

Theoretical prediction of linear free energy relationships using proton nucleomers

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Values of σ and σ^+ , for use in linear free energy relationships, are determined for *para* hydrogen atoms having nuclear charges other than 1 (nucleomers). Hammett ρ values for a variety of free energies of activation, reaction, and other extrathermodynamic properties (e.g., vibrational frequencies) are computed therefrom and compared to those computed using typical *para* functional groups. The nucleomer correlations show excellent qualitative agreement with standard correlations but the quantitative agreement is less good, typically underestimating the standard ρ -value by 10–60%. Copyright © 2007 John Wiley & Sons, Ltd.

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INTRODUCTION

Linear free energy relationships have a long history in the study of mechanistic organic chemistry.^[1–10] In early work, Hammett proposed that the effects of aryl substituents on benzoic acid ionization constants would correlate linearly with the effects of those same substituents on other reactions of substituted aromatics. That is, he suggested the prevalence of relationships of the form

$$\log\left(\frac{K_X^o}{K_H^o}\right) = \sigma_X \rho \quad (1)$$

where K_X is the equilibrium (or rate) constant for some reaction of an aromatic ring substituted with substituent X , and the specification of X includes whether it is *ortho*, *meta*, or *para* to the reacting functionality. The slope of the linear relationship, ρ , is characteristic for the reaction under study once substituent constants σ_X have been chosen. Hammett chose these constants so as to make $\rho = 1$ for the ionization constants of substituted benzoic acids in aqueous solution and as such this reaction defines the so-called σ scale.

Subsequent studies by Brown *et al.*^[11,12] emphasized that the influence of substituents on aromatic reactions typically involves a balance between inductive effects and resonance effects, and these workers pointed out that the σ scale was more appropriate for reactions dominated by the former (because of the nature of its defining reaction, benzoic acid ionization). They proposed an equivalent relationship for cases where resonance effects were dominant,

$$\log\left(\frac{K_X^o}{K_H^o}\right) = \sigma_X^+ \rho \quad (2)$$

where the values of the σ^+ scale were defined for *para* substituents so as to construct a linear free energy relationship for substituted cumyl chloride ionizations in aqueous acetone.

Note that the ratios of logarithms of equilibrium or rate constants appearing in Eqns 1 and 2 can be related to free energy changes according to

$$\Delta G_X^o - \Delta G_H^o = -2.303RT \log\left(\frac{K_X^o}{K_H^o}\right) \quad (3)$$

and

$$\Delta G_X^{\ddagger,o} - \Delta G_H^{\ddagger,o} = -2.303RT \log\left(\frac{k_X^o}{k_H^o}\right) \quad (4)$$

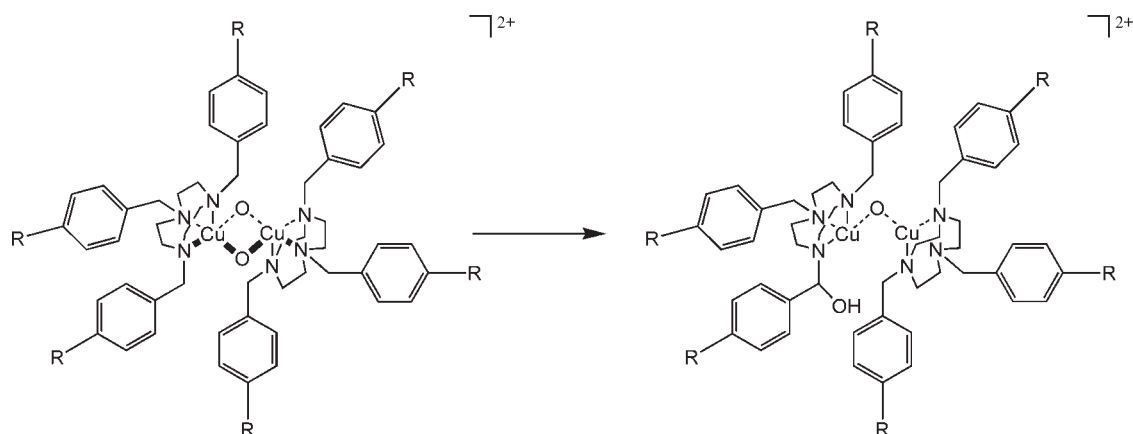
where R is the universal gas constant, T is temperature, and the relationship in Eqn 4 involving free energies of activation derives from transition-state (TS) theory.^[13]

Operationally, determination of experimental ρ values is accomplished by (i) the synthesis of various substituted versions of some substrate of interest, (ii) the measurement of the relevant equilibrium or rate constants (or possibly other non-free-energy related properties, although any observed linear relationship is then extrathermodynamic in nature), and (iii) the regression of the experimental data on tabulated σ or σ^+ values. The same process can also be undertaken within the context of a theoretical modeling study. That is, any process being studied computationally can be repeated with various substituents and a ρ -value determined for the level of theory being used.

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Scheme 1. Benzylic C–H bond activation by supported Cu_2O_2^+ core.

