J. Phys. Chem. A **2002,** *106,* 7413−7422

Computation of pK_a from Dielectric Continuum Theory

Daniel M. Chipman

Radiation Laboratory, University of Notre Dame, Notre Dame, Indiana 46556

Received: March 29, 2002; In Final Form: June 4, 2002

This work considers calculation of pK_a for a series of related alcohols, carboxylic acids, and ammonium ions spanning a wide range of acidities, using quantum mechanical treatment of solute electronic structure in conjunction with a dielectric continuum model for solvation of each bare solute. The electronic structure methods used are of sufficiently high quality to give very good agreement with experimental gas phase acidities. Dielectric continuum theory of solvation is used in a recently developed form that accurately takes account of solute charge density penetrating outside the solvent cavity that nominally encloses it. The cavity surface is defined by a single parameter characterizing an electronic isodensity contour, and contours are examined at and near the value 0.001 e/a_0^3 that has previously led to a good account of solvation effects on properties of neutral solutes in various solvents. In water, the pK_a values calculated for alcohols and carboxylic acids are generally much higher than experiment, while for ammonium ions they are comparable to experiment. Good results in water can be obtained from linear correlations that describe the effects of different substituents in solutes sharing the same acidic functional group, but different correlations apply for different acidic functional groups. For the polar nonprotic solvents DMSO and MeCN, pK_a values close to experimental results are obtained, and very good linear correlations are found that simultaneously describe well all the solutes considered. It is argued this indicates that dielectric continuum theory properly accounts for long-range bulk solvent effects on pK_a without the need for special parameterization of the cavity. To achieve good pK_a results in water, further account must be taken of specific short-range effects such as hydrogen bonding. Rather than distort the cavity from the physical solute−solvent interface region in order to artificially force dielectric continuum theory to serve this purpose, as is commonly done through detailed parameterization schemes, it is recommended that other complementary approaches more appropriate for describing short-range interactions should be sought to complete the treatment of solvation effects in water.

Introduction

Proton transfer is an ubiquitous and highly significant fundamental chemical event.[1] The propensity of a molecule to donate or accept a proton, as measured by its acidity and/or basicity, is therefore an important descriptor of its chemical reactivity.[2] Not all chemical species are readily amenable to experimental characterization, and there is consequently widespread interest in developing methods to calculate acidity/basicity from theoretical approaches.

For isolated molecules in the gas phase, a number of recent systematic electronic structure studies[3−14] on this property have been carried out at a high level. The general consensus of opinion is that acidity/basicity of small molecules in the gas phase can be calculated about as well as or even better than it can be measured, provided that extended basis sets are used and that electron correlation effects are recovered, either through post-Hartree−Fock or density functional approaches.

The situation is less satisfactory in solution, mostly due to the difficulty of quantitatively calculating solvation energies to the requisite accuracy, and this aspect is now a rapidly growing topic for research. Solvation effects required for evaluation of aqueous acidity/basicity have been studied by several different approaches, including molecular simulations,[15−22] dielectric continuum methods,[23−57] Langevin dipole models,[58] and integral equation techniques.[25,59−63] Dielectric continuum methods have also been used in a few calculations of acidity/basicity in nonaqueous solvents.[42,64−68] It is clear from this brief survey that dielectric continuum models have been the most popular for this problem, undoubtedly due to their unique combination[69,70] of simplicity, utility, and efficiency, and this basic approach is further studied in the present work.

It can be argued that dielectric continuum models are unlikely to be adequate for description of acidity/basicity in water, at least in the simplest treatment where a cavity is built immediately around the bare solute without any explicit consideration of first-shell solvent molecules. The obvious reason is that short-range effects such as hydrogen bonding, which are not explicitly represented in dielectric continuum models, can be much stronger in ions than in neutrals and so can have a large differential effect on the solvation energy of an acid compared to its conjugate base. It may therefore appear inappropriate to use simple dielectric continuum models for calculation of pK_a in aqueous solution. Nevertheless, a number of workers have claimed partial success with this approach for describing pK_a, usually in a series of closely related solutes. In many of those cases absolute agreement with experiment is not reached, but reasonably good linear regression fits are found for experimental results vs calculated results.

