3408 *J. Phys. Chem. A* **1997,** *101,* 3408−3415

Modified Interaction Properties Function for the Analysis and Prediction of Lewis Basicities

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Received: January 16, 1997; In Final Form: March 3, 1997[⊗]

Ab initio HF/6-31G* electrostatic potentials and average local ionization energies have been computed for 42 nitrogen, oxygen, and sulfur bases. The molecules are characterized by four computed quantities, V_{min}, the spatial minimum in the electrostatic potential, $P_{V_{\mathrm{min}}}$, a polarization correction to V_{min}, $\bar{I}_{\mathrm{S,min}}$, the surface minimum in the average local ionization energy, and Π, a global index derived from the calculated surface electrostatic potential. It is shown that shifts in the O−H stretching frequencies for methanol−base complexes, complexation enthalpies for phenol−base and iodine−base interactions, and gas phase protonation enthalpies can be well correlated to the computed quantities of the bases by a single type of relationship. An analysis of the importance of the different quantities for correlating a specific interaction provides information about the nature of the interaction.

Introduction

The interpretation and prediction of intermolecular interactions are of fundamental interest in many areas of chemistry and biology. Drago and co-workers have shown that complexation enthalpies for the interaction between many Lewis acids and bases in the gas phase or in apolar solvents can be correlated using the following type of relationship:[1−3]

$$-\Delta H = E_{\mathrm{A}}E_{\mathrm{B}} + C_{\mathrm{A}}C_{\mathrm{b}} + W \qquad (1)$$

where the E_{A}, E_{B}, C_{A}, C_{B}, and W are empirically derived parameters. E_{A} and C_{A} describe the acid, while E_{B} and C_{B} describe the base. W, which usually is zero, represents a contribution that can be associated either with a given acid reacting with a series of bases or with a given base reacting with a series of acids.[3] Equation 1 was found to be less successful in predicting the strength of interactions where either the base or the acid is ionic.[4,5] However it has been shown that this deficiency can be corrected with the inclusion of additional parameters.[5,6] Modifications to either the base or acid parameters have enabled other quantities than enthalpies, such as spectral shifts, to be correlated.[3,7] A major limitation in the applicability of eq 1 lies in the use of purely empirical parameters. The derivation of E and C parameters for a new acid or base requires data from at least four different experimental measurements.[8] The development of less empirical schemes for the prediction of molecular interactions is therefore of interest.

Politzer and co-workers have applied their general interaction properties function (GIPF) to the correlation and prediction of a number of parameters and properties that reflect molecular interaction tendencies.[9−17] The GIPF has the general form

$$\text{Property} = f\,[\text{area}, \bar{I}_{\mathrm{S,min}}\ V_{S,\mathrm{max}}, V_{S,\mathrm{min}}, V_{\mathrm{min}}, \Pi, \sigma^{2}_{\mathrm{tot}}, \nu] \qquad (2)$$

All quantities are calculated from ab initio SCF wave functions and are, with the exception of area and $\bar{I}_{\mathrm{S,min}}$, defined in terms of the molecular electrostatic potential. For each studied property, statistical analysis is used to select a subset of quantities that are able to accurately correlate the variations in the property. The quantities relevant to the present study will be defined and discussed in the next section of this article. In a recent study, the GIPF was used to correlate the magnitudes of the shift in the methanol O−H stretching frequency due to complexation with Lewis bases in carbon tetrachloride.[16] The following equation was found to provide a good correlation between the experimentally determined shifts and the calculated quantities of the bases:

$$\Delta\nu_{\mathrm{OH}} = \alpha V_{\mathrm{min}} + \beta\bar{I}_{S,\mathrm{min}} + \gamma\Pi + \delta \qquad (3)$$

In this work we will show that the applicability of this equation can be increased by the inclusion of one additional parameter, $P_{V_{\mathrm{min}}}$, which is a polarization correction to the electrostatic potential minimum V_{min}. This not only improves the correlation with the O−H shifts but also makes it possible to correlate the following properties: (1) enthalpies of complexation between Lewis bases and phenol in apolar solvents, (2) enthalpies of complexation between Lewis bases and iodine in apolar solvents, and (3) gas phase protonation enthalpies. We will also show that an analysis of the importance of the different quantities for correlating a specific interaction can provide information about the nature of the interaction.

Methodological Background

The interaction energy, $E(q,\mathbf{r})$, between a molecule and a point charge q located at a position $\mathbf{r}$ can be defined, using perturbation theory, as a power series in terms of q:

$$E(q,\mathbf{r}) = qE^{(1)}(\mathbf{r}) + q^{2}E^{(2)}(\mathbf{r}) + q^{3}E^{(3)}(\mathbf{r}) + ... \qquad (4)$$

$E^{(1)}(\mathbf{r})$ is the electrostatic potential of the molecule, commonly denoted as $V(\mathbf{r})$ and rigorously defined by

$$V(\mathbf{r}) = \sum_{\mathrm{A}}\frac{Z_{\mathrm{A}}}{|R_{\mathrm{A}} - \mathbf{r}|} - \int\frac{\rho(\mathbf{r}')\,\mathrm{d}\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (5)$$

where Z_{A} is the charge on nucleus A, located at $\mathbf{R}_{\mathrm{A}}$, and $\rho(\mathbf{r})$ is the electronic density function of the molecule. $E^{(2)}(\mathbf{r})$, the second-order contribution to the interaction energy, is defined within the framework of the ab initio LCAO-SCF theory by eq 6.[18]

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[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

S1089-5639(97)00222-3 CCC: $14.00 © 1997 American Chemical Society

$$P(\mathbf{r}) = \sum_{i}^{\text{occ}}\sum_{a}^{\text{vir}} \frac{1}{\epsilon_i - \epsilon_a}\left[\sum_{\mu}\sum_{\nu} c_{\mu i}c_{\nu a}\int \frac{\chi_\mu(\mathbf{r}')\,\chi_\nu(\mathbf{r}')\,\mathrm{d}\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|}\right]^2 \qquad (6)$$

