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Proton affinities and gas-phase basicities: theoretical methods and structural effects

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Abstract

The inherent effects of molecular structure on acid–base behavior have been a topic of debate for over 30 years. Three of the models developed to probe these effects are reviewed in this article. Each model is described briefly and the results from its application to representative systems are summarized. The first model was proposed by Taft and coworkers and subdivides intrinsic substituent effects on proton-transfer equilibria into field effects, polarizability effects and resonance effects. Various techniques used to factor out the individual contributions of these effects are described. The importance of intramolecular hydrogen bonding in determining proton affinity is also discussed. The second model was proposed by Maksic and Vianello and separates the protonation process into three sequential steps in which an electron is removed from the base, the electron is captured by the proton, and a homolytic chemical bond is formed between the radical cation and hydrogen atom. The third model was proposed by Pérez and coworkers and analyzes substituent effects on proton affinity with the aid of global and local descriptors of reactivity used in conjunction with the hard and soft acids and bases principle. Several of the composite methods designed to calculate accurate thermochemical data are also discussed briefly.

Keywords: Basicity; Energetics; Hydrogen bonds; Proton affinity; Structural effects; Substituent effects; Thermochemistry

1. Introduction: overview and definitions

Several hundred papers describing computational studies of proton affinity have appeared in the chemical literature in just the last year. The widespread interest in the basicity and accompanying proton affinity of molecules is not surprising due to the important role of the proton-transfer reaction in organic chemistry and biochemistry. The resulting protonated molecule is frequently a pivotal intermediate that guides the succeeding steps of the overall process. Knowledge of the intrinsic basicity of a compound in the gas phase is central to the understanding of its reactivity. It has now been well established that electronic structure calculations provide accurate gas-phase proton affinities as well as valuable information on the structures of the base and its conjugate acid. Another advantage of determining proton affinities computationally is that absolute rather than relative values of the proton affinity are obtained.

The equilibrium given in Eq. (1) can be viewed as the prototype for all heterolytic bond-association reactions [1]. Here n is the charge on the acid, which

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is typically +1 or 0:

$$H^+(g) + B^{n-1}(g) \leftrightarrows HB^n(g) \quad (1)$$

The negative of the standard free energy change for this reaction is the gas phase basicity of the base B^{n-1}, and the negative of the standard enthalpy change for this reaction is the proton affinity of B^{n-1}.

Proton affinities at 298 K (PA) are computed with Eqs. (2) and (3). Occasionally in the literature, the proton affinity is reported as ΔE^0:

$$PA = \Delta E^0 + \Delta E_t^{298} + \Delta E_r^{298} + \Delta(\Delta E_v)^{298} + \Delta PV \quad (2)$$

$$\Delta E^0 = [E_T(B^{n-1}) + E_T(H^+) - E_T(HB^n)] + \Delta ZPE \quad (3)$$

Here $E_T(H^+) = 0$ and $E_T(B^{n-1})$ and $E_T(HB^n)$ are the total energies of the base and its protonated form, respectively. ΔZPE is the difference in the zero-point vibrational energies of the reactants and products. $\Delta(\Delta E_v)^{298}$, ΔE_t^{298} and ΔE_r^{298} are the changes in the vibrational, translational, and rotational energy differences, respectively, of the reactants and products between 298 and 0 K. ΔPV is the change in the PV work term.

Assuming ideal behavior $\Delta PV = -RT$ for Reaction (1). Classically, $\Delta E_t^{298} = -3/2RT$ and ΔE_r^{298} is equal to $1/2RT$ for each rotational degree of freedom gained by protonation of the base. ΔZPE and $\Delta(\Delta E_v)^{298}$ are evaluated with standard statistical thermodynamics formulas [2].

The origin of intrinsic acid–base behavior is a subject of long-standing interest. Recognizing the fundamental principles involved in changes in proton affinity allows one to rationalize trends and to design molecules with desired properties. The effect of a substituent on proton affinity is a complex function of stabilization factors in both the base and its conjugate acid. A substituent induced increase in proton affinity occurs when the relative weights of these factors stabilize the acid with respect to the base. The change in proton affinity is not invariant for a particular substituent but depends on the structures of the substituted molecules.

An overview of computational methods utilized to evaluate proton affinities and gas phase basicities is presented in Section 2. Substituent effects on proton affinity are addressed in Section 3, with particular emphasis on the problem of the origin of intrinsic acid–base behavior.

2. Computational methods

Recently, there has been great progress towards the goal of predicting thermodynamic properties to "benchmark" (0.25 kcal/mol) or "chemical" (1 kcal/mol) accuracy [3–8]. Constructing a quantum mechanical model for calculating thermochemical properties entails five main steps [9]: (1) a target accuracy is specified; (2) the model is formulated; (3) computer code is written to implement the model; (4) computed results are compared to experimental results to validate the model; (5) the model is applied to molecules of interest by the end user. Addition or removal of a proton is an isogyric process, i.e., the number of unpaired electrons is identical on both sides of the reaction. Thus, the proton affinity is expected to converge more quickly with the level of calculation than other thermodynamic properties. Nevertheless, in order to obtain proton affinities to "benchmark" accuracy very high levels of correlation, e.g., CCSD(T) or QCISD(T), and very large basis sets incorporating high angular momentum functions must be utilized [3–8]. After extrapolation of the results to the complete basis set limit [10–13] correction terms for some smaller effects, such as core-valence and relativistic effects, must be added.

Martin and coworkers have followed the above protocol in their development of the W1 and more rigorous W2 methods [14,15]. The W1 and W2 energies consist of seven terms, namely the SCF component, the CCSD valence correlation component, the contribution of connected triple excitations, the inner-shell correlation contribution, the scalar relativistic contribution, the spin–orbit corrections and the molecular zero-point energy and thermal corrections. In both methods the first three contributions are extrapolated

to the infinite-basis limit. Another important point is that neither of these schemes relies on parameters derived from experiment. Unfortunately, application of approaches of this type is limited to small molecules, due to the large basis sets and the ca. N^7 scaling (where N is the number of basis functions) of the electron correlation calculations.

Other theoretical methods have been introduced to obtain thermochemical data to "chemical" rather than "benchmark" accuracy. The most popular of these methods are the G2 [16] and G3 [17] theories (and their more economical derivatives [18,19]) of Pople and coworkers, which aim to estimate energies at a high correlation level with a large basis set. The Gn procedures are based on a series of additivity approximations applied to relatively low level calculations, with zero-point and "higher-level" corrections. The G2 theory [16], for example, computes a base level energy using MP4/6-311G(d,p) at the MP2(full)/6-31G(d) optimized geometry. The base energy is then corrected for diffuse functions, additional d-functions on heavy atoms and p-functions on hydrogens, higher polarization functions on heavy atoms, and residual correlation effects. The G2 energy corresponds effectively to a QCISD(T)/6-311+G(3df,2p)//MP2(full)/6-31G(d) energy. The complete basis set (CBS) approaches of Petersson and co-workers [20–22] combine an extrapolation scheme to evaluate the projected second-order (MP2) energy in the limit of a complete basis set with empirical corrections to remove systematic errors in the calculations. A series of computations are performed with different numbers of basis functions and at different levels of theory. The results from these computations are then utilized to obtain an extrapolation to the complete basis set, fully correlated limit.