It is not hard to understand how partial success might be achieved within a limited range of solutes. Advantage can be taken of the fact that the solvation energy calculated from dielectric continuum theory for any solute can be altered over a wide range of values simply by changing the size of the cavity, which is often accomplished by adjusting the atomic radii used

10.1021/jp020847c CCC: $22.00

to define the cavity surface. Experimental solvation energies can be reproduced within a series of closely related solutes by using representative members of the series to calibrate individual atomic radii, which can depend on atom type, charge, hybridization, etc. One popular parameterization scheme of this nature[71] is often used for pK_a calculation, but in view of the fact that the parameters for ions were determined to fit experimental solvation energies that were themselves derived from experimental pK_a values, this can be a somewhat circular exercise. Such empirical approaches cannot be expected to have satisfactory predictive power for solutes unlike those in the training set. Accurate determination of pK_a over a wide range of solutes having different acidic/basic functional groups and different substituents remains elusive.

Our more ambitious ultimate goal is accurate calculation of pK_a for exotic solutes, such as free radicals, zwitterions, and excited states, where not enough is known in advance to permit extensive favorable parameterization. As an initial step in this direction, we examine here the extent that simple dielectric continuum theory can be used to calculate pK_a of common organic species without allowing for specific cavity parameterizations of different functional groups or substituents. We define the cavity surface in terms of a solute electronic isodensity contour,[72] which has the advantage of being physically related[73,74] to the actual solute−solvent interface. In its simplest form, this criterion uniquely determines the cavity shape and allows for adjustment of only a single parameter that affects the overall cavity size.

Representative alcohol, carboxylic acid, and amine functional groups are treated in this work. Acidities in the ROH, RCOOH, and RNH_3^+ compounds are determined with −R = −H (hydrogen), −Me (methyl), and −Ph (phenyl) substituents; for convenience water is considered as a member of the alcohol family. Experimental gas phase acidity values of these nine species span a range of nearly 200 kcal/mol. Experimental pK_a values in water show a range of about 12 pK_a units, corresponding to a span of about 16 kcal/mol, which is still substantial even though compressed by an order of magnitude from the gas phase range. This series therefore provides an interesting and challenging set of solutes, allowing for systematic evaluation of both functional group and substituent effects.

A further motivation for choosing these particular solutes is that experimental pK_a information is also available on most of them in the polar but nonprotic solvents dimethyl sulfoxide (DMSO) and acetonitrile (MeCN). These two solvents are not quite ideal for the purpose since DMSO is somewhat basic,[75] and even MeCN is slightly basic.[75] For this and other reasons, they may entertain specific interactions with the solutes considered here, especially the ionic ones. Therefore, one should not expect dielectric continuum theory alone to give a perfect account of pK_a in these two solvents. But since the interactions with ionic solutes of these two solvents should be weaker than those of water solvent, one can anticipate that dielectric continuum theory will work better for them than for water. Investigations of acidities in these nonaqueous solvents may therefore give useful insight into the unique properties of water solvent.

Theory and Methods

To accommodate cations, neutrals, and anions with a common notation, we express the acid−base equilibrium in terms of the generic dissociation reaction

$$\mathrm{A} \rightleftharpoons \mathrm{B} + \mathrm{P}$$

where A stands for an acid (here a neutral alcohol, neutral carboxylic acid, or ammonium cation), B is its conjugate base (here an anionic dissociated alcohol, anionic dissociated carboxylic acid, or neutral amine), and P is the positively charged proton. This reaction will first be studied in the gas phase before commencing to consider it in solution.

Gas Phase Acidity. The gas phase acidity is the Gibbs free energy change $\Delta G^0_{298\mathrm{K}}$ for the dissociation reaction as written above, based on a standard state of 1 atm at 298.15 K. It is useful to separate the free energy contributions due to the acid/base pair AB from those due to the proton P by writing

$$\Delta G^0_{298\mathrm{K}} = \Delta G_{\mathrm{AB}} + G_{\mathrm{P}} \qquad (1)$$

where to simplify later notation the standard state superscript and temperature subscript will henceforth be implicitly understood but no longer always explicitly written in all contributions. The contribution G_P of the proton in this standard state is −6.3 kcal/mol, based on the translational entropy given by the well-known Sackur−Tetrode equation.[76] In taking the B−A difference, the standard state convention actually drops out and does not affect the value of ΔG_{AB}.

