accordingly, it is now desirable to comprehensively and quantitatively examine and confirm the electronic effects of σ on intermolecular interactions, which have not yet been investigated thoroughly so far. We carried out energy decomposition analysis (EDA) of electronic interaction energy by means of ab initio molecular orbital (MO) calculations for the complexes of a series of substituted acetophenones with *N*′-methylacetamide (NMA), which is expected to serve a simple model of a ligand–protein complex: a series of substituted acetophenones and NMA represent a congeneric series of ligands and the peptide backbone (–CONH–) in a protein, respectively. In this study, we discuss the quantitative relationships of Hammett σ with various intermolecular interaction energy terms. Although a number of papers have been published concerning MO studies on a certain relation between Hammett σ and the intermolecular energy in each particular problem,[13–30] the aim of the current study is to examine the possibility whether or not σ is logically and quantitatively replaceable by the energy terms obtained through MO calculations on ligand–protein complexes.

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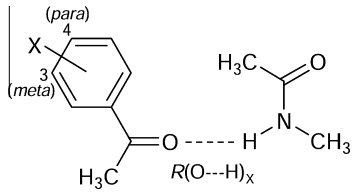

Figure 1. Complex of *N*′-methylacetamide (NMA) with X-substituted acetophenone.

A series of 41 complexes of *para*- and *meta*-substituted acetophenones with NMA, shown in Figure 1, were fully geometry-optimized using ab initio MO calculations. Substituents in acetophenone were selected so as (1) to cover a wide range of σ values, and (2) to be of relatively small size without a large number of conformational freedoms. The EDA developed by Kitaura and Morokuma[31] was performed to decompose the electronic intermolecular energy (ΔE^{HF}_{bind}) into components, that is, the electrostatic (*ES*), exchange repulsion (*EX*), polarization (*PL*), charge transfer (*CT*), and higher order mixed (*MIX*) terms. Table 1 briefly summarizes computational details as to the electronic (ΔE^{HF}_{bind}), dispersion interaction (E^{MP2}_{disp} and E^{M06-2X}_{disp}), solvation (ΔG_{sol}), and thermal terms (ΔG_{ther}), together with the results of population analysis (Δq), and Table 2 lists the Hammett σ values.[35]

To sum up so far, the overall intermolecular free-energy change (ΔG) between NMA and a substituted acetophenone is assumed to be expressible as the sum of the free-energy terms mentioned above (additivity assumption).

$$\Delta G = \Delta E^{HF}_{bind} + E_{disp} + \Delta G_{sol} + \Delta G_{ther} \quad (1)$$

It should be noted that the basis set superposition error (BSSE) correction was made for ΔE^{HF}_{bind}, but not for $\Delta E^{0}{}_{bind}{}^{HF}$ ($\Delta E^{HF}_{bind} = \Delta E^{0}{}_{bind}{}^{HF} + BSSE$, listed in Table 2). ΔE^{HF}_{bind} on the right-hand side of (Eq. (1)) is further decomposed into its components (EDA scheme).

$$\Delta E^{HF}_{bind} = ES + EX + CT + PL + MIX \quad (2)$$

As outlined below, we examined the correlation of σ with each energy term in Eqs. (1) and (2).

Figure 2a shows that σ exhibits a nice correlation (r (correlation coefficient) = 0.974) with the relative distance $\Delta R(O\cdots H)_X$ ($R(O\cdots H)_X - R(O\cdots H)_{X=H}$, as can be seen in Fig. 1). This result suggests that the introduction of an electron-donating group facilitates the tight complex formation and facilitates the intermolecular electron transfer from X-substituted acetophenone to NMA more efficiently than a withdrawing one. In fact, Figure 2b shows that the charge difference, Δq, accompanying the complex formation decreases, as σ increases. Figure 2a and b suggests that σ can quantitatively represent the association/dissociation energy change between a hydrogen-bonding donor (NMA) and an acceptor (substituted acetophenone), as being consistent with papers published so far.[13,16,19,21,24,26,28]