Comparing computational and experimental ρ values can be useful for validating the theoretical model, particularly for cases where free energies of activation are being computed in order to gain insight into the nature of TS structures, the characterization of which is certainly one of the most powerful aspects of a modeling study. Thus, for example, one of us computed TS structures for the reaction shown in Scheme 1 using a mixed quantum-mechanical/molecular mechanical protocol,^[14,15] the reaction in question involves a mechanistically interesting C–H bond activation by a Cu_2O_2^+ core and had been studied experimentally by Mahapatra *et al.*^[16] Analysis of the computed rate-determining TS electronic structures suggested that the nature of the reaction was best described as a hydrogen-atom transfer from a benzylic carbon to a core oxygen atom (as opposed to, e.g., proton-coupled electron transfer or hydride transfer between these atoms). To further validate this interpretation, Cramer *et al.*^[14,15] computed ρ by regression against σ values for $\text{R} = \text{H}, \text{CF}_3,$ and OH and showed that there was indeed good agreement between the computed values and those measured experimentally by Mahapatra *et al.*^[16] Given that the size and complexity of the molecules in Scheme 1 had imposed restrictions on the possible theoretical models that could be practically applied, this validation step was especially useful.

In sufficiently complex theoretical models, the computation of a large number of substituted systems can be quite tedious (we make this point with all due humility, noting that in most instances the computational tedium pales by comparison to its experimental counterpart). There is, however, a simplification that is only available to the alchemically minded theorist. When inductive effects are dominant, one may in principle introduce such effects without changing the atomic composition of the unsubstituted aromatic ring by adjusting the nuclear charge of the parent proton. Thus, increasing the proton charge to a value fractionally greater than one should inductively mimic the substitution of an electron-withdrawing group at that position, and reduction of the nuclear charge to a value fractionally less than one should mimic substitution by an electron-donating group. In this work, we address the utility of such an approach by examining its quantitative performance against full molecular calculations for the model reactions and properties listed in Fig. 1. Thus, we establish σ values for H atoms having variable nuclear charge (which we call hydrogen nucleomers) and explore whether these values are as transferable to a wide variety of situations as are those already tabulated for synthetically

accessible functional groups. We note that other theoretical approaches to replace standard σ values have been reported. For instance, Girones and Ponec^[17] have suggested their replacement with fragment quantum self-similarity measures in quantitative structure-activity relationships.

COMPUTATIONAL METHODS

All molecular geometries were fully optimized at four different levels of theory. In three cases, the B3LYP functional^[18–21] was employed with different basis sets, namely, MIDI!,^[22] 6-31+G(d,p),^[23] and aug-cc-pVDZ.^[24] For the remaining case the PBE functional^[25] was employed with the 6-31+G(d,p) basis set. Analytical vibrational frequencies were computed to verify the nature of all stationary points as either minima or TS structures; however, Hammett relationships involving energies were evaluated using the *electronic* energies in order to avoid possible complications associated with using the rigid-rotator quantum-mechanical-harmonic-oscillator approximation for thermal contributions to free energies.^[13]

For cases involving proton nucleomers, that is, molecules where the nuclear charge on an aryl proton was varied from its normal value of 1.0, we generally used the frozen geometry of the corresponding normal systems. In select instances, however, we reoptimized each nucleomer structure, for example, to compute adiabatic ionization potentials or variations in carbonyl vibrational frequencies.

Calculations were performed using the Gaussian03,^[26] MOLCAS v. 6.4,^[27] and Turbomole^[28] suites of electronic structure programs. In the cases of MOLCAS and Turbomole, the atomic charge can be varied as part of normal input. In the case of Gaussian03, a proton with a non-unit nuclear charge is most easily created by defining a ghost atom (not a hydrogen atom) to exist at the appropriate coordinates carrying the same basis functions as those defined for an H atom. In addition, a point charge is placed at the ghost atom's position with a value chosen so that the sum of the point charge and the molecular charge is the desired change in nucleomer charge. Thus, for example, the *para*-H nucleomer of benzaldehyde having additional charge +0.1 could be constructed as the 4-dehydrobenzaldehyde anion with a *para* ghost atom and point charge of magnitude +1.1 at the ghost atom's position. This procedure works for any nucleus.^[29,30] However, to avoid convergence difficulties