The standard test sets proposed by Pople and coworkers include proton affinities for eight molecules, NH_3, H_2O, C_2H_2, SiH_4, PH_3, H_2S, HCl and H_2 [16,17,23]. (For a review of the current status of the experimental proton affinity scale, see the companion paper by Meot-ner (Mautner) [24].) A comparison of the W1, W2 and G3 proton affinities for these molecules with respect to experiment shows mean absolute errors of 0.43, 0.50 and 1.2 kcal/mol, respectively [15]. The maximum absolute errors are 0.79, 0.91 and 2.3 kcal/mol, respectively. Based on the small deviations in the W1 and W2 data, Parthiban and Martin [15] recommend the less intensive W1 method for the calculation of benchmark quality proton affinities. They also note that the inner-shell correlation and scalar relativistic terms can "fairly safely" be disregarded when the method is applied to larger systems. A similar comparison has been made for the CBS-4, CBS-Q, G2(MP2) and G2 methods [25]. The test set also comprises eight molecules, but H_2 is replaced by C_2H_4. With respect to the experimental values, the observed RMS deviations in the proton affinities are 2.7 (CBS-4), 1.6 (CBS-Q), 1.1 (G2(MP2)) and 1.2 (G2) kcal/mol. The maximum absolute deviations are 5.4, 2.2, 1.6 and 1.7 kcal/mol, respectively.

Although the above results are encouraging, the test sets are limited to a few molecules with only one or two heavy atoms. It is therefore necessary (and prudent) to verify the accuracy of these methods for larger molecules. This calibration has been done for a number of different compounds for the Gn and CBS theories. A G2 theoretical proton affinity scale has been reported by East et al. [26] for an expanded set of 39 molecules with proton affinities ranging from 100 to 230 kcal/mol. These molecules contain up to six heavy (non-hydrogen) atoms. In order to avoid the introduction of anchoring errors, the relative experimental and theoretical proton affinities were compared. The $\Delta PA_{theory} - \Delta PA_{expt}$ values are all within the target accuracy of 2.0 kcal/mol, with most varying by 1.2 kcal/mol or less. Hammerum [27] has carried out a similar study on 29 simple organic molecules with the G3 method. There is good agreement between the G3 and experimental proton affinities as well as between the G3, G2(MP2) and CBS-Q values. Hammerum and Sølling [28] have also applied the G2(MP2) and CBS-Q procedures to 15 aliphatic imines and found that the proton affinities obtained with the two methods differ by no more than 0.5 kcal/mol. For practical reasons, the somewhat more economical CBS-Q method may be preferred for larger molecules.

Recently density functional theory (DFT) techniques have also evolved to a level of sophistication where they are able to produce thermochemical data within about 5 kcal/mol of experiment. The most widely used DFT method is the hybrid B3LYP exchange-correlation functional (Becke 3-parameter exchange with Lee–Yang–Parr correlation) [29,30]. DiLabio and co-workers [31] have developed a series of procedures similar to the G2 procedure which substitute a DFT calculation (generally B3LYP) for the computationally demanding correlation energy calculation. Coupling large basis set (e.g., 6-311+G(2d,2p)) single-point DFT energy evaluations with semi-empirical or low-level ab initio evaluations of the geometry and vibrational frequencies allows larger systems to be studied than can be studied with conventional ab initio methods. In an effort to extend the applicability of these techniques to systems with as many as 100 atoms, DiLabio and co-workers have used locally dense basis sets (LDBS) [32,33]. Similarly to the QM/MM approach, in the LDBS approach the part of the molecule where, for example, a bond is being broken is identified and treated with a large basis set. A smaller basis set or series of succeedingly smaller basis sets is utilized for the remaining parts of the molecule. Three partitioning schemes were examined in the study of the proton affinities of dipropylamine, dipropyl ether and dipropyl sulfide [33]. Each of these schemes has the NH, O or S moiety in the primary region (6-311+G(2d,2p) basis set). They differ in the assignment of CH_2 fragments to the secondary (6-311+G(d) basis set), tertiary (6-31G(d) basis set) and quaternary (STO-3G basis set) regions. The perturbation that arises with proton attachment is sufficiently delocalized to necessitate assigning the CH_2–CH_2 fragment to the secondary region and the terminal methyl groups to the tertiary region. With this partitioning scheme, the LDBS results are within 0.25 kcal/mol of the fully balanced basis set results and within about 3.5 kcal/mol of the experimental results. Conversely, the differences in the proton affinities are nearly equivalent for all three schemes [33].

For a more complete discussion of the procedures available for computing thermochemical data, see the ACS symposium proceedings edited by Irikura and Frurip [3–7] and the review article by Curtiss et al. [8]. Results obtained from conventional ab initio methods, density functional methods, semi-empirical methods and empirical methods are compared in the latter article.

2.1. Gas phase basicities

If gas phase basicities (GBs) rather than proton affinities are of interest, accurate methods for calculating third-law entropies are required. East and Radom [34] have proposed three general utility procedures for predicting absolute entropies. The procedures are designated E1, E2 and E3, in order of increasing sophistication, and use standard statistical thermodynamic formulas based on canonical partition functions. The three methods are identical for molecules with no internal rotation modes. Very low barrier internal rotations are treated as free rotations in the E1 model, and the remaining vibrational degrees of freedom are treated as harmonic oscillators. For single-rotor molecules, E2 and E3 replace the harmonic oscillator approximation with a single cosine potential. The E2 approach is similar for molecules with two internal rotation modes, in that each individual internal rotation is treated with a simple cosine potential. In contrast, the E3 model takes rotor–rotor potential coupling into account. East and Radom [34] computed new ab initio two-dimensional torsional potential energy surfaces for this purpose. The E1 procedure is sufficiently simple for general use and yields entropies accurate to about 0.5 cal/mol K for the 24 molecules for which comparisons to experiment could be made. The accuracy is improved to about 0.25 cal/mol K for the E3 procedure and to about 0.25–0.5 cal/mol K for the E2 procedure. However, as East and Radom point out, the data for the one- and two-rotor systems are quite limited and are therefore suggestive rather than definitive [34]. In fact, when the E3 model is applied to 25 experimentally observed proton-transfer reactions [26], the mean absolute deviation in the theoretical and experimental entropies of protonation is 1.3 cal/mol K and the maximum deviation is ∼3 cal/mol K. East

et al. [26] attribute these deviations primarily to uncertainties in the experimental data. The PAs and GBs are in excellent agreement with experiment.

Bouchoux et al. [35] have applied a method similar to E2 to examine the protonation thermochemistry of the first three members of the series of α,ω-alkyldiamines, 1,2-ethanediamine, 1,3-propanediamine and 1,4-butanediamine. The calculated and experimental ΔG values vary by ∼0.5 kcal/mol despite large discrepancies in the ΔS (∼5 cal/mol K) and ΔH (∼2.5 kcal/mol) values. Clearly the disagreement between theoretical and experimental protonation entropies remains to be explained.