The ϵ_i are the orbital energies and the $c_{\mu i}$ are the molecular orbital expansion coefficients in terms of the atomic orbital basis set χ_μ. $P(\mathbf{r})$ is commonly referred to as a polarization correction to the electrostatic potential. Earlier studies have shown that the contributions from terms greater than second order generally are small and can, for many chemical applications, be omitted without a significant loss of information.[18,19]

The electrostatic potential has been used extensively as a tool for qualitative and quantitative analysis of intermolecular interactions, including electrophilic and nucleophilic reactions as well as hydrogen-bonding and intermolecular recognition interactions.[10,20−26] In particular, $V(\mathbf{r})$ is very well suited for modeling of hydrogen-bonding interactions. Good quantitative correlations have been reported between maxima in $V(\mathbf{r})$ calculated on molecular surfaces, $V_{S,max}$, associated with hydrogens, and empirical hydrogen bond donating parameters.[16,24−26] Surface minima ($V_{S,min}$) and spatial minima (V_{min}) have been found to correlate well with empirical hydrogen bond accepting parameters.[16,25−28] However these correlations generally show some family dependence, for example, better correlations are obtained when oxygen and nitrogen bases are treated separately.

In comparison with $V(\mathbf{r})$, applications of the polarization correction, $P(\mathbf{r})$, as defined by eq 6, for studies of chemical reactivity and intermolecular interactions have been less common.[18,29,30] The general approach has been to calculate a total interaction index, “a polarization-corrected electrostatic potential”, using $V(\mathbf{r})$ and $P(\mathbf{r})$.

$$E(\mathbf{r}) = qV(\mathbf{r}) + q^2P(\mathbf{r}) \qquad (7)$$

where q is set to 1 au or −1 au depending upon whether nucleophilic or electrophilic processes are studied. Francl has demonstrated the applicability of the polarization-corrected potential for studies of nucleophilic attack in vinylic systems.[18] Dive and Dehareng have shown that the polarization-corrected potential can be used to deduce positions and relative reactivity for nucleophilic and electrophilic attack on aromatic compounds.[29,30]

The electrostatic potential, with or without polarization correction, has generally been used as a local interaction index reflecting the reactivities at certain sites on a molecule. However we have shown that additional useful information can be extracted if the electrostatic potential is calculated on the molecular surface and the distribution of the electrostatic potential is analyzed statistically in terms of global indices.[9,11,31,32] As a measure of polarity or charge separation in a molecule, we have proposed a quantity Π defined by[31]

$$\Pi = \frac{1}{A}\int_S |V(\mathbf{r}) - \bar{V}_s|\,\mathrm{d}S = \lim_{n\to\infty}\frac{1}{n}\sum_{i=1}^{n}|V(\mathbf{r}_i) - \bar{V}_s| \qquad (8)$$

where $V(\mathbf{r}_i)$ is the potential at the i^{th} point on the surface and $\bar{V}_S$ is its average value, $\bar{V}_S = (1/n)\sum_{i=1}^{n} V(\mathbf{r}_i)$. Π has been shown to correlate with an empirical polarity/polarizability parameter π^*[33] as well as with the dielectric constant.[31] Π has also in been used in combination with other calculated surface properties to correlate liquid/liquid partition coefficients and some physical properties of solids and liquids.[11−13,17]

The average local ionization energy $\bar{I}(\mathbf{r})$ is defined within the Hartree−Fock theory by[34]

$$\bar{I}(\mathbf{r}) = \sum_{i}\frac{\rho_i(\mathbf{r})|\epsilon_i|}{\rho(\mathbf{r})} \qquad (9)$$

where $\rho_i(\mathbf{r})$ is the electronic density of the i^{th} molecular orbital at the point $\mathbf{r}$ and ϵ_i is the orbital energy. According to Koopmans’ theorem, the energy required to remove an electron from a chemical system can be approximated by the absolute value of its orbital energy.[35] $\bar{I}(\mathbf{r})$ can therefore be interpreted as the average energy required to remove an electron from any point $\mathbf{r}$ in the space of an atom or molecule.

$\bar{I}(\mathbf{r})$ calculated on molecular surfaces defined by contours of constant electron density has been found to be an effective tool for the analysis of reactivity toward electrophiles.[10,34,36−38] The positions on a molecular surface where $\bar{I}(\mathbf{r})$ has its lowest values, $\bar{I}_{S,min}$, are viewed as the locations of the least tightly bound electrons and thus as the sites expected to be the most reactive toward electrophiles. However $\bar{I}(\mathbf{r})$ reflects a molecule’s ability to undergo charge transfer and polarization rather than its ability to interact electrostatically.[10] $\bar{I}(\mathbf{r})$ and $V(\mathbf{r})$ do therefore provide different kinds of information, although both are used as indices of reactivity toward electrophiles. We have previously shown that the $\bar{I}_{S,min}$ of some azines and azoles, and of the anionic conjugate bases of a group of 40 carbon, nitrogen, and oxygen acids, reflect these compound’s abilities to undergo protonation in aqueous solution. This is indicated by good correlations between $\bar{I}_{S,min}$ and pK_a.[36,37] However in a study of the first-, second-, and third-row hydrides of groups V−VII and their anions, $\bar{I}_{S,min}$ had to be combined with an electrostatic parameter, i.e. $V_{S,min}$, to give good general correlations with aqueous and gas phase acidities.[10] It can be noted that also Famini and coworkers have found good correlations for gas phase acidities using a combination of electrostatic and charge transfer/polarization descriptors.[39] However, in their study the descriptors reflect the properties of the acid rather than its conjugate base (the anion).