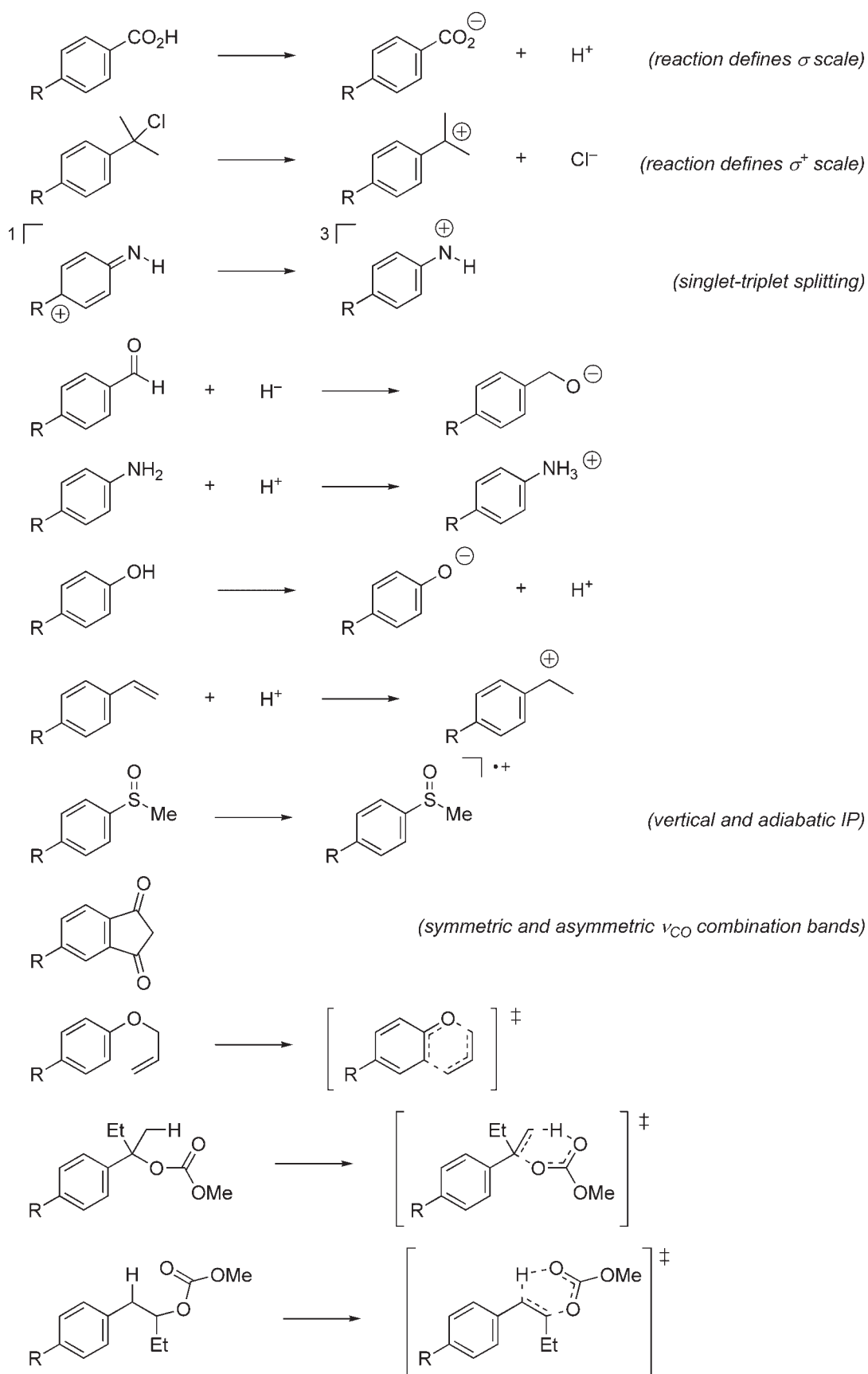


Figure 1. Reactions and molecules for which energy changes and other properties were computed for R = NH₂, OH, Me, Cl, CN, NO₂, and H atoms having nuclear charges of 0.80, 0.85, 0.90, 0.95, 1.00, 1.05, 1.10, 1.15, and 1.20 a.u.

Table 1. R and ρ' values versus σ and σ^+ for various reactions from different protocols