Like ΔE^{HF}_{bind}, all the EDA components listed in Table 2 show significant correlations with σ Figure 3a shows plots of ΔE^{HF}_{bind} and each EDA component against σ. The slope and variance show that major contributors to the stabilization and destabilization of ΔE^{HF}_{bind} are *ES* and *EX*. *ES* exhibits the steepest slope (1.36 kcal/mol) and variance (2.89×10^{-1} kcal^2/mol^2), and governs the variation of ΔE^{HF}_{bind} most dominantly. *EX* exhibits the second largest variance (5.38×10^{-2} kcal^2/mol^2), and a negative slope (−0.59 kcal/mol): introduction of an electron-withdrawing group leads to the destabilization of ΔE^{HF}_{bind}. The negative dependence of *EX* on σ is probably due to that *EX* increases (destabilization), as $R(O\cdots H)$ decreases. The variances of the rest of the EDA components (*CT*, *PL* and *MIX*) are much smaller than those of *ES* and *EX*, showing their smaller contributions to ΔE^{HF}_{bind}. As expected, *BSSE* exhibits a negative correlation of $r = -0.939$ with $\Delta E^{0}{}_{bind}{}^{HF}$.

Figure 3b shows plots of $\Delta E^{0}{}_{bind}{}^{HF}$, ΔE^{MP2}_{bind}, and ΔE^{M06-2X}_{bind} against σ. The slope with the 95% confidence interval of $\Delta E^{0}{}_{bind}{}^{HF}$ (1.24 ± 0.087) lies between those of ΔE^{MP2}_{bind} and ΔE^{M06-2X}_{bind} (1.19 ± 0.090 and 1.31 ± 0.092, respectively), indicating the slope values of the three lines are nearly the same. This suggests that the contribution of the stabilization due to the dispersion energy ($E_{disp} = E_{bind}{}^{MP2(M06\text{-}2X)} - \Delta E^{0}{}_{bind}{}^{HF}$) can be approximately considered to be nearly constant (∼−2 kcal/mol), regardless of any variation in σ. Although qualitatively and tentatively this fact may be explainable by the classical London's formula[36]: $E^{CL}_{disp} = -(3/2)\cdot\alpha_1\cdot\alpha_2\cdot(I_1\cdot I_2)/[(I_1+I_2)R^6_{eff}]$, where α and I are the

Table 1
Computational details

Type of calculation	Method/basis	Quantities[a]
Geometry optimization[b]	HF/6-31G(d,p)	$\Delta R(O\cdots H)_X$[c]
EDA[b]	HF/6-31G(d,p) MP2/6-31G(d,p) //HF/6-31G(d,p)	$\Delta E^{0}{}_{bind}{}^{HF}$, *ES*, *EX*, *CT*, *PL*, *MIX*, *BSSE*[d] ΔE^{MP2}_{bind}, E^{MP2}_{disp}[f]
Dispersion interaction energy[e]	M06-2X/6-31G(d,p) //HF/6-31G(d,p)	ΔE^{M06-2X}_{bind}, E^{M06-2X}_{disp}[g]
Solvation energy[e]	CPCM/HF/6-31G(d,p)	ΔG_{sol}[h]
Thermal energy[e]	HF/6-31G(d,p)	ΔG_{ther}[i]
Mulliken population analysis[b]	HF/6-31G(d,p)	Δq[j]