To obtain gas phase acidities, the computational problem is then to evaluate ΔG_{AB}. We resolve this into nuclear and electronic contributions according to

$$\Delta G_{\mathrm{AB}} = \Delta H^{\mathrm{ZPE}}_{\mathrm{AB}} + \Delta G^{0\rightarrow\mathrm{T}}_{\mathrm{AB}} + \Delta E^{\mathrm{elec}}_{\mathrm{AB}}$$

Here the first term $\Delta H^{\mathrm{ZPE}}_{\mathrm{AB}}$ comes from the total zero point nuclear vibrational energies, the second term $\Delta G^{0\rightarrow\mathrm{T}}_{\mathrm{AB}}$ represents thermal corrections arising from translational, rotational, and vibrational nuclear motions, and the last term $\Delta E^{\mathrm{elec}}_{\mathrm{AB}}$ is due to the internal electronic energies. The electronic energy of a species is the expectation value over the gas phase electronic wave function ψ of the internal Hamiltonian $\mathscr{H}^{\mathrm{int}}$, which includes nuclear repulsion.

The nuclear contributions $\Delta H^{\mathrm{ZPE}}_{\mathrm{AB}}$ and $\Delta G^{0\rightarrow\mathrm{T}}_{\mathrm{AB}}$ are obtained here from optimized gas phase structures, using for the most part standard statistical mechanical formulas[77] based on translations in an ideal gas, rotations of a rigid rotor, external symmetry numbers,[78−81] and scaled frequencies of independent harmonic oscillator normal mode vibrations. Evaluation of these thermodynamic quantities is often automated in standard electronic structure packages, but manual intervention is sometimes required to properly treat symmetry numbers if point group symmetry is not fully invoked and/or to correct the "vibrational" contributions of any low frequency modes that more properly correspond to free or slightly hindered internal rotors.[82,83] Contributions from internal rotors are treated here by the E1 method.[82] According to this prescription no correction is necessary for internal rotors having rotational barriers higher than 1.4RT (∼0.8 kcal/mol at 298 K), which are considered to be satisfactorily described as simple harmonic oscillators. For rotors having barriers less than 1.4RT the simple harmonic oscillator entropic contribution of the corresponding apparent vibrational mode is removed and replaced by the entropic contribution of a free rotor.[78]

The nuclear contributions $\Delta H^{\mathrm{ZPE}}_{\mathrm{AB}}$ and $\Delta G^{0\rightarrow\mathrm{T}}_{\mathrm{AB}}$ are obtained here from optimized gas phase structures, using for the most part standard statistical mechanical formulas[77] based on translations in an ideal gas, rotations of a rigid rotor, external symmetry numbers,[78−81] and scaled frequencies of independent harmonic oscillator normal mode vibrations. Evaluation of these thermodynamic quantities is often automated in standard electronic

structure packages, but manual intervention is sometimes required to properly treat symmetry numbers if point group symmetry is not fully invoked and/or to correct the "vibrational" contributions of any low frequency modes that more properly correspond to free or slightly hindered internal rotors.[82,83] Contributions from internal rotors are treated here by the E1 method.[82] According to this prescription no correction is necessary for internal rotors having rotational barriers higher than 1.4RT (~0.8 kcal/mol at 298K), which are considered to be satisfactorily described as simple harmonic oscillators. For rotors having barriers less than 1.4RT, the simple harmonic oscillator entropic contribution of the corresponding apparent vibrational mode is removed and replaced by the entropic contribution of a free rotor.[78]

Solution Phase Acidity. In solution, we are mainly concerned with the pK_a given by

$$\mathrm{p}K_a = \frac{\Delta G^0_{298\mathrm{K}}}{2.303RT}$$

where $\Delta G^0_{298\mathrm{K}}$ here is the free energy change for the dissociation reaction as written above but now with a standard state corresponding to a concentration of 1 mol/L, and temperature of 298.15 K. The factor 2.303RT amounts to 1.4 kcal/mol at 298 K. For the reaction under consideration, the change to 1 mol/L standard state in solution can be accommodated by adding 1.9 kcal/mol to any reaction free energies obtained under the gas phase convention of 1 atm. It is common and convenient to absorb this standard state correction into the value of the proton solvation energy $\Delta G_\mathrm{P}^{\mathrm{solv}}$, so the proton free energy in solution can be written as $G_\mathrm{P} = \Delta G_\mathrm{P}^{\mathrm{solv}} - 6.3$ kcal/mol where the value of $\Delta G_\mathrm{P}^{\mathrm{solv}}$ corresponds to the standard state conventions of 1 atm in gas and 1 mol/L in solution. In taking the B−A difference, the standard state convention adopted for the contributions of acid and base solvation energies actually drops out of the final pK_a. However, a convention must be specified if the acid and/or base solvation energies are to be reported separately. For these we adopt the Ben-Naim convention[84] that the solute is transferred from a fixed position in gas to a fixed position in solvent, which under the present assumptions of ideality is equivalent to adopting the same standard state in gas as in solution.