Methods and Procedure

We have used Gaussian 94[40] to compute optimized geometries at the HF/6-31G* level. Using these geometries, molecular properties were evaluated at the same level of theory. The 6-31G* basis set has been demonstrated to be well suited for the determination of equilibrium geometries[41] as well as electrostatic potentials and average local ionization energies.[34,37,42] However the results of calculations of polarization corrections to the electrostatic potential have been shown to be much more basis set dependent than calculations of the potential itself.[19,43] The use of basis sets containing diffuse polarization functions has been recommended.[19,43] We experimented therefore with replacing the polarization functions in 6-31G* with more diffuse functions. This generally led to increased magnitudes of $P(\mathbf{r})$, especially at distances beyond the van der Waals radii, but did simultaneously decreased the relative differences in $P(\mathbf{r})$ between different molecules. The performance of basis sets with multiple basis functions was not investigated, since these are computationally expensive to apply and since our results indicated that the 6-31G* basis set is sufficient for the current application. In this context it should also be noted that the 6-31G* basis set is larger and much more flexible than the STO-5G basis set, which has been used in many of the previous applications of the GIPF approach. $\bar{I}(\mathbf{r})$ and $V(\mathbf{r})$ were computed on molecular surfaces defined, following Bader et al.,[44] by the 0.001 au contour of the electron density. The objectives of the surface calculations were the minima in $\bar{I}(\mathbf{r})$ and $V(\mathbf{r})$, $\bar{I}_{S,min}$ and $V_{S,min}$ and the global quantity Π. Spatial minima in $V(\mathbf{r})$, V_{min},

TABLE 1: HF/6-31G* Computed Quantities

	V_{min} (kcal/mol)	$P_{V_{\mathrm{min}}}$ (kcal/mol)	$\bar{I}_{S,\mathrm{min}}$ (eV)	Π (kcal/mol)
Cl_3CCN	−39.1	−47.9	16.56	7.3
ClH_2CCN	−48.5	−49.6	15.95	16.9
HCO_2CH_3	−58.3	−47.0	15.00	22.2
C_6H_5CHO	−55.8	−53.6	15.16	12.7
$(CH_3CH_2S)_2$	−31.5	−39.3	10.88	9.0
CH_3CN	−57.8	−51.3	15.36	21.1
$CH_3CO_2CH_3$	−56.6	−51.5	15.06	12.9
$CH_3CO_2C_2H_5$	−57.4	−52.1	15.02	11.2
CH_3COCH_3	−57.5	−53.0	14.92	14.2
CH_3OH	−60.6	−41.9	14.85	12.6
$(CH_3)_2NCN$	−64.4	−54.7	15.01	18.1
CH_3CH_2OH	−61.0	−44.2	14.77	11.6
p-dithiane	−33.0	−40.6	10.43	10.6
p-dioxane	−53.7	−52.6	15.15	11.0
$(CH_3)_2S$	−37.9	−37.4	10.18	9.8
$(CH_3CH_2)_2S$	−39.2	−42.1	10.05	7.4
$(CH_3CH_2)_2O$	−55.8	−57.0	14.86	6.4
$(CH_3)_2NCHO$	−67.6	−54.3	14.36	15.6
tetrahydrothiophene	−39.4	−41.1	10.04	8.4
tetrahydrofuran	−62.0	−52.4	14.90	8.9
$(CH_3)_2NCOCH_3$	−68.8	−58.3	14.30	13.7
$(CH_3CH_2)_3P{=}S$	−47.7	−42.7	9.64	13.9
(3,5−Cl_2)pyridine	−55.1	−72.2	13.45	7.8
$(CH_3)_2S{=}O$	−76.8	−57.0	13.33	19.2
pyrimidine	−62.8	−69.4	13.14	12.8
$F_3CCH_2NH_2$	−66.7	−50.0	12.36	13.0
$(CH_3)_3P{=}O$	−78.6	−57.2	12.82	17.1
NH_3	−87.8	−36.8	11.83	18.9
pyridine *N*-oxide	−77.0	−69.0	12.90	18.1
pyridine	−70.8	−72.8	12.62	11.6
quinoline	−69.1	−78.0	12.60	11.1
(4-CH_3)pyridine	−73.0	−73.8	12.51	11.1
cyclopropylamine	−77.5	−55.6	11.73	8.9
(1-CH_3)imidazole	−82.1	−68.4	12.41	16.9
CH_3NH_2	−84.4	−47.5	11.52	11.2
$CH_3CH_2NH_2$	−83.4	−51.5	11.50	9.1
$CH_3(CH_2)_3NH_2$	−78.1	−59.0	11.41	7.4
$(CH_3)_2NH$	−83.8	−51.9	11.50	7.2
$(CH_3)_3N$	−71.3	−69.9	11.40	5.1
$(CH_3CH_2)_2NH$	−76.7	−67.4	11.33	5.7
$(CH_3CH_2)_3N$	−69.7	−83.7	11.30	3.9
quinuclidine	−76.6	−75.7	11.30	5.2

were also calculated. Finally, $P(\mathbf{r})$ were evaluated at the positions of the $V_{\mathrm{S,min}}$ and V_{min}. The SAS statistical analysis program package[45] was used to investigate relationships between computed quantities and experimentally-determined interaction indices.

Results and Discussion

Computed quantities for 42 oxygen, nitrogen, and sulfur bases are listed in Table 1. The listed V_{min} are the global minima in the electrostatic potential. For all molecules it was found that the global minimum is associated with the heteroatom most susceptible to electrophilic attack. $P_{V_{\mathrm{min}}}$ refers to $P(\mathbf{r})$ evaluated at the position of the V_{min}. The listed $\bar{I}_{\mathrm{S,min}}$ corresponds for all molecules but the nitriles to the $\bar{I}_{\mathrm{S,min}}$ located closest to the V_{min}. In general, we found that every V_{min} has a corresponding $\bar{I}_{\mathrm{S,min}}$ located close in space. However for the nitriles, where the V_{min} in all cases is located at the end of the nitrogen atom on a point collinear with the carbon−nitrogen bond, the closest $\bar{I}_{\mathrm{S,min}}$ is located in the bonding region between the carbon and the nitrogen. For the nitriles, we therefore use the value of $\bar{I}(\mathbf{r})$ for the position on the molecular surface that is closest to the position of the V_{min}. From a statistical analysis, it was found that of the evaluated quantities the four listed, V_{min}, $P_{V_{\mathrm{min}}}$, Π, and $\bar{I}_{\mathrm{S,min}}$, were best suited to correlate the experimentally determined interaction indices.