3. Substituent effects

Computational chemistry can enhance experimental studies of basicity in three complementary ways. First, by predicting new molecular systems that exhibit the desired basicity. Second, by investigating systems that are not amenable to experimental investigation. Third, by proposing simple quantum mechanical models that provide a more detailed understanding of the protonation process.

A number of papers have appeared in the literature in the last year that fit primarily into to the first two categories. Calculations on the proton affinities of biochemical systems and potential superbases are particularly well represented. Among the biochemical systems studied are arginine [36], clonidine and rilmenidine [37], glycolaldehyde [38], histamine [39], proline [40] and proline analogs [41], thiouracils [42], 6-thioxanthine [43], and 5-substituted uracil derivatives [44]. Among the potential superbases studied are diphosphines [45], guanidine–cyclopropenimine compounds [46], guanidines and phosphazenes [47], substituted naphthalenes [48,49], phosphorus imines and ylides [50], and polyguanides [51]. There have also been several new quantum mechanical models proposed to analyze the effects of substituents on gas phase basicities [52–57]. The remainder of this section will focus on several of these models. For purposes of comparison, we start by describing the approach advanced by Taft [1] some 30 years ago that is used by many current researchers. We then proceed to the very recent approaches developed by Maksic and Vianello [52] and Pérez and coworkers [53–56].

3.1. Field/inductive, polarizability and resonance effects

Taft subdivided generalized substituent effects into three main categories in his analysis of the inherent effects of molecular structure on acid–base behavior [1]. The substituent inductive/field effect describes the electrostatic interaction between charges and multipoles in the molecule. The leading term in this component is the charge–dipole interaction (Eq. (4)). In Eq. (4), Z_1e is the charge on the point charge q_1, μ the dipole moment of the "point" dipole, θ the angle of orientation of the dipole with respect to the axis connecting the point charge and the center of the dipole, D the dielectric constant, and r is the distance between the point charge and the dipole center [1]. According to this equation, a large dipole centered on the substituent with its negative end pointed toward the cationic center in an acid with $n = +1$ would stabilize the acid relative to its neutral conjugate base and increase the proton affinity of the base. Thus, the orientation of the dipole and the sign of the charge Z both determine whether the inductive effect is stabilizing or destabilizing:

$$E = \frac{Z_1 e \mu \cos\theta}{Dr^2} \tag{4}$$

The substituent polarizability effect describes the electrostatic interaction between charges and induced multipoles. The main contributor to this component is the charge-induced dipole interaction. If a charge $q_1 = Z_1e$ is separated by a distance r from the center of the polarizable material and α is the polarizability, the energy of this interaction is given by Eq. (5) [1]. A polarizable substituent will stabilize $HA^{n=+1}$ or $A^{n-1=-1}$, since according to Eq. (5) stabilization occurs regardless of whether Z is positive or negative:

$$E = -\frac{Z_1^2 e^2 \alpha}{2Dr^4} \tag{5}$$

The substituent resonance or pi electron delocalization effect is a measure of the ability of the substituent to transfer pi electronic charge to or from the active atomic center [1]. Substituents that are pi electron donors contain an atom (*F*) or a group of atoms (OCH_3) with a lone pair in a pseudo pi orbital of the (first) atom. Pi donor ability increases as the (first) atom becomes more negative or electropositive. Substituents that are pi electron acceptors contain unsaturated groups with unoccupied pseudo pi orbitals. Pi acceptor ability increases as the net charge on the group becomes more positive or the group becomes more electronegative. The equilibrium in Reaction (1) will shift in the direction of the system with the greater stabilization by pi electron delocalization. Although resonance effects are often predominant in solution, a combination of field/inductive and polarizability effects often predominates in the gas phase [1].

One of the problems in applying the above concepts to analyze substituent effects is that it is difficult to factor out the contributions from each of the three components. However, Taft has suggested several workable strategies that can be followed to isolate and evaluate the inductive, resonance and polarizability effects [1]. Utilizing these strategies he was able to rationalize, for example, the increase in the proton affinity of alkyl substituted amines compared to ammonia, the larger effect of alkyl substitution on the proton affinities of alcohols and ethers than of amines, and the increase in the proton affinity of meta- and para-substituted pyridinium ions with increasing sigma donating ability of the substituent.

3.1.1. Separation of field/inductive and polarizability effects

In order to separate out the field/inductive and polarizability effects of methyl substitution of hydrogens on the proton affinities of alcohols, the gas phase basicities and acidities of the alcohols were combined via Eqs. (6)–(8) [1]. Note that Reactions (6)–(8) are isodesmic reactions, since the number and types of bonds are conserved:

$$ROH_2^+ + CH_3OH \leftrightarrows CH_3OH_2^+ + ROH, \quad \delta\Delta G^\circ_{rx6} \approx F + P \tag{6}$$

$$RO^- + CH_3OH \leftrightarrows CH_3O^- + ROH, \quad \delta\Delta G^\circ_{rx7} \approx P - F \tag{7}$$

$$ROH_2^+ + CH_3O^- \leftrightarrows RO^- + CH_3OH_2^+, \quad \delta\Delta G^\circ_{rx8} \approx 2F \tag{8}$$

Eq. (5) suggests, to a first approximation, that the charge-induced dipole interaction will stabilize ROH_2^+ relative to $CH_3OH_2^+$ and RO^- relative to CH_3O^- to essentially the same extent. In contrast, to a first approximation, a charge–dipole interaction that stabilizes ROH_2^+ relative to $CH_3OH_2^+$ will destabilize RO^- relative to CH_3O^- to essentially the same extent. If the contribution to $\delta\Delta G^\circ$ of the polarizability effect is designated *P* and that of the field effect is designated *F*, these assumptions yield the values for $\delta\Delta G^\circ$ given in Eqs. (6)–(8). Values for $\delta\Delta G^\circ_{rx6}$ and $\delta\Delta G^\circ_{rx7}$ along with the corresponding *F* and *P* values are collected in Table 1 for seven alkyl substituents R [58].

The data show that both *F* and *P* stabilize the substituted alcohol acid relative to the base, i.e., for Reaction (6) the equilibrium shifts to the side of the substituted acid. However, the contribution made by the polarizability term is sufficiently dominant that there is a direct correlation between the increase in proton affinity and the magnitude of the polarizability substituent effect. Although additional work has indicated that a

Table 1
Field/inductive and polarizability substituent effects on the proton affinities of alcohols[a]

R	$\delta\Delta G^\circ_{rx6}$	$\delta\Delta G^\circ_{rx7}$	F[b]	P[b]
t-C_4H_9	11.5	5.9	2.8	8.7
i-C_3H_7	8.5	5.1	1.7	6.8
neo-C_5H_{11}	9.7	7.4	1.2	8.5
i-C_4H_9	8.5	5.8	1.3	7.2
n-C_3H_7	7.0	4.5	1.3	5.7
C_2H_5	4.8	3.1	0.9	3.9
CH_3	0.0	0.0	0.0	0.0

[a] Energies in kcal/mol [58].
[b] $F = \delta\Delta G^\circ_{rx8}/2$; $P = \delta\Delta G^\circ_{rx6} - F$.

better relationship for P_{rx6} and P_{rx7} is $P_{rx6} = 1.5P_{rx7}$, this change will not alter the above conclusions [1].