The proton solvation energy $\Delta G_\mathrm{P}^{\mathrm{solv}}$ is difficult to measure or calculate accurately. Experimental values are generally quoted under standard state conventions of 1 bar in gas and 1 molal in solution, which can be taken to differ negligibly from the convention of 1 atm in gas and 1 mol/L in solution. In water, experimental values covering the range −254 to −261 kcal/mol are often quoted,[85] while a recent report[86] gives the value to be −264.0 kcal/mol. Recent computational works[87−90] report the considerable range of values in water of −245.6, −262.2, −244.9, and −262.4 kcal/mol. Even less is known for sure about the proton solvation energy in nonaqueous solvents. Analysis of experimental data together with the TATB assumption have indicated[91] that $\Delta G_\mathrm{P}^{\mathrm{solv}}$ in DMSO is 4.6 kcal/mol more negative than in water, while in MeCN it is 11.1 kcal/mol more positive than in water. However, the validity of the TATB assumption has recently been seriously called into question.[92,93]

No attempt is made in the present work to independently determine $\Delta G_\mathrm{P}^{\mathrm{solv}}$. For water we simply adopt the recent experimental value[86] of −264.0 kcal/mol. For nonaqueous solvents we utilize this value in water together with the shifts given relative to water based on the TATB assumption[91] in order to obtain estimated values of −268.6 kcal/mol for DMSO and −252.9 kcal/mol for MeCN. The latter value is close to an independent estimate[42] of −250.4 kcal/mol. It should be kept in mind that these proton solvation energies may not be firm numbers, especially in the nonaqueous solvents, so absolute pK_a values determined here may be subject to an unknown shift that is characteristic of each solvent. Fortunately, the relative acidities of different solutes in the same solvent are independent of $\Delta G_\mathrm{P}^{\mathrm{solv}}$, so uncertainty over this matter is not a major limitation in carrying out meaningful studies.

The remaining ingredient for pK_a calculation is evaluation of the acid and base solvation energies, which are added to the calculated gas phase values described above to obtain the final values of ΔG_{AB} in solution. We assume ideal solutions, so the same statistical mechanical formulas[77] apply for nuclear contributions as in the gas phase. Even so, in principle, nuclear contributions could affect numerical values of the solvation energies due to solvation-induced changes in structures and/or vibrational frequencies. The most important of such changes will almost certainly be in the $\Delta H_{\mathrm{AB}}^{\mathrm{ZPE}}$ contribution to ΔG_{AB}. Note that since each normal mode contributes $1/2h\nu$ to the vibrational energy, it would require substantial cumulative frequency shifts from solvation of 700 cm^{-1} between acid and base to change $\Delta H_{\mathrm{AB}}^{\mathrm{ZPE}}$ by just 1.0 kcal/mol. None of the solutes considered here are expected to undergo large changes in structure upon solvation. Thus, neglect of solvation-induced frequency shifts should only produce errors of well under 1 kcal/mol in $\Delta H_{\mathrm{AB}}^{\mathrm{ZPE}}$. We therefore make the simplifying assumptions that nuclear contributions to ΔG_{AB} can be carried over unchanged from those evaluated in the gas phase and that electronic solvation energies can be evaluated at the optimum gas phase geometries.

In solution, the solute Hamiltonian is $\mathscr{H}^{\mathrm{int}} + \mathscr{V}^{\mathrm{rxn}}$, where $\mathscr{V}^{\mathrm{rxn}}$ is the solute−solvent interaction energy corresponding to the reaction potential determined from a classical dielectric continuum model[69,70] of the solvent. In this model, solvent polarization is characterized by the experimental bulk dielectric constant ϵ of the pure liquid and is obtained from the solute charge density by solution of Poisson's equation. The solute wave function Ψ in solution will relax in response to the solute−solvent interaction, so one contribution to the solvation energy comes from the change in internal solute energy determined as the difference between the expectation value of $\mathscr{H}^{\mathrm{int}}$ over Ψ compared to that over ψ. The major contribution to the solvation energy comes from one-half the expectation value of $\mathscr{V}^{\mathrm{rxn}}$ over Ψ, where the other half is expended as work to polarize the solvent assuming linear response.

In the case of formic acid, there are two low energy conformations to be considered, both planar. The most stable Z form has the acidic hydrogen pointing toward the neighboring oxygen atom, while the less stable E form has the acidic hydrogen rotated 180 ° away. In the gas phase these conformations differ by ~5 kcal/mol, due to the strength of a partial intramolecular hydrogen bond in the Z form that is broken in the E form, and so only the more stable Z form need be considered. However, the E form is more strongly solvated due to the acidic hydrogen being more exposed to solvent than in the Z form, and in solution the two conformations are found to differ by only ~1 kcal/mol or less. The solution free energies of the two conformations are therefore statistically combined, although in practice the result turns out to be never more than 0.2 kcal/mol from the value for the Z form alone.