[a] When a complex can take multiple low-energy conformers, the average energy of the Boltzmann distribution among low-energy conformers was used in the regression analyses.
[b] Performed using GAMESS.[32]
[c] $\Delta R(O\cdots H)_X = R(O\cdots H)_X - R(O\cdots H)_{X=H}$. See text.
[d] The basis set superposition error (BSSE) was estimated with the counterpoise method.[33]
[e] Performed using Gaussian09.[34]
[f] $E^{MP2}_{disp} = \Delta E^{MP2}_{bind} - \Delta E^{0}{}_{bind}{}^{HF}$.
[g] $E^{M06-2X}_{disp} = \Delta E^{M06-2X}_{bind} - \Delta E^{0}{}_{bind}{}^{HF}$.
[h] $\Delta G_{sol} = \Delta G_{bind}{}^{HF}$(solvent) − $\Delta E^{0}{}_{bind}{}^{HF}$(vacuum). Solvents: heptane (dielectric constant = 1.92), ether (4.34), *n*-octanol (9.86), and water (78.39).
[i] Calculated from vibrational, rotational, and translational partition functions of the reactants and product (complex) at 298 K. The vibrational contribution was calculated with the normal mode analysis, and the rotational and translational ones were calculated according to the classical statistical-mechanical theory.
[j] $\Delta q = \Sigma q_i(X\text{-}C_6H_4\text{-}COCH_3)^{complex}$. q_i denotes the Mulliken net atomic charge on the i-th atom. Summation is over atoms within X-substituted acetophenone in the complex state.

Table 2
Hammett σ and energy terms, $\Delta E^0{}_{bind}{}^{HF}$, *BSSE*, E_{disp} ΔG_{sol}, and ΔG_{ther}[a]

No.	−X	σ[b]	$\Delta E^0{}_{bind}{}^{HF}$[c]	*BSSE*	E_{disp}		ΔG_{sol}				ΔG_{ther}
					MP2	M06-2X	Heptane	Ether	*n*-Octanol	Water	
1	4-N(CH_3)$_2$	−0.83	−6.58	1.42	−2.00	−1.81	2.09	3.69	4.53	4.99	1.98
2	4-NHCH_3	−0.70	−6.52	1.42	−1.98	−1.80	2.05	3.65	4.43	4.94	1.94
3	4-NH_2	−0.66	−6.38	1.40	−1.96	−1.79	2.06	3.53	4.43	4.84	1.94
4	4-NHC_2H_5	−0.61	−6.55	1.42	−1.98	−1.81	2.09	3.63	4.44	4.95	1.95
5	4-OH	−0.37	−5.96	1.37	−1.97	−1.76	1.92	3.39	4.14	4.56	1.95
6	4-NHOH	−0.34	−6.09	1.37	−1.98	−1.78	1.98	3.43	4.25	4.66	1.94
7	4-OCH_3	−0.27	−6.07	1.38	−1.98	−1.77	1.99	3.41	4.28	4.65	1.95
8	4-OC_2H_5	−0.24	−6.10	1.38	−1.97	−1.77	2.00	3.47	4.25	4.66	1.95