System/theory	p -substituent	σ		σ^+	
		ρ'	R	ρ'	R
Benzoic acid ionization^a					
B3LYP/MIDI!	Actual	-12.2	-0.976	-7.9	-0.925
	$H \pm \Delta Z$	-12.2	-1.000	-12.6	-1.000
/6-31+G(d,p)	Actual	-12.5	-0.976	-8.0	-0.917
	$H \pm \Delta Z$	-12.5	-1.000	-11.8	-1.000
/aug-cc-pVDZ	Actual	-12.4	-0.978	-7.95	-0.918
	$H \pm \Delta Z$	-12.4	-1.000	-11.8	-1.000
PBE/6-31+G(d,p)	Actual	-12.7	-0.980	-8.2	-0.925
	$H \pm \Delta Z$	-12.7	-1.000	-11.8	-1.000
Cumyl chloride ionization^b					
B3LYP/MIDI!	Actual	22.0	0.974	15.2	0.991
	$H \pm \Delta Z$	14.8	1.000	15.3	1.000
/6-31+G(d,p)	Actual	22.1	0.986	15.0	0.984
	$H \pm \Delta Z$	15.9	1.000	15.0	1.000
/aug-cc-pVDZ	Actual	21.7	0.986	14.8	0.985
	$H \pm \Delta Z$	15.6	1.000	14.8	1.000
PBE/6-31+G(d,p)	Actual	21.6	0.981	14.8	0.985
	$H \pm \Delta Z$	15.9	1.000	14.8	1.000
Arylnitrenium S–T splitting					
B3LYP/MIDI!	Actual	-6.7	-0.938	-4.8	-0.984
	$H \pm \Delta Z$	-2.2	-1.000	-2.2	-1.000
/6-31+G(d,p)	Actual	-7.2	-0.937	-5.2	-0.979
	$H \pm \Delta Z$	-2.4	-1.000	-2.3	-1.000
/aug-cc-pVDZ	Actual	-7.0	-0.930	-5.0	-0.975
	$H \pm \Delta Z$	-2.4	-1.000	-2.2	-1.000
PBE/6-31+G(d,p)	Actual	-7.1	-0.922	-5.1	-0.970
	$H \pm \Delta Z$	-2.3	-1.000	-2.2	-1.000
Benzaldehyde hydride affinity					
B3LYP/MIDI!	Actual	-14.9	-0.979	-9.65	-0.928
	$H \pm \Delta Z$	-13.4	-1.000	-13.9	-1.000
/6-31+G(d,p)	Actual	-16.1	-0.976	-10.4	-0.918
	$H \pm \Delta Z$	-14.1	-1.000	-13.3	-1.000
/aug-cc-pVDZ	Actual	-15.9	-0.979	-10.2	-0.922
	$H \pm \Delta Z$	-13.9	-1.000	-13.2	-1.000
PBE/6-31+G(d,p)	Actual	-17.8	-0.973	-11.5	-0.917
	$H \pm \Delta Z$	-14.7	-1.000	-13.6	-1.000
Aniline basicity					
B3LYP/MIDI!	Actual	15.1	0.993	10.0	0.962
	$H \pm \Delta Z$	12.7	1.000	13.1	1.000
/6-31+G(d,p)	Actual	16.5	0.989	10.7	0.943
	$H \pm \Delta Z$	14.8	1.000	14.1	1.000
/aug-cc-pVDZ	Actual	16.2	0.965	10.5	0.867
	$H \pm \Delta Z$	15.0	1.000	14.3	1.000
PBE/6-31+G(d,p)	Actual	16.6	0.985	10.8	0.937
	$H \pm \Delta Z$	15.1	1.000	14.0	1.000
Phenol acidity					
B3LYP/MIDI!	Actual	-20.7	-0.962	-13.2	-0.900
	$H \pm \Delta Z$	-15.4	1.000	-15.9	-1.000
/6-31+G(d,p)	Actual	-21.0	-0.951	-13.3	-0.883
	$H \pm \Delta Z$	-15.2	-1.000	-14.4	-1.000
/aug-cc-pVDZ	Actual	-21.6	-0.929	-13.8	-0.871
	$H \pm \Delta Z$	-15.2	-1.000	-14.5	-1.000

(Continues)

Table 1. (Continued)

System/theory	<i>p</i> -substituent	σ		σ^+	
		ρ'	<i>R</i>	ρ'	<i>R</i>
PBE/6-31+G(d,p)	Actual	-20.8	-0.953	-13.2	-0.885
	H \pm ΔZ	-15.5	-1.000	-14.4	1.000
Styrene proton affinity B3LYP/MIDI!	Actual	24.4	0.976	17.0	0.992
	H \pm ΔZ	16.0	1.000	16.6	1.000
/6-31+G(d,p)	Actual	24.5	0.986	16.7	0.984
	H \pm ΔZ	17.1	1.000	16.2	1.000
/aug-cc-pVDZ	Actual	25.8	0.949	17.6	0.949
	H \pm ΔZ	16.8	1.000	16.0	1.000
PBE/6-31+G(d,p)	Actual	23.6	0.982	16.2	0.985
	H \pm ΔZ	17.1	1.000	15.9	1.000
Methylphenylsulfoxide IP ^c B3LYP/MIDI!	Actual	17.9	0.979	12.4	0.991
	H \pm ΔZ	18.0	0.968	12.5	0.981
/6-31+G(d,p)	Actual	13.3	1.000	13.7	1.000
	H \pm ΔZ	13.3	1.000	13.8	1.000
/aug-cc-pVDZ	Actual	19.5	0.981	13.2	0.978
	H \pm ΔZ	19.4	0.978	13.2	0.977
PBE/6-31+G(d,p)	Actual	14.7	1.000	14.0	1.000
	H \pm ΔZ	14.7	1.000	14.0	1.000
/aug-cc-pVDZ	Actual	20.7	0.938	14.2	0.945
	H \pm ΔZ	18.8	0.979	12.8	0.978
PBE/6-31+G(d,p)	Actual	14.4	1.000	13.7	1.000
	H \pm ΔZ	14.4	1.000	13.7	1.000
5,7-Indanedione $\nu_{C=O}$ ^d B3LYP/MIDI!	Actual	18.7	0.969	12.9	0.983
	H \pm ΔZ	19.0	0.970	13.1	0.980
/6-31+G(d,p)	Actual	15.2	1.000	14.2	1.000
	H \pm ΔZ	15.3	1.000	14.2	1.000
/aug-cc-pVDZ	Actual	6.8	0.985	4.6	0.988
	H \pm ΔZ	7.2	0.985	4.9	0.984
PBE/6-31+G(d,p)	Actual	3.9	1.000	4.0	1.000
	H \pm ΔZ	3.8	0.999	3.9	0.999
/aug-cc-pVDZ	Actual	13.7	0.994	9.3	0.986
	H \pm ΔZ	12.9	0.997	8.6	0.980
PBE/6-31+G(d,p)	Actual	7.1	0.998	6.7	0.998
	H \pm ΔZ	7.3	0.999	6.9	0.999
/aug-cc-pVDZ	Actual	13.1	0.992	8.9	0.990
	H \pm ΔZ	12.4	0.998	8.4	0.985
PBE/6-31+G(d,p)	Actual	7.0	0.993	6.7	0.993
	H \pm ΔZ	7.2	0.997	6.9	0.997
/aug-cc-pVDZ	Actual	12.7	0.987	8.7	0.988
	H \pm ΔZ	12.4	0.995	8.4	0.985
Claisen rearrangement B3LYP/MIDI!	Actual	7.1	0.998	6.6	0.998
	H \pm ΔZ	7.4	0.999	6.8	0.999
/6-31+G(d,p)	Actual	1.9	0.956	1.3	0.990
	H \pm ΔZ	0.7	0.998	0.8	0.998
/aug-cc-pVDZ	Actual	1.8	0.966	1.3	0.996
	H \pm ΔZ	0.8	0.997	0.8	0.997
PBE/6-31+G(d,p)	Actual	1.7	0.970	1.2	0.992
	H \pm ΔZ	0.8	0.997	0.8	0.997