One way the magnitude of the substituent effect for oxygen bases relative to nitrogen bases can be assessed is by evaluating ΔPA for the isodesmic Reactions (9) and (10) [1]. Taft has reported data for R = CH_3, C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, and *t*-C_4H_9 among other groups. When the experimental ΔPA values are compared for analogous R groups, it is observed that the increase in proton affinity is about 35% larger for the oxygen bases than for the nitrogen bases. This was primarily attributed to a larger polarizability effect for the oxygen bases as a result of the greater electron demand from the oxonium ion center compared to the ammonium ion center. That is, the more electropositive nitrogen and larger number of hydrogens make the ammonium ion center better able to bear a positive charge. For this reason, the electron density transferred from the R group(s) to the added proton (onium moiety) is expected to be larger for the oxygen bases compared to water than for the nitrogen bases compared to ammonia (ammonium moiety):

$$R_2OH^+ + H_2O \leftrightarrows OH_3^+ + R_2O, \quad \delta\,\Delta H^\circ_{rx9} = PA(R_2O) - PA(H_2O) \tag{9}$$

$$R_2NH_2^+ + NH_3 \leftrightarrows NH_4^+ + R_2NH, \quad \delta\,\Delta H^\circ_{rx10} = PA(R_2NH) - PA(NH_3) \tag{10}$$

3.1.2. Separation of field/inductive and resonance effects

The approach recommended by Taft to measure resonance effects in conjugated organic systems is to choose reactions for which the reference compounds have the same number of carbon atoms, as well as similar substituents and structures, as the compounds of interest [1]. Taft utilized this approach in his analysis of the preferential resonance stabilization of, for example, neutral *N*-phenyl piperidine with respect to the cationic acid. More recently, Rablen [59] utilized a similar approach to investigate the origin of the enhanced acidity of acetic acid, carbonic acid, acetamidine and guanidine relative to alcohols and amines. The energy changes associated with a series of isodesmic reactions were evaluated ab initio to assess whether the enhanced acidity is primarily due to resonance or inductive stabilization of the anion. The calculations were performed at the CBS-Q [20] and three lower levels of theory. The isodesmic reactions Rablen examined for acetic acid are given in Eqs. (11) and (12) [59]. The reference compound was chosen to be *t*-butyl alcohol in order to replace the oxygen atoms of acetic acid with non-polar substituents of a similar size:

$$(CH_3)_3COH + CH_3COO^- \leftrightarrows (CH_3)_3CO^- + CH_3COOH \tag{11}$$

$$(CH_3)_2CO + CH_3CO(H)OH^+ \leftrightarrows (CH_3)_2COH^+ + CH_3COOH \tag{12}$$

The CBS-Q value for ΔE_{rx11} is 27.9 kcal/mol; the value for ΔE_{rx12} is −6.2 kcal/mol [59]. Thus, at this level of calculation the proton affinity of CH_3COO^- is 27.9 kcal/mol lower than that of $(CH_3)_3O^-$, and the proton affinity of CH_3COOH is 6.2 kcal/mol lower than that of $(CH_3)_2CO$. The stabilization of the acetate anion relative to acetic acid (Reaction (11)) can be attributed to either a more favorable resonance interaction or a more favorable inductive interaction in the anion [59]. The second resonance structure for acetic acid is a zwitterion, and there is less stabilization than for the symmetrical anion. Also, the carbonyl bond dipole will interact more strongly with the negatively charged oxygen atom in the anion than with the neutral hydroxyl group in the acid. On the other hand, protonated acetic acid will be stabilized relative to acetic acid (Reaction (12)) if the resonance contribution predominates but will be destabilized relative to acetic acid if the inductive contribution predominates. The C–OH bond dipole will interact favorably with the unprotonated carbonyl oxygen but will interact unfavorably with the protonated carbonyl oxygen. Since acetic acid is stabilized relative to protonated acetic acid ($\Delta E_{rx12} < 0$), the results imply that the inductive contribution outweighs the resonance contribution [59]. Rablen assumes that the resonance and inductive effects for Reaction (11) are approximately

equal to those for Reaction (12), which leads to the conclusion that 75% of the enhanced acidity of acetic acid (reduced basicity of acetate anion) is due to inductive effects for Reaction (11) and about 25% is due to resonance effects. When acetic acid is replaced by carbonic acid $(OH)_2CO$ in Reactions (11) and (12), substituting the methyl group with a hydroxy group further increases the acidity and decreases the basicity [59]. The proton affinity of carbonic acid is decreased with respect to acetic acid even though $(OH)_2COH^+$ has three equivalent resonance structures, which provides additional support for the conclusion that inductive effects are of greater importance than resonance effects in these systems [59]. This conclusion agrees with that of Siggel et al. [60], and Taft et al. [61].

Reactions (13) and (14) involving acetamidine and *t*-butyl amine are the exact nitrogen analogues of Reactions (11) and (12) [59]. The CBS-Q energy changes associated with these reactions are $\Delta E_{rx13} = 26.7$ and $\Delta E_{rx14} = 8.4$ kcal/mol. In this case, the calculations indicate that acetamidine has a lower proton affinity than *t*-butyl amine and that acetamidine has a higher proton affinity than acetone imine. Apparently for the nitrogen bases the resonance substituent effects outweigh the inductive substituent effects, which is not entirely unexpected since nitrogen is less electronegative than oxygen. Quantitatively, resonance effects contribute about 60% to the enhanced acidity and basicity of acetamidine, whereas inductive effects contribute about 40% [59]. Replacing the methyl group with an amino group again provides further support for the conclusion that resonance supplies the majority of the stabilization in the nitrogen systems. Guanidine has an enhanced acidity and basicity compared to acetamidine:

$$(CH_3)_3CNH_2 + CH_3C(NH)NH^- \leftrightarrows (CH_3)_3CNH^- + CH_3CN(H)NH_2 \quad (13)$$

$$(CH_3)_2CNH + CH_3C(NH_2)NH_2^+ \leftrightarrows (CH_3)_2CNH_2^+ + CH_3CN(H)NH_2 \quad (14)$$