9	4-CH_3	−0.17	−5.89	1.36	−1.93	−1.70	1.89	3.31	4.04	4.53	1.95
10	4-CH_2CH_3	−0.15	−5.90	1.36	−1.91	−1.69	1.93	3.35	4.21	4.54	1.95
11	4-CH_2OCH_3	0.01	−5.81	1.35	−1.92	−1.68	1.92	3.32	4.11	4.50	1.93
12	4-F	0.06	−5.48	1.32	−1.98	−1.73	1.85	3.18	3.90	4.23	1.93
13	4-CH_2Cl	0.12	−5.43	1.32	−1.97	−1.69	1.80	3.12	3.82	4.21	1.93
14	4-SH	0.15	−5.60	1.33	−1.97	−1.73	1.85	3.22	3.94	4.31	1.94
15	4-Cl	0.23	−5.29	1.32	−2.04	−1.75	1.77	3.11	3.77	4.09	1.93
16	4-CHO	0.42	−5.05	1.23	−1.96	−1.60	1.71	2.96	3.65	3.93	1.91
17	4-$COCH_3$	0.50	−5.23	1.31	−2.05	−1.73	1.78	3.04	3.75	4.11	1.92
18	4-CF_3	0.54	−5.04	1.30	−2.06	−1.75	1.71	2.90	3.63	3.93	1.93
19	4-CN	0.66	−4.72	1.24	−2.04	−1.70	1.63	2.86	3.45	3.75	1.90
20	4-NO_2	0.78	−4.57	1.28	−2.24	−1.82	1.59	2.74	3.39	3.59	1.91
21	H	0.00	−5.70	1.33	−1.93	−1.68	1.91	3.26	4.07	4.46	1.94
22	3-N(CH_3)$_2$	−0.16	−5.79	1.34	−2.04	−1.74	1.98	3.37	4.25	4.50	1.95
23	3-NHCH_3	−0.21	−5.85	1.34	−2.09	−1.77	1.99	3.40	4.23	4.56	1.94
24	3-NH_2	−0.16	−5.78	1.33	−2.06	−1.76	1.95	3.36	4.16	4.50	1.93
25	3-NHC_2H_5	−0.24	−5.87	1.33	−2.09	−1.78	1.98	3.39	4.19	4.59	1.94
26	3-OH	0.12	−5.51	1.31	−2.07	−1.76	1.86	3.21	3.95	4.30	1.93
27	3-NHOH	−0.04	−5.72	1.33	−2.06	−1.77	1.92	3.32	4.08	4.47	1.94
28	3-OCH_3	0.12	−5.63	1.33	−2.07	−1.76	1.92	3.29	4.10	4.42	1.94
29	3-OC_2H_5	0.10	−5.68	1.33	−2.08	−1.77	1.93	3.31	4.15	4.46	1.94
30	3-CH_3	−0.07	−5.78	1.34	−1.97	−1.70	1.89	3.30	4.06	4.48	1.94
31	3-CH_2CH_3	−0.07	−5.79	1.35	−1.98	−1.72	1.92	3.31	4.07	4.50	1.95
32	3-CH_2OCH_3	0.08	−5.79	1.34	−1.95	−1.68	1.94	3.32	4.11	4.50	1.95
33	3-F	0.34	−5.28	1.30	−2.04	−1.75	1.79	3.07	3.80	4.14	1.93
34	3-CH_2Cl	0.11	−5.40	1.32	−1.97	−1.69	1.80	3.10	3.83	4.18	1.93
35	3-SH	0.25	−5.40	1.32	−1.95	−1.67	1.81	3.13	3.85	4.22	1.91
36	3-Cl	0.37	−5.21	1.31	−2.01	−1.72	1.76	3.06	3.75	4.08	1.93
37	3-CHO	0.35	−5.18	1.27	−1.91	−1.61	1.73	2.98	3.72	4.00	1.92
38	3-$COCH_3$	0.38	−5.34	1.31	−1.96	−1.67	1.82	3.11	3.89	4.16	1.92
39	3-CF_3	0.43	−5.12	1.30	−1.99	−1.70	1.73	3.00	3.70	3.99	1.93
40	3-CN	0.56	−4.82	1.27	−1.96	−1.66	1.64	2.84	3.48	3.75	1.91
41	3-NO_2	0.71	−4.72	1.28	−2.07	−1.73	1.63	2.81	3.50	3.73	1.91