(Continues)

Table 1. (Continued)

System/theory	<i>p</i> -substituent	σ		σ^+	
		ρ'	<i>R</i>	ρ'	<i>R</i>
PBE/6-31+G(d,p)	Actual	2.2	0.975	1.5	0.990
	H \pm Δ Z	0.9	0.998	0.9	0.998
Carbonate fragmentation I					
B3LYP/MIDI!	Actual	1.7	0.974	1.2	0.996
	H \pm Δ Z	0.7	1.000	0.7	1.000
/6-31+G(d,p)	Actual	3.8	0.976	2.6	0.989
	H \pm Δ Z	1.5	1.000	1.5	1.000
/aug-cc-pVDZ	Actual	3.7	0.974	2.6	0.991
	H \pm Δ Z	1.5	1.000	1.4	1.000
PBE/6-31+G(d,p)	Actual	3.1	0.961	2.2	0.986
	H \pm Δ Z	1.2	0.999	1.1	0.999
Carbonate fragmentation II					
B3LYP/MIDI!	Actual	-1.1	-0.978	-0.7	-0.946
	H \pm Δ Z	-0.3	-0.995	-0.3	-0.995
/6-31+G(d,p)	Actual	-0.7	-0.919	-0.5	-0.888
	H \pm Δ Z	0.0	0.582	0.0	0.582
/aug-cc-pVDZ	Actual	-0.7	-0.933	-0.5	-0.900
	H \pm Δ Z	0.0	-0.771	0.0	-0.771
PBE/6-31+G(d,p)	Actual	-1.0	-0.931	-0.6	-0.890
	H \pm Δ Z	-0.1	-0.960	-0.1	-0.960

^a Reaction used to define σ scale.
^b Reaction used to define σ^+ scale.
^c Data above are for vertical ionization potential and below for adiabatic ionization potential.
^d Data above are for asymmetric combination stretch and below for symmetric combination stretch.

associated with very poor initial guess wave functions when highly charged molecules are combined with large point charges (to simulate a heavier atom) it is typically advisable to carry out a calculation on the 'normal' molecule first and use that wave function for the initial guess.

RESULTS AND DISCUSSION

We consider first benzoic acid ionization. In order to compare theory directly to theory, thereby avoiding complications associated with, for example, solvation effects, we combine Eqns 1 and 3, absorb all other constants ($-2.303RT$) into the slope, and ignore thermal contributions to free energies to arrive at

$$\Delta E_X^o - \Delta E_H^o = \sigma_X \rho' \quad (5)$$

where computed values of ρ' are not expected to be equal to measured values of ρ but may be used straightforwardly for defining σ_X values for hydrogen nucleomers. In the case of benzoic acid ionization, regression of computed energy changes for the first reaction shown in Fig. 1 on σ_X values^[31] for the standard functional groups $X = \text{NH}_2, \text{OH}, \text{Me}, \text{H}, \text{Cl}, \text{CN},$ and NO_2 led to highly linear correlations at all four theoretical levels (absolute values of Pearson correlation coefficient R in excess of 0.976) with quite similar values of ρ' , from -12.2 to -12.7 (Table 1, row labeled 'Actual' *para* substituent). The regression for PBE/6-31+G(d,p) is shown in Fig. 2. As expected, regression on σ_X^+ values led to reduced quality linear correlations and smaller corresponding values of ρ' (Table 1).

We next computed energy changes for the ionization of parent benzoic acid with the charge of the *para* hydrogen nucleus changed to values of 0.80, 0.85, 0.90, 0.95, 1.00 (i.e., a normal hydrogen nucleus), 1.05, 1.10, 1.15, and 1.20 a.u. At each level of theory, keeping the geometry of the parent benzoic acid frozen for maximum simplicity, the linear correlations between the ionization energy changes and the variations in nuclear charges were perfect (absolute values of $R = 1.000$); σ_X values were assigned for each level of theory so as to make the slopes of the respective correlations equal to those computed using actual *para* substituents (Table 1; row labeled H \pm Δ Z). The derived values, together with the normal functional group values used in this study, are listed in Table 2. The variation in the ionization energy was about 4.1 kcal mol⁻¹ per 0.05 unit change in the proton nuclear charge.