Rablen obtained a second estimate of the magnitude of the inductive and resonance effects in the above reactions by extending the study to evaluate the contributions of hydroxy, amino and fluorine substituents to the acidity and basicity of a series of alcohols and amines [59]. Reactions (15)–(18) are four of the isodesmic reactions examined in this part of the study:

$$(CH_3)_3COH + (CH_3)_2FCO^- \leftrightarrows (CH_3)_3CO^- + (CH_3)_2FCOH \quad (15)$$

$$(CH_3)_3COH + (CH_3)_2FCOH_2^+ \leftrightarrows (CH_3)_3COH_2^+ + (CH_3)_2FCOH \quad (16)$$

$$(CH_3)_3COH + CH_3F_2CO^- \leftrightarrows (CH_3)_3CO^- + CH_3F_2COH \quad (17)$$

$$(CH_3)_3COH + CH_3F_2COH_2^+ \leftrightarrows (CH_3)_3COH_2^+ + CH_3F_2COH \quad (18)$$

The ΔE's of 16.3 kcal/mol for Reaction (15) and −13.3 kcal/mol for Reaction (16) indicate that the fluorine substituent decreases the proton affinity of both $(CH_3)_2FCO^-$ and $(CH_3)_2FCOH$. The ΔE's of 30.6 kcal/mol for Reaction (17) and −29.6 kcal/mol for Reaction (18) show that the effects are essentially additive. When compared to the neutral system, the stabilization of the anion or destabilization of the cation brought about by fluorination can be explained by either hyperconjugation or inductive (electrostatic) considerations [59]. As long as a lone pair of electrons on the oxygen is oriented anti with respect to the adjacent σ^*_{CF} orbitals hyperconjugative stabilization can occur. It is expected that this interaction will be enhanced for the anion relative to the neutral system and inhibited in the cation relative to the neutral system. In terms of an electrostatic argument, the C–F bond dipole will interact more favorably with the anionic oxygen atom and less favorably with the cationic OH_2^+ group than with the OH group [59].

One way to test the importance of hyperconjugation in these molecules is to examine the bond length changes that occur with substitution. A hyperconjugative interaction should lengthen the C–F bond and shorten the C–O bond in the anion compared to the neutral alcohol. Such bond length changes

are observed for the B3LYP/6-31+G(d,p) optimum geometries [59]. For example, the C–O bond in $(CH_3)_2FCO^-$ is 0.14 Å shorter than the C–O bond in $(CH_3)_2FCOH$, whereas the C–F bond is 0.32 Å longer in $(CH_3)_2FCO^-$ than in $(CH_3)_2FCOH$. Unfortunately, however, these changes in bond length can just as easily be explained based on electrostatic reasoning [59]. The negative charge on the oxygen atom in the anion will repel the negatively charged fluorine atom and attract the positively charged carbon atom. Perhaps even more significantly, the C–O bond shortening in *t*-butyl alcohol is only slightly smaller at 0.10 Å, and the lengthening of the C–F bonds that are oriented properly with respect to the lone pairs deviates from those that are not by only 0.00–0.02 Å. These results suggest that the changes in geometry are due to electrostatic rather than hyperconjugative factors [59].

In fact, the effect of the fluorine, hydroxyl, and amine substituents on the acidity and basicity of alcohols and amines is predicted very well by a simple electrostatic model with only one adjustable parameter [59]. According to the model proposed by Rablen, the electrostatic contributions of polar bonds must be additive, and cations and anions must make a contribution that is equal in magnitude but opposite in sign. In addition, each type of polar bond must make a contribution that is proportional to the difference in electronegativity between the atoms in the bond [59]. When the model is used to calculate the portion of the isodesmic reaction energies due to electrostatic effects, a correlation coefficient r^2 of 0.99 and a slope of 11.0 kcal/mol are obtained for those molecules without π bonds. Based on this slope, each C–F bond contributes 15.4 kcal/mol, each C–O bond 8.8 kcal/mol, and each C–N bond 4.4 kcal/mol to the change in proton affinity [59].

Once the magnitude of the electrostatic contribution has been determined, the magnitude of the resonance contribution can be estimated. In agreement with the earlier results, the data from this approach show that resonance interactions are largest for carbon at 22.6 kcal/mol, about half as large for nitrogen at 13.7 kcal/mol and smallest for oxygen at 6.1 kcal/mol. Thus, the resonance contribution decreases as electronegativity increases. Moreover, cations are stabilized less by resonance interactions than are anions [59].

The importance of resonance effects in controlling the basicity of imines is underscored by Kovacevic et al.'s study of substituted guanidine compounds [46]. In this work cyclopropenimine fragments were combined with guanidine $HN=C(NH_2)_2$ to tailor (super)bases with high proton affinity. Four of the seven bases examined by Kovacevic et al. [46] were built on the framework with one cyclopropenimine molecule shown in Scheme 1. The remaining bases were built on the framework with two cyclopropenimine molecules. X and Y represent H, NH_2 or $N(CH_3)_2$, R represents H or CH_3, and R^1 represents H, CH_3 or C_2H_5.

The proton affinities were calculated with Eq. (3) using MP2/6-311+G(d,p)//HF/6-31G(d) or scaled HF/6-31G(d) total energies and are given in Table 2. Eq. (19) gives the relationship between the scaled HF energies and the proton affinity, where ΔE is the difference in the total energies of the base and its conjugate acid [46]:

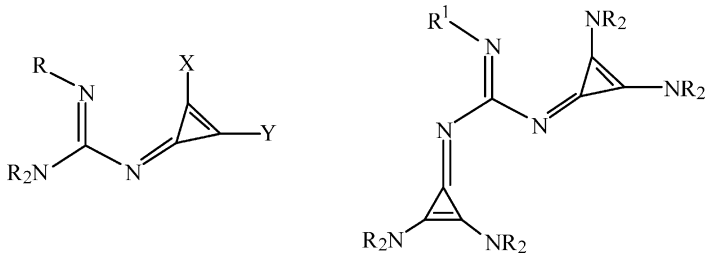
$$PA(HF_{sc}) = 0.8924\Delta E + 10.4, \quad \text{(kcal/mol)} \qquad (19)$$

The preferred site of protonation is uniformly the imino nitrogen substituted with a single R or R^1 group. All seven bases have a proton affinity higher than that of guanidine (233.7 kcal/mol [51]) and at least one of them has a proton affinity higher than that of the Schwesinger and co-workers proton sponge

Table 2
Proton affinities of cyclopropenimine-substituted guanidines[a]

Base				$PA(HF_{sc})$	PA(MP2)
X	Y	R	R^1		
H	H	H		242.9	240.1
H	NH_2	H		251.0	248.9
NH_2	NH_2	H		251.1	250.6
$N(CH_3)_2$	$N(CH_3)_2$	CH_3		262.8	
		H	H	267.9	267.3
		H	C_2H_5	270.4	
		CH_3	CH_3	280.1	

[a] MP2/6-311+G(d,p) and scaled HF/6-31G(d) data from ref. [46]. PAs in kcal/mol.



Scheme 1.

(269.5 kcal/mol [50]), which is recognized as one of the strongest organic superbases.