It should first be noted that there are no significant cross correlations between the four calculated quantities; that is, none of the four can be expressed as a linear combination of the other three. This can be seen from the statistical VIF values for the different correlations that are listed in Table 2. A fair correlation between $P_{V_{\mathrm{min}}}$ and $\bar{I}_{\mathrm{S,min}}$ could have been anticipated, since both quantities have been denoted as reflecting polarization contributions to intermolecular interactions.[10,18] It is rather surprising that $P_{V_{\mathrm{min}}}$ for the sulfur-containing molecules generally is slightly smaller in magnitude than for their oxygen-containing analogs, since sulfur has a much higher atomic polarizability than oxygen. The reason for this is probably that the oxygen V_{min} are located much closer to the nuclei than the sulfur V_{min}. It should also be noted that the $\bar{I}_{\mathrm{S,min}}$ for the sulfur-containing molecules are lower than for any of the other compounds.

As shown in Table 2, shifts in the O−H stretching frequencies for methanol−base complexes (ν_{OH}) as well as formation enthalpies for phenol−base ($\Delta H_{\mathrm{Phen.}}$) and iodine−base complexes (ΔH_{I2}) and gas phase proton affinities ($-\Delta H_{\mathrm{H^+}}$) are well correlated by a single type of relationship:

$$-\Delta H(\text{or } \Delta\nu_{\mathrm{OH}}) = \alpha V_{\mathrm{min}} + \beta P_{V_{\mathrm{min}}} + \gamma\, \bar{I}_{S,\mathrm{min}} + \delta\Pi + \epsilon \quad (10)$$

The correlation coefficients are all better than 0.974. The V_{min} term is not significant for the ΔH_{I2} correlation, and the Π term is insignificant for the $\Delta H_{\mathrm{H^+}}$ correlation. As expected, the linear expansion coefficients show that the strength of an interaction generally increases with decreasing values of V_{min}, $P_{V_{\mathrm{min}}}$, and $\bar{I}_{\mathrm{S,min}}$. The fact that interaction strength also increases with a decreasing value of Π is more surprising, since low polarity is expected to oppose bonding. A plausible explanation is that the Π parameter to some degree accounts for the solvent effects on these interactions. Since the physical interpretation of Π in these relationships is unclear, it is comforting that we in all cases are able to get good correlations also without Π (see Table 2).

As a measure of the relative importance of the different quantities in the various correlations, we have listed the statistical t-scores. The t-scores can provide some insight into the physical nature of the different interactions. For example, a large t-score for V_{min} compared with the scores for $\bar{I}_{\mathrm{S,min}}$ and $P_{V_{\mathrm{min}}}$ indicate that the interaction is mainly electrostatic in nature. On the other hand, large relative t-scores for $\bar{I}_{\mathrm{S,min}}$ and $P_{V_{\mathrm{min}}}$ indicates large contributions from polarization and charge transfer. It should be noted that a number of schemes for partitioning of intermolecular interaction energies have been devised and no unique definitions for the electrostatic, polarization, and charge transfer energies exist. The quantities V_{min}, $P_{V_{\mathrm{min}}}$, and $\bar{I}_{\mathrm{S,min}}$ are closely related to the energy terms that appear when the widely used Morokuma scheme[46,47] for energy decomposition is applied to gas phase protonation of bases. The electrostatic energy in the Morokuma scheme is identical to the electrostatic potential, $V(\mathbf{r})$, at the protonation site. Since the protonation site often is located close to the V_{min} position, V_{min} is a good estimate of the electrostatic energy. The polarization energy in the same scheme is equivalent to $P(\mathbf{r})$ at the protonation site if the third-order and higher order terms in eq 4 are neglected. As has already been mentioned, these terms are generally small, and $P_{V_{\mathrm{min}}}$ is therefore a good estimate of the polarization energy. The charge transfer energy is essentially the remaining part of the interaction energy when the electrostatic energy and the polarization energy have been subtracted. It is the energy associated with electron transfer from occupied orbitals on the base to the unoccupied orbitals of the proton. This energy is highly dependent on the energies of the orbitals that have large densities in the vicinity of the protonation site and is therefore

TABLE 2: Calculated Coefficients and Statistical Data for Linear Relationships

		property = $\alpha V_{\min} + \beta P(\mathbf{r}_{V,\min}) + \gamma I_{S,\min} + \delta\Pi + \epsilon$								
no.	property[a]	α	β	γ	δ	ϵ	no. of molecules	correlation coefficient	standard deviation	F statistics
1	$-\Delta H_{Ph}$	−0.0778	−0.0513	−0.345	n.i.[c]	3.20	25	0.978	0.38	159.5
	(t−stat)	(17.85)	(5.34)	(13.08)		(4.53)				
	[VIF][b]	[1.24]	[1.18]	[1.02]						
2	$-\Delta H_{Ph}$	−0.0867	−0.0369	−0.245	−0.0693	2.93	25	0.989	0.27	231.2
	(t−stat)	(18.02)	(5.97)	(6.63)	(4.42)	(5.65)				
	[VIF][b]	[1.50]	[1.69]	[1.64]	[1.99]					
3	$\Delta\nu_{OH}$	−4.01	−3.16	−32.2	n.i.[c]	193.2	37	0.965	29	150.3
	(t−stat)	(11.07)	(6.59)	(12.9)		(4.83)				
	[VIF][b]	[1.30]	[1.31]	[1.01]						
4	$\Delta\nu_{OH}$	−4.71	−2.38	−27.8	−5.39	201.1	37	0.985	19	257.9
	(t−stat)	(17.57)	(6.86)	(15.3)	(6.37)	(7.45)				
	[VIF][b]	[1.56]	[1.49]	[1.18]	[1.39]					
5	$-\Delta H_{I2}$	n.s.[d]	−0.1098	−1.336	n.i.[c]	17.21	26	0.949	1.02	103.5
	(t−stat)		(6.34)	(11.71)		(8.86)				
	[VIF][b]		[1.03]	[1.03]						
6	$-\Delta H_{I2}$	n.s.[d]	−0.0932	−1.123	−0.1735	17.42	26	0.974	0.74	136.2
	(t−stat)		(7.08)	(11.78)	(4.59)	(12.26)				
	[VIF][b]		[1.11]	[1.34]	[1.45]					
7	$-\Delta H_{H^+(g)}$	−0.294	−0.698	−4.37	n.s.[d]	206.47	36	0.975	3.56	205.7
	(t−stat)	(5.87)	(12.49)	(12.59)		(31.4)				
	[VIF][b]	[1.33]	[1.22]	[1.13]						