For the σ^+ scale, an identical protocol was followed for the ionization of cumyl chloride. With actual functional group substituents and correlating against their respective σ_X^+ values,^[31] very high correlation coefficients were found with computed energy changes; R values exceeded 0.984 for all levels of theory and similar ρ' values of 14.8–15.2 were obtained (Table 1 and Fig. 3 for PBE/6-31+G(d,p) correlation). It is noteworthy that correlations of equally good quality were obtained when regressing on σ_X values instead of σ_X^+ values, indicating that the gas-phase calculations do not fully reflect differences in experimental conditions that distinguish one scale from the other. Again, nucleomer energy changes were computed and σ_X^+ values were assigned so as to match ρ' values computed from actual functional groups. The various σ_X^+ values are listed in

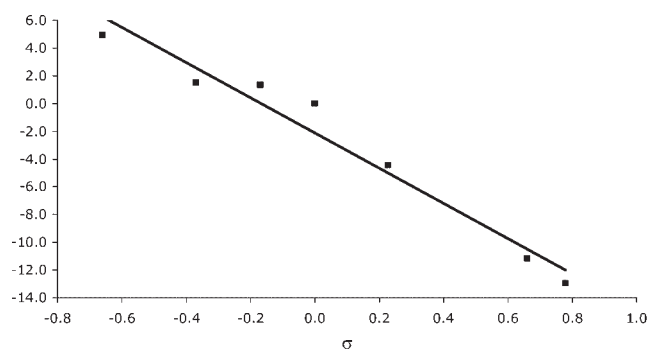


Figure 2. Computed energy changes for substituted benzoic acid ionization versus σ_X for various *para* substituents at the PBE/6-31+G(d,p) level

Table 3. Once again, nucleomer energy-change correlations were perfectly linear with nuclear charge variation.

We note that DiLabio and Ingold,^[32] using a similar computational protocol but with B3LYP/6-311+G(2d,2p) electronic energies and AM1 geometries and thermal contributions predicted a ρ' -value of 16.3, which is quite close to those reported here. DiLabio and Ingold^[32] noted that including solvation effects with the SM5.42R/AM1 continuum solvation model^[33] led to improved agreement with experiment, with a computed ρ' -value of 7.7 only slightly exceeding the experimentally determined value of 6.2.

We next considered the influence of *para* substitution on singlet-triplet (S-T) splitting in substituted nitrogen ions. Because singlet arylnitrenium ions have been implicated in carcinogenesis,^[34–39] the study of the influence of substituents on the relative energies of the singlet and triplet states of such systems has been a topic of considerable theoretical interest.^[40–46] In this context, Sullivan *et al.*^[44] have previously computed linear correlations against σ and σ^+ values for several actual functional groups and reported optimal linear correlation with the latter

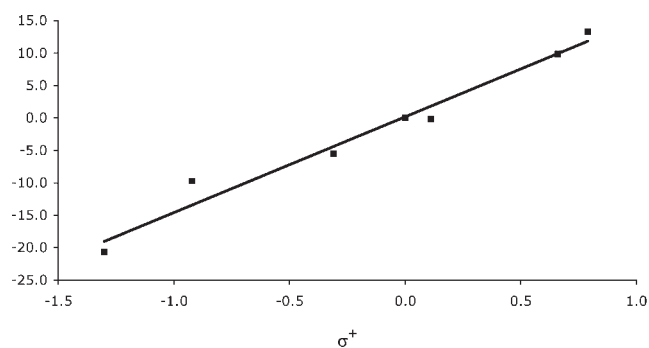


Figure 3. Computed energy changes for substituted cumyl chloride ionization versus σ_X^+ for various *para* substituents at the PBE/6-31+G(d,p) G(d,p) level

scale at the BPW91/cc-pVDZ level of theory (including thermal free-energy contributions and aqueous solvation effects with the SM5.42R continuum solvation model^[47]). We observed similarly good correlations with σ^+ values for the levels of theory employed here, with gas-phase ρ' values of about -5.0 . By contrast, correlation against the nucleomer σ^+ values listed in Table 3 was somewhat disappointing. While the linear correlations were all essentially perfect, the computed ρ' values were only about -2.2 , which is less than half the value computed for actual substituents. This probably reflects the significant geometric differences between singlet and triplet species that can be enhanced by appropriate substituents other than H. Thus, as illustrated in Fig. 1 and confirmed by IR spectroscopy,^[43] the singlet nitrenium is best represented as a substituted cyclohexadienium ion while the triplet nitrenium really has true nitrenium ion character. As a H nucleomer cannot hybridize with the cyclohexadienium cation the way a more complex functional group can, the computed group influence is strongly reduced when only nucleomers are considered.