[a] In kcal/mol.
[b] Taken form Ref. 35.
[c] $\Delta E^{HF}_{bind} = \Delta E^0{}_{bind}{}^{HF} + BSSE$.

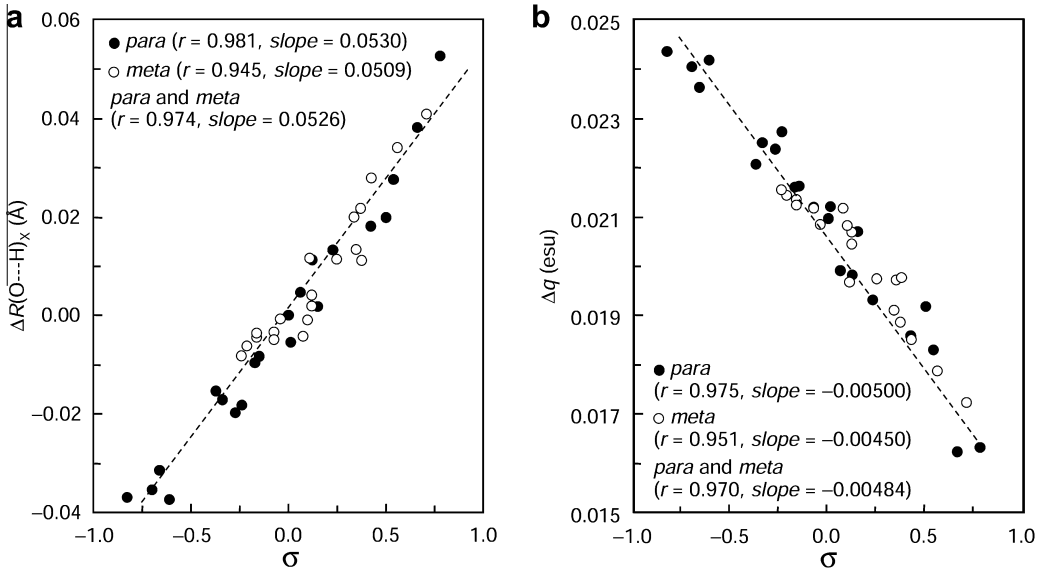

Figure 2. Plots of Hammett σ with (a) the relative intermolecular distance ($\Delta R(O\cdots H)_X$): $R(O\cdots H)_{X=H}$ = 2.16 Å, and (b) charge difference accompanied with complex formation (Δq): $\Delta q_{X=H}$ = 0.0209 esu.

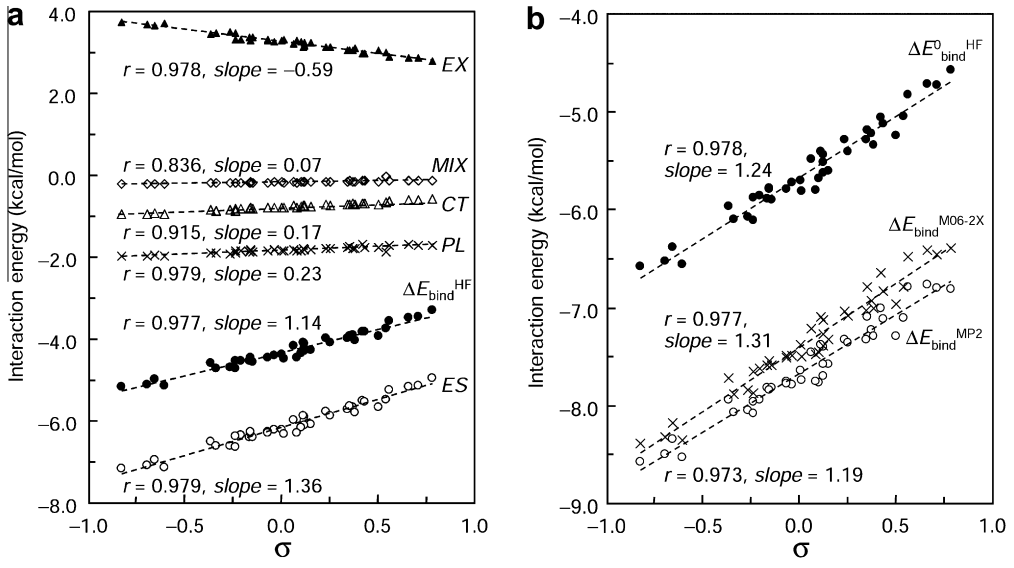

Figure 3. Plots of Hammett σ with (a) the electronic interaction energy terms ΔE_{bind}^{HF} and EDA components, and (b) $\Delta E^0{}_{bind}{}^{HF}$, ΔE_{bind}^{MP2}, and ΔE_{bind}^{M06-2X}.