[a] ΔH in kcal/mol, $\Delta\nu_{OH}$ in cm^{-1}. The values used in the correlations are listed in Tables 3−6. [b] The variance inflation factor (VIF) is defined as $1/(1 - R^2)$ where R is the correlation coefficient of one variable against the other. A low value (close to 1) indicates a low degree of cross correlation. Values below 5 are generally considered as acceptable.[64] [c] Not included. [d] Not significant.

expected to be related to $\bar{I}_{S,\min}$. It should be noted that the partitioning between polarization and charge transfer is rather sensitive to the choice of basis set. In the limit of a complete basis set it is no longer possible to distinguish between polarization and charge transfer.[48] In the following discussion, we will therefore focus on the influence of electrostatics versus polarization and charge transfer and not try to distinguish between the two latter terms.

Enthalpies for the Formation of 1:1 Phenol−Base Complexes. In Table 3 are experimentally determined enthalpies for the formation of 1:1 phenol−base complexes in apolar solvents listed, together with predicted enthalpies calculated from our best three- and four-parameter correlations. The experimental values are taken from the compilations by Drago and co-workers.[1,2] Drago has argued that solvent effects on complexation enthalpies can be minimized by using cyclohexane or other alkanes as solvents for sulfur donors and strong nitrogen donors, such as pyridines and amines, and carbon tetrachloride for oxygen donors and weak nitrogen donors, such as nitriles.[49,50] However there has been some controversy regarding the physical basis for this selection of solvents.[51,52] It can therefore not be excluded that the listed values in some cases have significant contributions from solvent effects. In addition, it should be noted that some of the values have not been determined directly by calorimetric measurements but rather from spectroscopic data.

As shown in Table 2, we found very good correlations with the experimental values using both three ($V_{\min}$, $P_{V_{\min}}$, and $\bar{I}_{S,\min}$) and four parameters (eq 10); the correlation coefficients are 0.978 and 0.988, respectively. The t-scores for the four-parameter correlation show that $V_{\min}$ is by far the most important parameter followed by $\bar{I}_{S,\min}$, $P_{V_{\min}}$, and Π. The high significance of the $V_{\min}$ parameter is also indicated by the existence of a linear correlation between the enthalpy and $V_{\min}$ with a correlation coefficient of 0.84. It is not surprising that $V_{\min}$ is the most important of the parameters, since hydrogen bonding has been shown to be largely electrostatic in nature.[10,53,54] However the fact that the relationship improves significantly by the inclusion of $\bar{I}_{S,\min}$ and $P_{V_{\min}}$ indicates that charge transfer and polarization effects cannot be neglected when correlating the hydrogen bond strengths for such a diverse group of bases as this. The statistical analysis also finds the inclusion of Π to be significant; the standard deviation improves from 0.37 to 0.26 kcal/mol and the F value from 120 to 250. However considering the accuracy of the experimental enthalpies, it is questionable if this improvement really is physically significant. Table 3 shows that the three worst outliers in the three-parameter correlation are *p*-dioxane, diethyl ether, and dimethyl sulfoxide. The predicted value for *p*-dioxane underestimates the enthalpy by 0.75 kcal/mol compared with Drago's experimental value[2] of 5.6 kcal. Fritzsche[55] has estimated the enthalpy to 5.00 kcal/mol and West et al.[56] to 5.26 kcal/mol; both values are in reasonable agreement with our predicted value (4.85 kcal/mol). Also for diethyl ether the experimental estimates from different sources differ considerably. Drago[2] reports 6.0, West et al.[56] 5.41, and Gramstadt[57] 4.8 kcal/mol. Our estimated value based on the three-parameter equation is 5.34, in good agreement with the value of West. For dimethyl sulfoxide Gramstadt[57] has reported a enthalpy of 8.0 kcal/mol, which is significantly higher than the recommended value of Drago,[2] 6.9 kcal/mol. Our predicted value, 7.5 kcal/mol, is again found to lie in between the experimental estimates. If these three outlier molecules are removed from the data set, the three-parameter equation gives almost as good a correlation as the four-parameter equation. We therefore conclude that on the basis of the accuracy of the experimental data it is not realistic to expect a standard deviation much below 0.4 kcal/mol. Since this is achieved already by the three-parameter equation, it is difficult to assign the significance of the fourth parameter, Π.

O−H Frequency Shifts in Methanol−Base Complexes. Table 4 lists experimentally determined shifts in the methanol O−H stretching frequency for methanol−base complexes in carbon tetrachloride, together with predicted shifts calculated from our best three- and four-parameter linear relationships. Frequency shifts have been used extensively as measures of the strength of molecular interactions.[2,8,50,52,58−60] As was mentioned earlier, Hagelin et al.[16] found a good linear relationship ($R = 0.966$) between methanol frequency shifts and $V_{\min}$,