Computational Details. Calculations were carried out with the HONDO[94] computer program. Both Hartree−Fock (HF) and B3LYP[95,96] wave functions were considered, the latter bringing

TABLE 1: Nuclear Contributions $\Delta H_{\mathrm{AB}}^{\mathrm{ZPE}}$ and $\Delta G_{\mathrm{AB}}^{0\rightarrow\mathrm{T}}$, and Their Total $\Delta G_{\mathrm{AB}}^{\mathrm{nuc}}$, to Gas Phase Acidity in kcal/mol, as Calculated by Scaled[a] HF/6-31+G* and B3LYP/6-31+G* Methods, and External[b] Symmetry Numbers σ

acid/base	$\Delta H_{\mathrm{AB}}^{\mathrm{ZPE}}$		$\sigma_{\mathrm{A}}/\sigma_{\mathrm{B}}$	$\Delta G_{\mathrm{AB}}^{0\rightarrow\mathrm{T}}$		$\Delta G_{\mathrm{AB}}^{\mathrm{nuc}}$	
	HF	B3LYP		HF	B3LYP	HF	B3LYP
H_2O/OH^-	−8.0	−7.9	2/1	0.9	0.9	−7.1	−7.0
$MeOH/MeO^-$	−9.5	−9.9	1/3	1.0	1.0	−8.6	−9.0
$PhOH/PhO^-$	−8.5	−8.6	1/2	0.6	0.5	−7.9	−8.1
$HCOOH/HCOO^-$	−8.4	−8.4	1/2	0.6	0.6	−7.8	−7.8
$MeCOOH/MeCOO^-$	−8.4	−8.4	1/1	0.6	0.6	−7.8	−7.8
$PhCOOH/PhCOO^-$	−8.4	−8.5	1/2	0.5	0.4	−7.9	−8.1
NH_4^+/NH_3	−9.4	−9.5	12/3	−0.5	−0.5	−9.8	−9.9
$MeNH_3^+/MeNH_2$	−9.4	−9.5	3/1	−0.5	−0.5	−9.8	−10.0
$PhNH_3^+/PhNH_2$	−9.1	−8.9	1/1	−0.4	−0.4	−9.4	−9.3

[a] Vibrational frequencies have been uniformly scaled[100] by a factor of 0.9153 for HF/6-31+G* and by 0.9806 for B3LYP/6-31+G* calculations. [b] The MeCOOH, $MeCOO^-$, and $PhNH_3^+$ species each also have a "vibration" treated instead as an internal rotor, with internal symmetry number as noted in the text.

in electron correlation effects in a manner specifically parameterized for thermochemistry. The economical 6-31+G* basis set[97−99] having split-valence plus heavy-atom polarization and diffuse functions was used for geometry optimizations. Harmonic vibrational frequencies were determined from analytic second derivatives in the case of HF/6-31+G*, and from doubled-sided finite differences of analytic first derivatives in the case of B3LYP/6-31+G*. Vibrational frequencies were then scaled by empirical factors of 0.9153 for HF/6-31+G* and 0.9806 for B3LYP/6-31+G*, as recommended[100] to give good fits to experimental zero point energies. Single point energy calculations at the optimized geometries were carried out with the large aug-cc-pVTZ basis.[101,102]

Solvation free energies were determined with the recently developed SSC(V)PE method[103] (surface and simulation plus correction of volume polarization for electrostatics). This is an implementation of dielectric continuum theory for description of electrostatic interactions between solute and bulk solvent. The method pays particular attention to properly accounting for electrostatic effects arising from quantum mechanical penetration of the solute charge density outside the cavity, as studied in previous work.[104−110] The solute charge density and the reaction field it produces are both iterated until mutual self-consistency. No corrections are made for nonelectrostatic effects, which will partially cancel in taking the acid−base difference.