The increase in proton affinity relative to guanidine is attributed to a greater resonance stabilization of the guanidine–cyclopropenimine protonated bases than that of protonated guanidine [46]. Replacing a hydrogen atom with an amino group also enhances the resonance effect in the protonated systems due to a strong interaction between the nitrogen lone pair and the π-network. The methyl substituents enhance the delocalization of the positive charge upon protonation. The qualitative evidence for the importance of the resonance effect in stabilizing these conjugate acids includes the following structural changes brought about by protonation: (1) the lengthening of the double bonds and shortening of the single bonds; (2) the decrease in bond order (total and π) for the double bonds and increase in bond order for the single bonds; (3) the increase in planarity of the NR_2 groups; and (4) the aromatization of the cyclopropenimine ring(s).

The resonance contribution to the proton affinity can be quantified through the use of homodesmic chemical reactions, where the hybridization is approximately conserved. The relevant reactions for the simplest guanidine–cyclopropenimine base are given in Eqs. (20) and (21) [46]:

$$H_2N\text{–}C(=NH)\text{–}N\text{–}c\text{-}C_3H_2 + H_3C\text{–}NH_2 \rightarrow H_2N\text{–}C(=NH)\text{–}NH_2 + H_3C\text{–}N\text{–}c\text{-}C_3H_2 \quad (20)$$

$$H_2N\text{–}C(=NH_2)\text{–}N\text{–}c\text{-}C_3H_2{}^+ + H_3C\text{–}NH_2 \rightarrow H_2N\text{–}C(=NH_2)\text{–}NH_2{}^+ + H_3C\text{–}N\text{–}c\text{-}C_3H_2 \quad (21)$$

The increase in the resonance effect in the cation induced by the cyclopropenimine substitution of guanidine is equal to the difference in the ΔE values for these two reactions. When this quantity (7.1 kcal/mol) is added to the resonance contribution to the PA of guanidine (24–27 kcal/mol [51]), the resonance stabilization of $H_2N\text{–}C(=NH_2)\text{–}N\text{–}c\text{-}C_3H_2{}^+$ is calculated to be 31–34 kcal/mol. The analogous calculation for $H_2N\text{–}C(=NH_2)\text{–}N\text{–}c\text{-}C_3(NH_2)_2{}^+$ yields an estimate of 41–44 kcal/mol for the resonance effect in this acid.

3.2. Internal hydrogen bonding

As Taft notes in his discussion of generalized substituent effects, considering just the three categories of field/inductive, polarizability, and resonance effects is not adequate for substituents that form cyclic chelates with a charge center [1]. More specifically for systems in which an internal hydrogen bond is formed, this structural effect is often the dominant influence on the proton affinity. The importance of intramolecular hydrogen bonding in determining proton affinity is illustrated by the α,ω-alkyldiamines. In their G2(MP2) [18] study of 1,2-ethanediamine, 1,3-propanediamine and 1,4-butanediamine, Bouchoux et al. find that the most stable conformer of each of these neutral systems has a gauche NCCN arrangement that allows formation of a N–H···N hydrogen bond [35]. The gauche arrangement is also preferred for the protonated systems. Table 3 lists the values for the proton affinities, gas phase basicities, H···N bond distances and N–H···N bond angles computed by Bouchoux et al. [35].

Table 3
Thermochemical and structural data for α,ω-alkyldiamines[a]

System	PA	GB	R(H···N)	N–H···N
$NH_2(CH_2)_2NH_2$	226.5	217.6	2.41	106.4
$NH_2(CH_2)_2NH_3^+$			1.89	121.5
$NH_2(CH_2)_3NH_2$	233.7	223.9	2.22	125.1
$NH_2(CH_2)_3NH_3^+$			1.69	148.0
$NH_2(CH_2)_4NH_2$	239.0	227.9	2.06	147.8
$NH_2(CH_2)_4NH_3^+$			1.59	164.0

[a] G2(MP2) data, ref. [35]. PA and GB in kcal/mol, R(H···N) in Å, and N–H···N in degrees (°).

The shorter H···N distance and larger (more linear) N–H···N angle in each acid compared to its conjugate base indicates that the acid is stabilized with respect to the base by the internal hydrogen bonding. This result accounts for the relatively high proton affinities and gas phase basicities of these compounds. Similar structural changes are observed as the number of methylene groups increases, which accounts for the increase in proton affinity with chain length [35].

3.3. Three-step protonation process

Maksic and Vianello [52] have taken a different approach to address the question of the origin of the intrinsic basicity of neutral bases. Their analysis involves breaking down Eq. (1) into the three-step process represented in Eqs. (22)–(24). Then the proton affinity of base B is given by Eq. (25):

$$B \rightarrow B^{\bullet +} + e^-, \quad \Delta H = (IP)_1^{ad} \tag{22}$$

$$H^+ + e^- \rightarrow H^\bullet, \quad \Delta H = EA(H^+) \tag{23}$$

$$B^{\bullet +} + H^\bullet \rightarrow BH^+, \quad \Delta H = BAE \tag{24}$$

$$PA = BAE + EA(H^+) - (IP)_1^{ad} \tag{25}$$

In Eq. (25), BAE is the magnitude of the homolytic bond association energy of BH^+ or, alternatively, the homolytic bond dissociation energy of BH^+. $EA(H^+)$ is the magnitude of the electron affinity of H^+ or, alternatively, the electron detachment energy of $H^\bullet$, and it has a value of 313.6 kcal/mol. $(IP)_1^{ad}$ is the first adiabatic ionization energy, i.e., the energy required to remove the mostly weakly bound electron. One way to interpret $(IP)_1^{ad}$ is that it is the cost in energy required to form the homolytic bond. Since generally $(IP)_1^{ad} < EA(H^+)$, Eq. (25) explains the observation that the proton affinity is usually much larger than the homolytic bond energy [52].

Since the adiabatic ionization energy is evaluated with the optimized structures of B and B^+, it cannot be associated with properties of the initial base only. Koopmans' theorem was used to differentiate between the initial state (base) and final state (conjugate acid) effects [52]. Thus, the contribution to the proton affinity resulting from features of the electron distribution in the base is obtained from the negative of the orbital energy of the lone pair orbital, $(IP)_n^{Koop} = -\varepsilon_n$. In order to calculate IP_n^{Koop} the base must be in its ground state and the single-determinant approximation (Hartree–Fock method) must be utilized. The difference between the adiabatic ionization energy and the ionization energy from Koopmans' theorem yields the contribution to the ionization energy from final state effects (Eq. (26)):

$$E(ei)_{rex}^{(n)} = (IP)_n^{Koop} - IP_1^{ad} \tag{26}$$

Maksic and Vianello [52] designate $E(ei)_{rex}^n$ the relaxation energy, recognizing that this designation is not truly descriptive in some cases. $E(ei)_{rex}^n$ includes a component due to the relaxation of the geometry and electron distribution during the protonation process and may include a component $(IP)_n^{ad} - (IP)_1^{ad}$, if the lone pair orbital is not the HOMO.