TABLE 3: Experimental and Predicted Phenol−Base Complexation Enthalpies

	$-\Delta H_{\mathrm{Phen}}(\mathrm{exp})$[a] (kcal/mol)	$-\Delta H_{\mathrm{Phen}}(\mathrm{rel.1})$[b] (kcal/mol)	$-\Delta H_{\mathrm{Phen}}(\mathrm{rel.2})$[c] (kcal/mol)
Cl_3CCN	n.a.	3.0	3.5
ClH_2CCN	4.2	4.0	3.9
HCO_2CH_3	n.a.	5.0	4.5
C_6H_5CHO	n.a.	5.1	5.2
$(CH_3CH_2S)_2$	n.a.	3.9	3.8
CH_3CN	4.6	5.0	4.6
$CH_3CO_2CH_3$	4.8	5.1	5.2
$CH_3CO_2C_2H_5$	4.8	5.2	5.4
CH_3COCH_3	5.1	5.2	5.2
CH_3OH	n.a.	4.9	5.2
$(CH_3)_2NCN$	5.4	5.8	5.6
CH_3CH_2OH	n.a.	5.1	5.4
p-dithiane	n.a.	4.3	4.0
p-dioxane	5.6	4.8	5.0
$(CH_3)_2S$	4.6	4.6	4.4
$(CH_3CH_2)_2S$	4.6	4.9	4.9
$(CH_3CH_2)_2O$	6.0	5.3	5.8
$(CH_3)_2NCHO$	6.1	6.3	6.2
tetrahydrothiophene	4.9	4.9	4.8
tetrahydrofuran	6.0	5.6	6.0
$(CH_3)_2NCOCH_3$	6.8	6.6	6.6
$(CH_3CH_2)_3P{=}S$	n.a.	5.8	5.3
$(3,5\text{-}Cl_2)$pyridine	n.a.	6.5	6.5
$(CH_3)_2S{=}O$	6.9	7.5	7.1
pyrimidine	n.a.	7.1	6.8
$F_3CCH_2NH_2$	n.a.	6.7	6.6
$(CH_3)_3P{=}O$	(7.7)[d]	7.8	7.5
NH_3	7.8	7.8	7.7
pyridine *N*-oxide	7.9	8.3	7.7
pyridine	8.0	8.1	7.9
quinoline	(8.3)[d]	8.2	7.9
$(4\text{-}CH_3)$pyridine	(8.3)[d]	8.4	8.2
cyclopropylamine	n.a.	8.0	8.2
$(1\text{-}CH_3)$imidazole	n.a.	8.8	8.4
CH_3NH_2	8.6	8.2	8.4
$CH_3CH_2NH_2$	8.6	8.4	8.6
$(CH_3)_2NH$	8.6	8.4	8.6
$CH_3(CH_2)_3NH_2$	n.a.	8.4	8.8
$(CH_3)_3N$	8.8	8.4	8.5
$(CH_3CH_2)_2NH$	8.6	8.7	8.9
$(CH_3CH_2)_3N$	9.1	9.0	9.0
quinuclidine	9.0	9.1	9.2

[a] Experimentally determined enthalpies for 1:1 phenol−base complexation in apolar solvents. Unless otherwise indicated the values are from ref 2. Values in parentheses were not included in the correlations with computed quantities. [b] Predicted values from relationship 1 in Table 2. [c] Predicted values from relationship 2 in Table 2. [d] Estimates based on similar enthalpies, ref 61.

TABLE 4: Experimental and Predicted O−H Frequency Shifts ($\Delta\nu_{OH}$) in Methanol−Base Complexes

	$\Delta\nu_{OH}(\mathrm{exp})$[a] ($cm^{-1}$)	$\Delta\nu_{OH}(\mathrm{rel.3})$[b] ($cm^{-1}$)	$\Delta\nu_{OH}(\mathrm{rel.4})$[c] ($cm^{-1}$)
Cl_3CCN	23	−32	0
ClH_2CCN	48	31	14
HCO_2CH_3	54	93	52
C_6H_5CHO	65	98	102
$(CH_3CH_2S)_2$	75	93	92
CH_3CN	75	93	55
$CH_3CO_2CH_3$	77	98	103
$CH_3CO_2C_2H_5$	83	104	118
CH_3COCH_3	115	111	107
CH_3OH	116	90	106
$(CH_3)_2NCN$	117	141	120
CH_3CH_2OH	120	102	121
p-dithiane	121	118	107
p-dioxane	126	87	99
$(CH_3)_2S$	137	136	134
$(CH_3CH_2)_2S$	146	160	167
$(CH_3CH_2)_2O$	150	119	153
$(CH_3)_2NCHO$	150	173	166
tetrahydrothiophene	154	158	161
tetrahydrofuran	158	128	156
$(CH_3)_2NCOCH_3$	179	193	193
$(CH_3CH_2)_3P{=}S$	195	209	185
$(3,5\text{-}Cl_2)$pyridine	200	209	217
$(CH_3)_2S{=}O$	205	252	225
pyrimidine	213	241	229
$F_3CCH_2NH_2$	250	221	221
$(CH_3)_3P{=}O$	266	276	260
NH_3	275	280	272
pyridine *N*-oxide	278	305	272
pyridine	286	301	295
quinoline	n.a.	311	303
$(4\text{-}CH_3)$pyridine	304	316	314
cyclopropylamine	310	302	325
$(1\text{-}CH_3)$imidazole	313	339	315
CH_3NH_2	344	310	331
$CH_3CH_2NH_2$	n.a.	320	348
$(CH_3)_2NH$	n.a.	325	353
$CH_3(CH_2)_3NH_2$	354	323	361
$(CH_3)_3N$	n.a.	333	359
$(CH_3CH_2)_2NH$	398	349	378
$(CH_3CH_2)_3N$	429	373	394
quinuclidine	n.a.	375	400

[a] Experimentally determined OH frequency shifts for methanol−base complexes in carbon tetrachloride. These values were obtained by Berthelot and co-workers, ref 16, 59, 60. [b] Predicted values from relationship 3 in Table 2. [c] Predicted values from relationship 4 in Table 2.

$\overline{I}_{S,min}$, and Π for a set of 33 different bases. We found a correlation of similar quality for our set of molecules, which is a slight extension of the Hagelin set, using the same parameters. The correlation improves slightly if Π is substituted for $P_{V_{min}}$; the correlation coefficient increases from 0.962 to 0.965. However the best correlation is found when both $P_{V_{min}}$ and Π are included (eq 10). The correlation coefficient improves from 0.965 to 0.985, the standard deviation from 29 to 19 cm^{-1}, and the F value from 150 to 260 going from the best three-parameter to the four-parameter correlation. Since the accuracy of the experimental data can be assumed to be much better than 19 cm^{-1}, we believe this improvement to be significant.