The cavity shape is taken to be determined by an electronic isodensity contour[72−74] of the solute. Studies have shown[111,112] that contour values in the range of 0.0005−0.002 e/a_0^3, with some statistical preference for a value of about 0.001 e/a_0^3, generally lead to a good description of the electrostatic contribution to the solvation energy for many neutral solutes in various solvents. Calculations were carried out systematically for contour values of 0.0005, 0.001, and 0.002 e/a_0^3, and for certain other contour values as needed in specific instances. The results for a given solute in a given solvent were found to vary slowly and smoothly with the logarithm of the contour value, and this was used as the basis for spline interpolation to determine results at intermediate contour values. Cavity surface integrations used a set of 1202 points and weights taken from the literature.[113] Tests indicated that this is sufficient to determine solvation energies to a precision of 0.1 kcal/mol or better for the solutes examined here.

Solvent dielectric constants at 298 K are taken to be 78.304 for water, 46.45 for DMSO, and 35.94 for MeCN. This is the only solvent descriptor in dielectric continuum theory, which is primarily designed to give the long range electrostatic effects of solute interaction with isotropic homogeneous bulk solvent. It should be noted that short-range nonelectrostatic interactions such as cavitation, exchange repulsion, and dispersion attraction are not explicitly treated in dielectric continuum theory, nor are anisotropies and inhomogeneities in the short-range electrostatic interactions with first-shell solvent molecules. Thus, hydrogen bonding is difficult to describe with dielectric continuum theory.

Gas Phase Results

Nuclear Motion Contributions. Table 1 summarizes results for the two contributions $\Delta H_{\mathrm{AB}}^{\mathrm{ZPE}}$ and $\Delta G_{\mathrm{AB}}^{0\rightarrow\mathrm{T}}$ to acidity arising from the difference between acid/base nuclear degrees of freedom in the gas phase. Due to the use of frequency scaling, HF/6-31+G* and B3LYP/6-31+G* results for the nuclear contributions turn out to be quite close to one another, usually within 0.1 kcal/mol and never differing by more than 0.4 kcal/mol, and so will be discussed together.

The largest part of the nuclear contributions comes from the zero point vibrational energies $\Delta H_{\mathrm{AB}}^{\mathrm{ZPE}}$. While these ZPE contributions are quite significant in magnitude, typically about −9 kcal/mol, they are roughly constant spanning a range of about 2 kcal/mol. This range would be even smaller without water/hydroxide, which is unusual because only two degrees of freedom for hydrogen vibrational motions are lost, instead of the usual three, when converting acid to base.

Corrections to thermal contributions arising from external symmetry numbers and internal rotors are sometimes notable. The external symmetry numbers adopted here are indicated in Table 1. The resultant contributions to acidity of $-RT\log(\sigma_{\mathrm{A}}/\sigma_{\mathrm{B}})$ range between the extremes of +0.7 kcal/mol for MeOH/MeO^- and −0.8 kcal/mol for NH_4^+/NH_3. There is a substantial number of potential $-OH$, $-CH_3$, and $-NH_3$ internal rotors in the molecules considered in this work, but most were found to have barriers well above $1.4RT$, indicating satisfactory description as harmonic oscillators.[82] Manual correction for internal rotation was required only in three cases. The $-CH_3$ rotor in $MeCOO^-$ and the $-NH_3$ rotor in $PhNH_3^+$ were found to have very low barriers of <0.1 kcal/mol, and so were considered as essentially free rotors. The $-CH_3$ rotor in MeCOOH was found to have a barrier of about ∼0.5 kcal/mol in the gas phase, which is lowered to about half of that value upon solvation, so this was considered as a $<1.4RT$ hindered rotor case under the E1 classification.[82] Values of the internal symmetry numbers,[78−81] which are needed to evaluate the rotor entropies, are taken to be 3 in MeCOOH, 6 in $MeCOO^-$, and 6 in $PhNH_3^+$. These latter two values are consistent with those previously specified[78] for the respective isoelectronic species $MeNO_2$ and $PhCH_3$. In practice, these internal rotor corrections to ΔG_{AB} turn out to be significant, amounting to 1.1 (HF/6-31+G*) or 1.2 (B3LYP/

TABLE 2: Electronic Contributions $\Delta E_{\mathrm{AB}}^{\mathrm{elec}}$ to Gas Phase Acidity in kcal/mol, as Calculated by HF/6-31+G*, HF/aug-cc-pVTZ, B3LYP/6-31+G*, and B3LYP/aug-cc-pVTZ Methods