polarizability and ionization potentials, respectively, subscripts 1 and 2 denote NMA and a substituted acetophenone, respectively, and R_{eff} represents an effective intermolecular distance between NMA and the substituted acetophenone. R_{eff} can be approximately expressed as $\Delta R(O\cdots H) + C$ (note $R_{eff}{}^6 \approx C^6 + 6\,\Delta R(O\cdots H)\,C^5$, when $\Delta R(O\cdots H) \ll C$ (constant distance)). We obtain $E_{disp}^{CL} \approx -(3/4)\cdot\alpha_1\cdot\alpha_2\cdot(I_2/R_{eff}^6)$ assuming $I_1 \approx I_2$. This assumption is probably justifiable, because the HOMO levels of NMA and substituted acetophenones are close to each other [at −10.5 and −7.7 ∼ −10.2 eV (HF/6-31G(d,p))]. Two positive correlations are observed (1) between σ and $R_{eff}{}^6$ ($R_{eff}{}^6 = a_1\cdot\sigma + b_1$, $(b_1/a_1) > 6$, $r = 0.97$) and (2) between σ and I_2 [estimated from the HOMO energy: $I_2 = a_2\cdot\sigma + b_2$, $(b_2/a_2) = 5.6$, $r = 0.90$]. On the condition that α_2 is nearly constant within the range between $\sigma = \pm1$, E_{disp}^{CL} does not vary with σ greatly, probably because of $b_1 \gg |a_1\cdot\sigma|$ and $b_2 \gg |a_2\cdot\sigma|$ as well as the positive dependence of I_2 and $R_{eff}{}^6$ (numerator and denominator of E_{disp}^{CL}, respectively) on σ. Thus, E_{disp}^{CL} probably takes a nearly constant value, $-(3/4)\cdot\alpha_1\cdot\alpha_2\cdot(b_2/b_1)$.

Figure 4 shows plots of the solvation free-energy term (ΔG_{sol}) for four different solvent systems against σ As well as ΔE_{bind}^{HF} in vacuum ΔG_{sol} in the four solvents correlates linearly with σ ($r \geq 0.946$). According to the Born solvation model,[37] the larger the dielectric constant of solvent is, the greater the desolvation energy is. This is probably reflected by differences in the slopes and intercepts among the four lines shown in Figure 4. The negative dependence of ΔG_{sol} on σ suggests that the desolvation energy of the carbonyl moiety in a substituted acetophenone counteracts the intrinsic binding energy of the same moiety with NMA. In fact, high anti-correlations are found between $\Delta E^0{}_{bind}{}^{HF}$and ΔG_{sol} ($r = -0.978$ in heptane; −0.990 in ether; −0.981; in *n*-octanol; and −0.995 in water).

There is a statistically significant but poor correlation ($r = 0.855$) between the thermal free-energy term (ΔG_{ther}) and σ. The variance (2.59×10^{-4} kcal^2/mol^2) of ΔG_{ther} is so negligible that ΔG_{ther} is considered to be nearly constant (∼1.9 kcal/mol) within the range of variation in σ.

Table 3 summarizes the correlation equations of σ with overall free-energy change ΔG in (Eq. (1)). The correlation equations listed in Table 3 show that ΔG behaves linearly with σ, which is an electronic parameter originally not intended to represent intermolecular energy. It is noteworthy that as the dielectric constant of the solvent increases, (1) the slope (a) of ΔG in the correlation equations decreases, and (2) the intercept (*const*) increases, because the destabilizing contribution of ΔG_{sol} counteracts the stabilizing one of $\Delta E^0{}_{bind}{}^{HF}$ linearly and the latter contribution overwhelms the former one. Needless to say, the numerical values, a and *const*

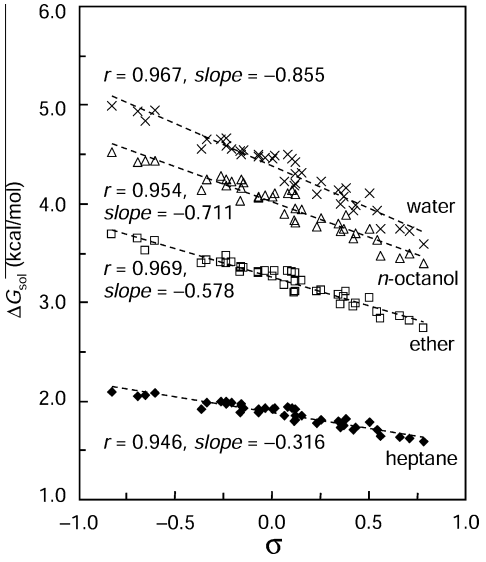

Figure 4. Plots of of Hammett σ with the solvation energy term ΔG_{sol}.