Table 2. Values of σ_X for functional groups and H atom nucleomers having nuclear charge Z

<i>p</i> -X	Z	Expt. ^a	Theory level			
			B3LYP/MIDI!	B3LYP/6-31+G(d,p)	B3LYP/aug-cc-pVDZ	PBE/6-31+G(d,p)
NH ₂		-0.660				
OH		-0.370				
Me		-0.170				
H	0.80		-1.456	-1.310	-1.337	-1.292
	0.85		-1.092	-0.983	-1.003	-0.969
	0.90		-0.728	-0.655	-0.668	-0.646
	0.95		-0.364	-0.328	-0.334	-0.323
	1.00	0.000				
	1.05		0.364	0.328	0.334	0.323
	1.10		0.728	0.655	0.668	0.646
	1.15		1.092	0.983	1.003	0.969
	1.20		1.456	1.310	1.337	1.292
Cl		0.227				
CN		0.660				
NO ₂		0.778				

^a From Reference [31].

Table 3. Values of σ_X^+ for functional groups and H atom nucleomers having nuclear charge Z

<i>p</i> -X	<i>Z</i>	Expt. ^a	Theory level			
			B3LYP/MIDI!	B3LYP/6-31+G(d,p)	B3LYP/aug-cc-pVDZ	PBE/6-31+G(d,p)
NH ₂		-1.300				
OH		-0.920				
Me		-0.310				
H	0.80		-1.456	-1.310	-1.337	-1.292
	0.85		-1.092	-0.983	-1.003	-0.969
	0.90		-0.728	-0.655	-0.668	-0.646
	0.95		-0.364	-0.328	-0.334	-0.323
	1.00	0.000				
	1.05		0.364	0.328	0.334	0.323
	1.10		0.728	0.655	0.668	0.646
	1.15		1.092	0.983	1.003	0.969
	1.20		1.456	1.310	1.337	1.292
Cl		0.110				
CN		0.660				
NO ₂		0.790				

^a From Reference [31].

More favorable results are obtained for the fourth reaction in Fig. 1, the hydride affinity of substituted benzaldehydes. Excellent correlations with σ are computed at all levels, with large negative ρ' values. Correlations with σ^+ are less linear, as expected for this reaction which should have no particular sensitivity to resonance stabilization. Correlation of reaction energies computed for H nucleomers against the σ values determined from benzoic acid ionization gives linear correlations with ρ' values about 10–15% smaller than those computed from actual substituted benzaldehydes at the various theoretical levels. Figure 4 shows the data from both sets of calculations on a common plot.

Similarly good quality correlations for both actual substituents and H nucleomers are computed for the basicities of substituted anilines and acidities of substituted phenols (reactions 5 and 6 of Scheme 1, respectively). As with the benzaldehyde hydride affinities, in each case correlations of energy changes for actual

substituents against σ values are more linear than those against σ^+ values – substantially so in the case of phenol acidities – although correlations against either set of nucleomer values are perfectly linear. Also similar to the benzaldehydes case, the ρ values computed for the H nucleomers using the σ scale are about 10–15% smaller than those computed from actual substituted anilines at the various theoretical levels. In the phenol case that disparity increases to about 30%, reflecting perhaps a deficiency in the use of nucleomers when a heteroatom directly attached to the aromatic ring carries a full charge and is otherwise unsubstituted.

Extremely good agreements – ρ' values within 2–3% – are obtained between actual substituent and nucleomer correlations against σ^+ values for substituted styrene proton affinities (Reaction 7 of Scheme 1). This is perhaps not surprising given that the product carbenium ion differs from the cumyl cation only by methyl substitution at the cationic center.

Another reaction that generates a positively charged functional group is the ionization of substituted methyl phenyl sulfoxides (Reaction 8 of Scheme 1), originally studied experimentally and computationally for a series of substituted examples by Baciocchi and Gerini.^[48] In this case, we considered both the vertical ionization potential, that is, taking the radical cation geometry to be the same as that optimized for the neutral precursor, and also the adiabatic potential taking geometric relaxation of the radical cation into account. In the case of the nucleomers, the vertical IP then corresponds to using the neutral, unsubstituted geometry for nucleomer calculations, and the adiabatic IP is computed using the relaxed geometry of methyl phenyl sulfoxide radical cation (but *not* further relaxing when changing the nuclear charge). In this case, correlations against σ and σ^+ values are computed to be about equally linear at all theoretical levels. Moreover, ρ' values are about the same for the vertical and adiabatic processes, with the exception of the B3LYP/aug-cc-pVDZ level, where the adiabatic ρ' -value is computed to be about 10% smaller than the vertical one.