	HF		B3LYP	
acid/base	6-31+G*	aug-cc-pVTZ	6-31+G*	aug-cc-pVTZ
H_2O/OH^-	402.4	407.0	392.8	395.3
$MeOH/MeO^-$	395.2	399.8	385.1	388.0
$PhOH/PhO^-$	359.6	364.9	351.0	355.7
$HCOOH/HCOO^-$	352.0	358.1	344.5	349.4
$MeCOOH/MeCOO^-$	356.7	362.4	349.4	353.8
$PhCOOH/PhCOO^-$	349.8	355.2	342.9	347.2
NH_4^+/NH_3	214.5	215.9	211.8	211.1
$MeNH_3^+/MeNH_2$	225.9	227.9	222.5	222.6
$PhNH_3^+/PhNH_2$	220.8	222.7	217.4	217.9

TABLE 3: Free Energy ΔG_{298K}^{0} for Gas Phase Acidity in kcal/mol, as Calculated by HF/6-31+G*, HF/Aug-cc-pVTZ, B3LYP/6-31+G*, and B3LYP/Aug-cc-pVTZ Methods and Compared to Experiment (expt)

	HF *		B3LYP		
acid/base	6-31+G*	aug-cc-pVTZ	6-31+G*	aug-cc-pVTZ	expt
H_2O/OH^-	389.0	393.6	379.5	382.0	384.1
$MeOH/MeO^-$	380.4	385.0	369.8	372.8	375
$PhOH/PhO^-$	345.3	350.7	336.6	341.3	343
$HCOOH/HCOO^-$	337.9	344.0	330.5	335.3	338
$MeCOOH/MeCOO^-$	342.6	348.2	335.3	339.7	341
$PhCOOH/PhCOO^-$	335.6	341.0	328.6	332.9	333
NH_4^+/NH_3	198.4	199.8	195.6	194.9	195.7
$MeNH_3^+/MeNH_2$	209.8	211.7	206.2	206.3	206.6
$PhNH_3^+/PhNH_2$	205.1	207.0	201.8	202.3	203.3

6-31+G*) kcal/mol for $MeCOOH/MeCOO^-$, and to 1.2 (HF/6-31+G*) or 1.7 (B3LYP/6-31+G*) kcal/mol for $PhNH_3^+/PhNH_2$.

Net thermal corrections to the nuclear motion energies $\Delta G_{\mathrm{AB}}^{0\rightarrow \mathrm{T}}$ are not large, generally being about 1 kcal/mol or less in magnitude. However, they span a range of about 1.5 kcal/mol, which is almost as large as the range spanned by ZPE corrections.

The total nuclear contributions $\Delta H_{\mathrm{AB}}^{\mathrm{ZPE}} + \Delta G_{\mathrm{AB}}^{0\rightarrow \mathrm{T}}$ vary from about -7 to -10 kcal/mol in the various molecules considered, thus spanning a range of about 3 kcal/mol. It is concluded that nuclear degrees of freedom make important contributions to the absolute acidity/basicity of a molecule. These contributions are somewhat systematic, so that smaller but still significant contributions are made to the relative acidity/basicity. While the thermal contributions are considerably less than the ZPE contributions in absolute magnitude, they are not negligible and indeed account for almost as much of the variation from one species to the next as does the ZPE.

Electronic Contributions. In Table 2 we explore the sensitivity of the electronic contribution $\Delta E_{\mathrm{AB}}^{\mathrm{elec}}$ to the basis set (6-31+G* vs aug-cc-pVTZ) and to the wave function model (HF vs B3LYP). Moving from the small 6-31+G* basis to the large aug-cc-pVTZ basis usually increases $\Delta E_{\mathrm{AB}}^{\mathrm{elec}}$ by an average of about 4 kcal/mol with HF and about 2 kcal/mol with B3LYP. There is a broad range of shifts, with about 5 kcal/mol separating the smallest and largest basis set shifts within each wave function model. Some more systematic trends are found for individual functional groups. Thus, the carboxylic acids are usually raised the most, alcohols a little less, and amines only moderately if at all by basis set enhancement.

Including electron correlation by changing from HF to B3LYP always decreases $\Delta E_{\mathrm{AB}}^{\mathrm{elec}}$ by an average of about -7 kcal/mol with the 6-31+G* basis and about -8 kcal/mol with the aug-cc-pVTZ basis. There is a broad range of shifts, with about 7 kcal/mol separating the smallest and largest wave function shifts with either basis set. Some more systematic trends are again found for individual functional groups. Thus, the alcohols are lowered the most, carboxylic acids somewhat less, and amines significantly less by electron correlation recovery.