The statistical t-scores for the four-parameter relationship shows that V_{min} is the most important parameter also for correlating the shifts in the methanol stretching frequency. However the relative significance of $\overline{I}_{S,min}$ is much larger than in the previous correlation with phenol−base complexation energies, indicating that the importance of charge transfer is greater. This is in agreement with the theory that O−H stretching frequencies for alcohols bonded to Lewis bases are strongly dependent upon the increase in the electron density in the O−H bond due to electron transfer from the base to the acid.[50] This theory has been used to explain the fact that in correlations between complexation energies and shifts in O−H stretching frequencies separate relationships apply to oxygen and nitrogen bases, and to sulfur bases.[50]

Enthalpies for the Formation of 1:1 Iodine−Base Complexes. In Table 3 are listed experimentally determined enthalpies for the formation of 1:1 iodine−base complexes in apolar solvents, together with predicted enthalpies calculated using our best three- and four-parameter correlations. The experimental values are taken from the compilations by Drago and co-workers.[1,2,61] They used the same criteria for the selection of solvents for the measurements as were used for the phenol−base enthalpies. Available data from calorimetric measurements in different solvents indicate that the solvent effects on the enthalpies may be substantial and highly irregular.[52] For example, there is a large difference between the enthalpy for dimethylacetamide measured in heptane and carbon tetrachloride; the values are 5.0 and 3.9 kcal/mol, respectively.[52]

TABLE 5: Experimental and Predicted Iodine−Base Complexation Enthalpies

	$-\Delta H_{I_2}$(exp)[a] (kcal/mol)	$-\Delta H_{I_2}$(rel.5)[b] (kcal/mol)	$-\Delta H_{I_2}$(rel.6)[c] (kcal/mol)
Cl_3CCN	n.a.	0.3	2.0
ClH_2CCN	1.5	1.3	1.2
HCO_2CH_3	n.a.	2.3	1.1
C_6H_5CHO	n.a.	2.9	3.2
$(CH_3CH_2S)_2$	n.a.	7.0	7.3
CH_3CN	1.9	2.3	1.3
$CH_3CO_2CH_3$	2.5	2.8	3.1
$CH_3CO_2C_2H_5$	2.8	2.9	3.5
CH_3COCH_3	3.3	3.1	3.1
CH_3OH	1.9[d]	1.9	2.4
$(CH_3)_2NCN$	2.8	3.2	2.5
CH_3CH_2OH	n.a.	2.3	2.9
p-dithiane	n.a.	7.7	7.6
p-dioxane	3.5	2.8	3.4
$(CH_3)_2S$	(7.8)[e]	7.7	7.8
$(CH_3CH_2)_2S$	7.8	8.4	8.7
$(CH_3CH_2)_2O$	4.2	3.6	4.9
$(CH_3)_2NCHO$	3.7	4.0	3.7
tetrahydrothiophene	8.3	8.3	8.5
tetrahydrofuran	5.3	3.1	4.0
$(CH_3)_2NCOCH_3$	4.0	4.5	4.4
$(CH_3CH_2)_3P{=}S$	n.a.	9.0	8.2
$(3,5-Cl_2)$pyridine	n.a.	7.2	7.7
$(CH_3)_2S{=}O$	4.4	5.7	4.5
pyrimidine	n.a.	7.3	7.0
$F_3CCH_2NH_2$	n.a.	6.2	6.0
$(CH_3)_3P{=}O$	n.a.	6.4	5.4
NH_3	4.8	5.4	4.3
pyridine *N*-oxide	5.9	7.6	6.3
pyridine	7.8	8.4	8.1
quinoline	7.2[f]	9.0	8.7
$(4-CH_3)$pyridine	8.9[f]	8.7	8.4
cyclopropylamine	n.a.	7.7	7.9
$(1-CH_3)$imidazole	n.a.	8.2	7.0
CH_3NH_2	7.1	7.0	7.0
$CH_3CH_2NH_2$	7.4	7.5	7.7
$(CH_3)_2NH$	9.8	8.5	8.8
$CH_3(CH_2)_3NH_2$	n.a.	7.6	8.1
$(CH_3)_3N$	12.1	9.7	10.3
$(CH_3CH_2)_2NH$	9.7	9.5	10.0
$(CH_3CH_2)_3N$	12.0	11.4	11.9
quinuclidine	(13.9)	10.5	11.0

[a] Experimentally determined enthalpies for 1:1 iodine−base complexation in apolar solvents. Unless otherwise indicated the values are from ref 2. Values in parentheses were not included in the correlations with computed quantities. [b] Predicted values from relationship 5 in Table 2. [c] Predicted values from relationship 6 in Table 2. [d] Reference 1. [e] Estimate based on similar enthalpies, ref 2. [f] Reference 61.