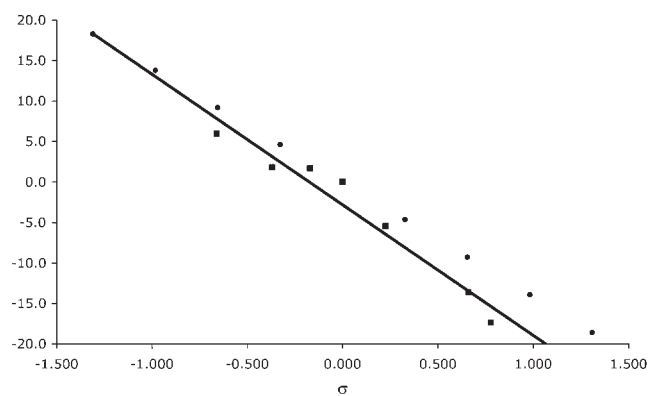


Figure 4. Computed energy changes for substituted benzaldehyde hydride affinities versus σ_X for various actual *para* substituents (squares) and H nucleomers (circles) at the PBE/6-31+G(d,p) level. The line is a linear fit to the data for actual substituents

Nucleomer correlations are perfectly linear in either scale. The predicted ρ' values against the σ scale are too low by 25–30% while those against the σ^+ scale are within about 10% of those computed for actual substituents, sometimes overestimating, sometimes underestimating. In the absence of intuition, it is not obvious that one would be able to clearly determine whether correlation against σ or σ^+ values is more physical. Of course, the qualitative conclusions would be similar in either instance.

The situation is somewhat similar with respect to correlations of indanedione carbonyl stretching frequencies (one being a symmetric combination and the other asymmetric) against σ and σ^+ values. This correlation is extrathermodynamic, but a strong linear relationship is found nonetheless (the individual frequencies vary over a range of about 20 cm^{-1} across the actual substituents). Once again, there is no particular distinction between correlations against σ and σ^+ . There is a surprisingly large basis set effect on the predicted ρ' values, with the MIDI! basis predicting much smaller variations in the stretching frequencies as a function of substitution. This effect is faithfully reproduced in the nucleomer correlations. Again, however, the nucleomer correlations against σ values lead to ρ' values too small by fairly substantial margins: 40–45%. Underestimation is also consistent on the σ^+ scale, but the magnitude is reduced to about 20%.

Returning to a correlation of free energy changes, but now free energies of activation, as opposed to reaction, we consider the Claisen rearrangement of *para* substituted allyl phenyl ethers (Reaction 10 of Fig. 1). Correlating the kinetics of this reaction against σ^+ values represented a very early example of linear free energy relationships.^[49,50] White *et al.* measured a ρ' -value of about 1.4 correlating rearrangement rates against σ^+ values in carbital as solvent. The theoretical gas phase values for actual substituents listed in Table 1 are in quite good agreement with this result, and moreover have Pearson correlation coefficients in excess of 0.99, reflecting the weak solvent influence known for this reaction.^[49] While nucleomer correlations are also very good, the predicted ρ' values are too small by a fairly substantial margin. We speculate that this may reflect the failure of nucleomers to properly represent the polarizability of actual substituents, as opposed to simply their polarity. As TS structures are usually more polarizable than equilibrium structures, this discrepancy should become more important when free energies of activation are considered compared to free energies of reaction.

Consistent with this analysis, nucleomer ρ' values are again about 50% too small compared to values computed with actual substituents for the first carbonate fragmentation shown as Reaction 11 in Fig. 1, although the proper qualitative trend is predicted. However, for the second carbonate fragmentation (Reaction 12 of Fig. 1), where the substituent influence is rather small, quite poor correlations are observed when nucleomer correlations are computed with the B3LYP functional and large basis sets. Curiously, with the smaller MIDI! basis set, a reasonable correlation is obtained with B3LYP even though the magnitude is again underestimated. At the PBE/6-31+G(d,p) level the activation free energy is predicted to be essentially independent of nucleomer.

While the nucleomer correlations at the B3LYP/MIDI! level underestimate the influence of substitution effects, they do correctly predict that rearrangement rates are (i) more sensitive to aryl substitution at the α position on the carbonate alkyl chain, as opposed to the β position and (ii) show contrasting sensitivity

to electron-withdrawing versus electron-donating substituents. Van Speybroeck *et al.*,^[51] who previously studied these reactions at the B3LYP/6-311G(d,p) level, noted these same trends and used them reasonably to conclude that the TS structure has more C—O bond breaking, with development of carbocationic character at the α position, than any corresponding bond making. Owing to the complexity of the substituted carbonates, Van Speybroeck *et al.* developed initial geometries from PM3 calculations in order to be more efficient. This system, then, is a nice demonstration of when using nucleomers can be efficient, since only a single TS structure needs to be located for each reaction, and that only for the unsubstituted parent system.

CONCLUSIONS

Hammett ρ values computed from H nucleomer σ and σ^+ constants show good qualitative agreement with ρ values computed from typical *para* functional group substitution for a number of energetic and extrathermodynamic correlations, but quantitative agreement is sometimes disappointing. As H nucleomers cannot enjoy resonance interactions with the aromatic π system, there is typically little distinction between the nucleomer σ and σ^+ scales. In addition, in most instances the magnitudes of the ρ values computed from nucleomer correlations are some 10–60% smaller than those computed from actual *para* substituents. We speculate that some of this difference may be attributed to the lack of polarizability of the nucleomers compared to actual organic functional groups. Nevertheless, nucleomer correlations provide a very quick estimation of ρ values and should prove useful for evaluation of the full range of linear free energy relationships.

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