Combining Eqs. (25) and (26) generates an expression (Eq. (27)) for the proton affinity (in kcal/mol) that allows initial and final state effects to be isolated. In summary, the initial state (base) effects are given by $(IP)_n^{Koop}$, and the total final state (conjugate acid) effects are given by the sum of the remaining three terms [52]:

$$PA = -(IP)_n^{Koop} + E(ei)_{rex}^{(n)} + BAE + 313.6 \tag{27}$$

The approach taken by Maksic and Vianello [52] has the advantage of being rigorous; the only approximations introduced are those from inaccuracies in the ab initio computations. However, as Maksic and Vianello strongly emphasize, the approach is also idealized. An

electron is not completely removed from the base and given to the proton, so the initial effects obtained from this analysis are too large by an estimated 20–25%. Nevertheless, the general qualitative conclusions are correct.

Maksic and Vianello [52] have applied their analysis to nitrogen bases, including amines, imines, polyguanides, and phosphazenes and have found that these neutral bases can be split into three categories. The first category is comprised of those bases, e.g., alkylated ammonia and alkyl derivatives of methyleneimine, for which the proton affinity is determined by initial state effects. The third category is comprised of those bases, e.g., amine derivatives of methyleneimine and polyguanides, for which the proton affinity is governed by final state effects. The third category is comprised of those bases, e.g., phosphazenes, for which the proton affinity is controlled by a combination of initial and final state effects. The relaxation energy makes an important contribution to the relative proton affinities of the compounds in the second and third categories.

For illustrative purposes, consider the specific example of the effect of methyl substitution of the hydrogens in ammonia and how Maksic and Vianello's interpretation of this effect compares with that of other researchers. Table 4 presents the experimental and calculated proton affinities and the values of the first four terms in Eq. (27) for NH_3, CH_3NH_2, $(CH_3)_2NH$ and $(CH_3)_3N$ [52].

The decrease in $(IP)_1^{Koop}$ in the $(CH_3)_mNH_{3-m}$, $m = 0$–3, series of bases as m increases indicates that the lone pair electron is less tightly bound as the number of methyl groups increases. Maksic and Vianello [52] attribute this result primarily to the decrease in the s-character of the lone pair as m increases. The %s-character of the lone pair has values of 25, 21.6, 17.7 and 14.1% as the base varies from NH_3 to $(CH_3)_3N$. The decrease in BAE can also be correlated with the decrease in the %s-character, since both are directly related to the overlap integrals. In fact, Maksic and Vianello find a fairly good linear relationship between $(IP)_1^{Koop}$ and the %s-character and between BAE and the %s-character for these bases [52].

One unexpected result from this work is that the relaxation energy is essentially identical for each of these bases. This observed constancy appears to be inconsistent with the generally accepted idea (see above) that the polarizability of a molecule increases as the number of alkyl groups increases. In order to explore this apparent inconsistency further, Maksic and Vianello [52] separate the relaxation energy into two components, the orbital and nuclear relaxation. The orbital relaxation is defined as $(IP)_1^{Koop} - (IP)_1^{v}$, where $(IP)_1^{v}$ designates the first vertical ionization energy. The vertical ionization energy is obtained by maintaining the ground-state geometry of the neutral base in the radical cation $B^{\bullet+}$ and optimizing only the molecular orbitals of the cation. The orbital relaxation energy ranges from 22.1 to 25.6 kcal/mol as m increases, which is in agreement with the expected increase in polarizability. The contribution of the relaxation energy to the homolytic bond energy can also be calculated from the difference BAE − $(BAE)_{frc}$. The term $(BAE)_{frc}$

Table 4
Proton affinities, ionization energies and homolytic bond energies of methylated amines[a]

Base	PA[b,c]	IP_1^{ad}[b]	IP_1^{Koop}	$E(ei)_{rex}$	BAE	BAE − $(BAE)_{frc}$
NH_3	204.1 (204.0)	229.5 (232.2 ± 0.5)	270.3	40.8	119.0	22.5
CH_3NH_2	214.6 (214.9)	205.5 (205.2 ± 2.3)	246.3	40.8	106.4	26.6
$(CH_3)_2NH$	221.6 (222.2)	191.4 (190.0 ± 1.8)	231.4	40.0	97.9	36.5
$(CH_3)_3N$	226.0 (226.8)	180.3 (181.0 ± 1.2)	221.2	40.9	91.7	41.0

[a] All values in kcal/mol. IP_1^{Koop} calculated with HF/6-311+G(d,p) single point energies. All other values calculated with MP2/6-311+G(d,p)//B3LYP/6-31G(d) single-point energies [52].
[b] Experimental value in parentheses, ref. [62].
[c] Calculated value from Eq. (27).

is evaluated by determining the bond dissociation energy when only the N–H^+ bond length is optimized in BH^+. The remaining geometrical parameters are kept frozen at their values in the equilibrium structure of the radical cation. The data in the last column of Table 4 show that, again as expected, the relaxation contribution does increase as m gets larger. Overall however, according to this analysis, the proton affinity increases with the number of methyl groups because the drop in $(IP)_1^{Koop}$ predominates over the drop in BAE (Table 4). Therefore, it is concluded that the relative gas-phase proton affinities of the $(CH_3)_mNH_{3-m}$, $m = 0$–3, series of bases are dictated by the ground state properties of the initial base and not the final state properties of the conjugate acid [52].

Although Maksic and Vianello's [52] analysis is quite general, it should be most applicable to a series of related molecules. Once the trend in proton affinities has been rationalized for the series, it should be possible to make predictions based on those trends. For example, Maksic et al. [63] believe that this approach will be helpful in designing neutral organic superbases. The origin of this opinion is the unanticipated result that the high proton affinity of 1,1-diaminoethylene is due to a very small $(IP)_1^{Koop}$ value [52]. This observation led to a study of polyenes substituted by CH_3 and NH_2 groups at suitably chosen positions [63]. Maksic et al.'s preliminary results indicate that these molecules are surprisingly strong carbon bases.

3.4. Global and local reactivity indices

Several research groups have investigated substituent effects on basicity from the perspective of how the substituent alters the global and local reactivity patterns of the base. Among the research groups are those of Pérez and coworkers [53–56], Nguyen and coworkers [64], and Geerlings and coworkers [65,66]. Since Pérez and coworkers have published several papers in this area in the last 2 years, this account will focus on their model. In this model, polarization (electronic) effects are probed as changes in the local softness Δs_k at the basic center k brought about by the substitution. In contrast, inductive (electrostatic) effects are probed as changes in the electronic chemical potential (electron density) $\Delta\rho_k$ at the basic center k brought about by the substitution [53–56]. These data are used in conjunction with Pearson's HSAB rule [67] to analyze the substituent effects. According to this rule, if the proton is considered as absolutely hard, then the higher the value of the chemical hardness of a base the larger its proton affinity.