TABLE 6: Experimental and Predicted Proton Affinities

	$-\Delta H_{H^+}$(exp)[a] (kcal/mol)	$-\Delta H_{H^+}$(rel.7)[b] (kcal/mol)
Cl_3CCN	175.8	179.0
ClH_2CCN	179.5	185.6
HCO_2CH_3	188.4	190.9
C_6H_5CHO	200.2	194.0
$(CH_3CH_2S)_2$	n.a.	195.6
CH_3CN	188.2	192.2
$CH_3CO_2CH_3$	197.8	193.3
$CH_3CO_2C_2H_5$	200.7	194.1
CH_3COCH_3	196.7	195.2
CH_3OH	181.9	188.6
$(CH_3)_2NCN$	205.0	198.0
CH_3CH_2OH	188.2	190.7
p-dithiane	n.a.	198.9
p-dioxane	193.8	192.8
$(CH_3)_2S$	200.6	199.2
$(CH_3CH_2)_2S$	205.0	203.5
$(CH_3CH_2)_2O$	200.2	197.7
$(CH_3)_2NCHO$	(211.4)	201.5
tetrahydrothiophene	204.6	202.9
tetrahydrofuran	198.8	196.2
$(CH_3)_2NCOCH_3$	(216.2)	204.9
$(CH_3CH_2)_3P{=}S$	n.a.	208.2
$(3,5-Cl_2)$pyridine	n.a.	214.3
$(CH_3)_2S{=}O$	211.3	210.6
pyrimidine	210.8	216.0
$F_3CCH_2NH_2$	202.5	207.0
$(CH_3)_3P{=}O$	217.1	213.5
NH_3	204.0	206.3
pyridine *N*-oxide	220.3	220.9
pyridine	220.8	223.0
quinoline	226.5	226.2
$(4-CH_3)$pyridine	225.2	224.8
cyclopropylamine	215.2	216.8
$(1-CH_3)$imidazole	228.9	224.1
CH_3NH_2	214.1	214.0
$CH_3CH_2NH_2$	217.0	216.7
$(CH_3)_2NH$	220.6	220.7
$CH_3(CH_2)_3NH_2$	217.9	217.1
$(CH_3)_3N$	225.1	226.4
$(CH_3CH_2)_2NH$	225.9	226.6
$(CH_3CH_2)_3N$	232.3	236.0
quinuclidine	233.1	232.4

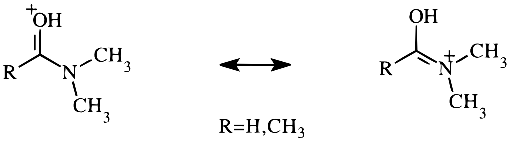
[a] Experimental values are taken from ref 65. Values in parentheses were not included in the correlations with computed quantities. [b] Predicted values from relationship 7 in Table 2.

On the other hand, for acetone the two enthalpies are much more similar, 3.65 and 3.3 kcal/mol.[2,52]

The best correlation between experimental enthalpies and calculated quantities was found for a three-parameter relationship with $P_{V_{\min}}$, $\bar{I}_{S,\min}$, and Π as the parameters; the correlation coefficient is 0.974. Quinuclidine was not included in the data set, since all investigated relationships underestimate its enthalpy by 2−4 kcal/mol. The addition of $V_{\min}$ did not lead to a significant improvement of the best two-parameter relationship or the three-parameter relationship. The t-scores shows $\bar{I}_{S,\min}$ to be the most important parameter followed by $P_{V_{\min}}$ and Π. It is not surprising that $\bar{I}_{S,\min}$ and $P_{V_{\min}}$ are the most important parameters in this correlation, since charge transfer and dispersion interactions are likely to play a more important role than electrostatics for complexation with iodine due to its large polarizability and low polarity. Still it is remarkable that the electrostatic term $V_{\min}$ is not significant. A plausible explanation is that the electrostatic interaction between the base and the solvent that is lost upon complexation is of the same magnitude as the electrostatic interaction that is formed between the base and iodine and that the net electrostatic effect on the complexation enthalpy therefore is close to nil. While the overall relationship is rather good, there are some obvious outliers. In particular, the enthalpies for quinuclidine and trimethylamine are both largely underestimated by our linear relationships.

Gas Phase Proton Affinities. As shown in Table 6, the proton affinities are more than a order of a magnitude larger than the enthalpies of the previously discussed Lewis acid−base interactions. Protonation does also lead to significant changes in the electron distributions of the bases and to changes in their molecular geometries. An approach that is based purely on properties of the isolated bases is therefore less likely to be successful for correlating proton affinities than for correlating regular Lewis acid−base interactions. It is accordingly very encouraging that the standard deviation for our three-parameter correlation with proton affinities is as low as 3.6 kcal/mol, in particular since the proton affinities span a range of almost 60 kcal/mol. According to the t-scores, $P_{V_{\min}}$ and $\bar{I}_{S,\min}$ are the two most important parameters in the correlation. This suggests that polarization and charge transfer are the major components of the total interaction energy, which is not surprising since a bare proton is strongly polarizing and the interaction leads to the formation of a covalent bond. The contribution from $V_{\min}$ is also highly significant, while inclusion of Π does not improve the relationship. Our findings are in qualitative agreement with the results of Morokuma energy decomposition analyses of the proton affinities of neutral bases. These studies showed that the polarization and charge transfer terms together for most bases are larger than the electrostatic term.[62,63] Furthermore, the authors arrived at these results despite that the 4-31G basis set, which is known to overestimate electrostatic effects, was used.

It should be noted that the correlation with protonation enthalpies does not include dimethylformamide and dimethylacetamide. The relationship underestimates the proton affinities of dimethylformamide and dimethylacetamide by 12.0 and 12.6 kcal/mol, respectively. We suggest that these discrepancies can probably be attributed to a significant resonance stabilization of the protonated forms of the two compounds:



Analogous resonance structures can be drawn for the unprotonated forms. However resonance stabilization is likely to be less important here, since resonance will lead to a non-advantageous charge separation. This is also consistent with our HF/6-31G* optimized geometry of dimethylformamide, which shows the amine group to be slightly pyramidal, indicating a low degree of resonance stabilization.

Summary and Conclusions

We have shown that shifts in the O−H stretching frequencies for methanol−base complexes, complexation enthalpies for phenol−base and iodine−base interactions, and gas phase proton affinities can be correlated with ab initio computed quantities of the bases by a single type of relationship. Due to the different natures of these four types of interactions, it is likely that this relationship has the potential to correlate a wide range of intermolecular interactions and provide a means predicting the interacting tendencies of poorly characterized bases without the need for experimental measurements. We have also shown that an analysis of the importance of the different quantities for correlating a specific interaction can provide information about the nature of the interaction.

Acknowledgment. The author thanks Professor Peter Politzer and Professor Jane S. Murray for helpful discussions. Financial support from the Swedish Natural Sciences Research Council (NFR) is gratefully acknowledged.

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