Table 3
Correlation between the overall free-energy change ΔG and Hammett σ. $\Delta G^a = a\ \sigma + const$ ($n = 41$)

solvent	Dielectric constant	*a*	*const*	r^b
Vacuum[c]	1.00	1.168	−4.126	0.978
Heptane	1.92	0.851	−2.244	0.980
Ether	4.34	0.591	−0.871	0.970
n-Octanol	9.86	0.458	−0.106	0.943
Water	78.39	0.313	0.258	0.940

[a] Calculated by (Eq. (1)) ($E_{disp} = E_{disp}{}^{M06\text{-}2X}$).
[b] Correlation coefficient.
[c] $\Delta G_{sol} = 0$ kcal/mol.

(and those described so far), vary depending on the choice of basis sets in MO calculations. However, the inequality relations, $a_1 > a_2 > a_3 > a_4 > a_5$ and $const_1 < const_2 < const_3 < const_4 < const_5$, do not vary (1 = vacuum, 2 = heptane, 3 = ether, 4 = *n*-octanol, and 5 = water), when a basis set different from the current one (6-31G(d,p)) is used.

The sum of σ_m and σ_p has often been assumed to represent the electronic effects of *meta*- and *para*-substituents attached to a benzene ring,[38] although the additivity of σ_m and σ_p is not obvious in terms of an intermolecular interaction. The difference of the relative electronic interaction energy ($\Delta E^0{}_{bind}{}^{HF}{}_{(mp)}$) of 49 di-substituted acetophenones at the *meta*- and *para*-positions with NMA from that of the unsubstituted acetophenone ($\Delta E^0{}_{bind}{}^{HF}{}_{(HH)}$) [$\Delta E^0{}_{bind}{}^{HF}{}_{(mp)} - \Delta E^0{}_{bind}{}^{HF}{}_{(HH)}$] is linear with ($\sigma_m + \sigma_p$) ($r = 0.989$, *slope* = 1.03). This result guarantees the approximation, $\sigma_{mp} = \sigma_m + \sigma_p$.

In summary, the electronic intermolecular interaction energy (ΔE^{HF}_{bind}) along with all the EDA components (*ES*, *EX*, *CT*, *PL*, and *MIX*) show nice correlations with σ. Among the components, *ES* is the largest contributor to the stabilization of ΔE^{HF}_{bind}. The dispersion energy term (E_{disp}) remains nearly constant with σ. The overall free-energy change (ΔG) is expressed as a simple linear equation of σ. The anti-correlation between the solvation energy (ΔG_{sol}) and $\Delta E^0{}_{bind}{}^{HF}$ terms suggests that the desolvation of the carbonyl moiety in a substituted acetophenone accompanying the complex formation counteracts ΔE^{HF}_{bind}. In the case of the intermolecular interaction of carbonic anhydrase with a congeneric series of inhibitors,[6,7] the excellent linearity of σ with ΔG_{sol} and $\Delta E^0{}_{bind}{}^{HF}$ indicates two possibilities, at least, as to the most critical energy term that governs the overall free-energy change. The traditional QSAR equation shows an excellent linearity between σ and log ($1/K_i$): K_i inhibitory equilibrium constant, but does not allow identification of the activity-determining factor. The LERE-QSAR one unequivocally shows that the stabilization due to ΔG_{sol} overwhelms the destabilization due to ΔE^{HF}_{bind}, which shows a nearly perfect anti-correlation with ΔG_{sol}. Thus, careful correlation analysis of σ with representative intermolecular energy terms can provide clues for a deeper understanding of the complex formation mechanism.

In conclusion, the current results suggest that the intermolecular energy terms obtained through molecular calculations such as the FMO one for full complex structures of a congeneric series of ligands with a protein basically follow the LFEP (linear free-energy principle), as represented by Hammett σ, and can bridge the gap between the Hansch-Fujita type traditional and modern QSAR approaches, although several challenging problems regarding the physicochemical nature of protein–ligand interactions remain to be solved.

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