The criterion utilized to analyze inductive effects is given by the expressions in Eq. (28), whereas polarization effects are explored through Eq. (29) [56]:

$$\Delta\rho_k = f_k\,\Delta N \approx s_k\,\Delta\mu \tag{28}$$

$$\Delta s_k = s_k - s_k^\circ = S\,\Delta f_k + f_k^\circ\,\Delta S \tag{29}$$

In these equations, μ is the electronic chemical potential, N the number of electrons, S the global softness of the molecule, f_k and f_k° are the Fukui functions localized at active site k for the substituted and reference molecules, respectively, and s_k and s_k° are the local softness at site k for the substituted and reference molecules, respectively. The global softness of the molecule is calculated via Eq. (30), where IE is the vertical ionization energy and EA is the vertical electron affinity. The chemical potential is obtained from the relationship in Eq. (31) [68]:

$$S = \frac{1}{IE - EA} \approx \frac{1}{\varepsilon_{LUMO} - \varepsilon_{HOMO}} \tag{30}$$

$$\mu = \frac{IE + EA}{2} \approx \frac{\varepsilon_{LUMO} + \varepsilon_{HOMO}}{2} \tag{31}$$

Pérez and coworkers evaluate the condensed Fukui functions on atom k in terms of the HOMO coefficients and overlap matrix [69]. The local softness parameter is defined as $s_k = f_k S$. Calculating $\Delta\rho_k$ in terms of $\Delta\mu$ rather than ΔN avoids possible problems associated with the population analysis required to determine ΔN [56]. Electronic charge distributions are generally dependent on the method and basis set utilized to perform the population analysis.

The systems to which this model has been applied include alkyl amines [55], alkyl alcohols [53–56], alkyl thioalcohols [54], alkyl silanols [56] and haloacetic acids [68]. For purposes of comparison,

Table 5
Proton affinities, descriptors of reactivity and electron population[a]

Base	PA_{exp}[b]	f_x^-	S	s_k^-	q_x
NH_3	204.0	0.9659	3.17	3.03	−0.9959
CH_3NH_2	214.9	0.8416	3.35	2.82	−0.8332
$(CH_3)_2NH$	222.2	0.7799	3.40	2.65	−0.6757
$(CH_3)_3N$	226.8	0.7459	3.54	2.64	−0.5313
CH_3O^-	379.2	0.7572	3.70	2.80	−0.8940
$CH_3CH_2O^-$	376.1	0.7405	3.86	2.86	−0.8977
$(CH_3)_2CHO^-$	374.1	0.7381	3.95	2.92	−0.9096
$(CH_3)_3CO^-$	373.3	0.7550	4.06	3.06	−0.9285
$(CH_3)_3CCH_2O^-$	371.8	0.7416	4.22	3.13	−0.8945

[a] Calculated values based on HF/6-31G(d) data, ref [55]. PAs in kcal/mol, descriptors of reactivity in hartrees.
[b] Ref. [62] for amines, ref. [70] for alkoxides.

the discussion here will be limited to the alkyl amines and alkyl alcohols. Table 5 collects the values of the Fukui function, global softness, local softness and Mulliken electron population at atom k for the two series of bases [55]. In this table X = N or O.

The enhanced proton affinity as methyl groups are added to ammonia correlates inversely with a decrease in the absolute Fukui function and the local softness at the basic nitrogen center. That is, the basicity increases with methyl substitution since the local hardness at the basic site increases. As has been seen by other researchers, the change in electron density on the nitrogen does not correlate with the change in proton affinity. Thus, similarly to Maksic and Vianello [52], Pérez et al. [55] find that the alkyl substituent effect in amines is an initial state effect.

Although for the nitrogen series f_k^- is the dominant term in the parameter s_k^-, for the alkoxide series S is the dominant term (Table 5) [55]. As a result, for the latter series the decrease in proton affinity correlates with the increase in the global softness of the base and the local softness at the oxygen atom. In this case, the proton affinity decreases with alkyl substitution since the local hardness at the basic oxygen site decreases.

Despite the fact that the method is not rigorous, employing global and local descriptors of reactivity to rationalize substituent effects has proved useful for a number of systems [53–56,68]. However, there are some drawbacks to this approach. First, local descriptors have been found to predict the relative basicities of heteroatoms incorrectly [64,71]. Second, the approach falls short in providing a description of the influence of final state effects in the protonation process [52,64].

4. Summary

The procedure required to compute thermochemical data to very high accuracy via quantum mechanical calculations is now known. Recently, composite approaches incorporating some or all of the steps in this procedure have been developed. As a result, it is now possible to calculate proton affinities to “benchmark” accuracy (0.25 kcal/mol). These calculations are so computationally demanding, however, they can only be applied to small systems. “Chemical” accuracy (1 kcal/mol) can be achieved for systems containing up to about 10 heavy atoms, but for larger systems it may be necessary to sacrifice accuracy for computational efficiency. Methods have also been developed to improve calculated entropies, but they are not yet calibrated as fully as are those for calculated enthalpies.

Gas-phase proton affinities can be utilized to identify structural effects on inherent molecular basicities. The effect of a substituent on the proton-transfer equilibrium is a complex function of stabilization factors in both the base and its conjugate acid. Many researchers have expended considerable effort in calculating proton affinities and elucidating the contributing stabilization factors. One of the most popular models applied to analyze substituent effects on basicity is that of Taft [1]. According to this approach, in the absence of chelation field/inductive, polarizability and resonance effects are the predominant effects in acid–base behavior. The use of isodesmic and homodesmic reactions has proved to be advantageous in separating out and quantifying these three components. When internal hydrogen bonding occurs, this structural effect is often the determinant factor in the proton affinity.

Among the more recent models proposed to gain insight into the underlying principles of the protonation process are those of Maksic and Vianello [52] and Pérez and coworkers [53–56]. Maksic and Vianello

describe the protonation process in terms of a three-step thermochemical cycle. The base is ionized to form the radical cation, the proton captures the electron to form a hydrogen atom and the radical cation and hydrogen atom combine to form the conjugate acid. The contribution of initial state (base) effects to the proton affinity is equal to the ionization energy of the lone pair electron given by Koopmans' theorem. The contribution of the final state (conjugate acid) effects is equal to the sum of the remaining thermochemical terms in the proton affinity expression. The disadvantage of this approach is that it overemphasizes the contribution made by initial state effects. The advantages of this approach are that it is general and rigorous and that it separates out initial and final state effects.

Pérez and coworkers [53–56] separate substituent effects into polarization and inductive effects. The polarization (electronic) effects are probed as changes in the local softness at the active site induced by the substitution. Inductive (electrostatic) effects are probed as changes in the electronic chemical potential at the active site induced by the substitution. These data are used in conjunction with the HSAB rule. Pérez and coworkers have been able to rationalize substituent effects in a number of systems with this model. However, local descriptors do not always predict the relative basicities of heteroatoms correctly. Other disadvantages of this approach are that it is not rigorous and it does not fully account for the influence of final state effects in the protonation process.

All three of these models have been used to analyze the effect of methyl substitution of hydrogens on the proton affinities of amines. Taft [1] finds a direct correlation between the proton affinity and the polarizability of the base. In contrast, the results of Maksic and Vianello [52] indicate that the predominant factor is not the increase in the polarizability but the increase in the electron donating ability of the base. Pérez and coworkers [55] attribute the increase in proton affinity to an increase in local hardness at the nitrogen with methyl substitution. Thus, the latter two groups both conclude that initial state effects rather than final state effects are dominant in these systems.

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