The general increase in $\Delta E_{\mathrm{AB}}^{\mathrm{elec}}$ due to improving the basis set combines with the even larger general decrease due to including electron correlation to provide a net decrease due to the two effects combined. Thus, comparing HF/6-31+G* to B3LYP/aug-cc-pVTZ results, $\Delta E_{\mathrm{AB}}^{\mathrm{elec}}$ is decreased by an average of about -4 kcal/mol overall. There is still a broad range of shifts, with nearly 5 kcal/mol separating the smallest and largest. The largest overall decreases occur for the alcohols, with smaller and more systematic decreases for the carboxylic acids and amines.

It is concluded that alcohols and carboxylic acids are affected the most by both basis set improvements and electron correlation recovery, probably because of the greater difficulty in accurately characterizing anions than either neutrals or cations. There is some cancellation of errors in combining the effects of basis set improvement and of electron correlation recovery, whence $\Delta E_{\mathrm{AB}}^{\mathrm{elec}}$ for the alcohols are affected overall by about -4 to -7 kcal/mol while carboxylic acids and amines are each affected overall by about -3 kcal/mol.

Comparison to Experiment. Gas phase acidities, as obtained by combining calculated nuclear, electronic, and free proton contributions, are reported in Table 3. Comparison of shifts due to basis set improvement and to electron correlation recovery closely tracks the trends already discussed above for the electronic contributions, so here we will concentrate mainly on how results from the various computational methods compare to experiment.

Table 3 also includes experimental results taken from the NIST Webbook that are given directly as acidities[114] for the alcohols and carboxylic acids, and are readily obtained for the ammonium cations from the basicities[115] of the conjugate base amines. For each of H_2O, NH_3, $MeNH_2$, and $PhNH_2$ this source[114,115] lists a single experimental value precise to 0.1 kcal/mol, and these values are so reported here. For each of the remaining systems MeOH, PhOH, HCOOH, MeCOOH, and PhCOOH this source lists several experimental values, each given to 0.1 kcal/mol but with typical error bars of ±1 to ±2 kcal/mol. In such cases we report here an average of the several listed values, rounded off to 1 kcal/mol in light of the larger probable error.

HF/6-31+G* gas phase acidities are uniformly higher than experiment, by an average of about 3 kcal/mol. With improvement of the basis set, HF/aug-cc-pVTZ acidities are all substantially raised, leading to an average of about 7 kcal/mol above experiment. Recovering electron correlation but without improving the basis set, B3LYP/6-31+G* acidities are all substantially lowered, leading to an average of about -4 kcal/mol from experiment. Combining the effects of improving the basis set and recovering electron correlation, B3LYP/aug-cc-pVTZ acidities are slightly lowered, leading to values ranging from about 0 to -3 kcal/mol from experiment, and averaging just -1 kcal/mol from experiment.

It is concluded that the simple HF/6-31+G* method gives a reasonable account of the experimental results, due to a systematic cancellation of errors, and that the B3LYP/aug-cc-pVTZ method reliably allows for gas phase acidities to be

TABLE 4: Free Energy of Solvation in kcal/mol Calculated from the SSC(V)PE Method for Each Acid A and Base B Conjugate Pair[a]

		HF/6-31+G*		B3LYP/aug-cc-pVTZ	
acid/base	contour	ΔG_A^{solv}	ΔG_B^{solv}	ΔG_A^{solv}	ΔG_B^{solv}
H_2O/OH^-	0.0005	−7.1	−75.1	−4.7	−69.1
	0.001	−9.4	−82.1	−6.5	−75.9
	0.002	−12.7	−89.8	−9.6	−83.1
	expt	−6.3	−105.0	−6.3	−105.0
$MeOH/MeO^-$	0.0005	−4.8	−68.0	−3.3	−62.6
	0.001	−6.4	−73.3	−4.6	−67.6
	0.002	−8.9	−79.0	−6.9	−72.8
	expt	−5.1	−94.0	−5.1	−94.0
$PhOH/PhO^-$	0.0005	−6.2	−56.1	−4.3	−52.8
	0.001	−8.6	−60.2	−6.2	−56.6
	0.002	−12.3	−64.9	−9.4	−60.9
	expt	−6.6	−68.6	−6.6	−68.6
$HCOOH/HCOO^-$	0.0005	−7.6	−64.7	−5.3	−60.8
	0.001	−10.4	−68.9	−7.6	−64.9
	0.002	−14.7	−73.7	−11.4	−69.4
	expt		−74.6		−74.6
$MeCOOH/MeCOO^-$	0.0005	−7.0	−64.2	−5.0	−59.8
	0.001	−9.7	−68.9	−7.2	−64.4
	0.002	−13.8	−74.2	−10.9	−69.4
	expt	−6.7	−70.7	−6.7	−70.7
$PhCOOH/PhCOO^-$	0.0005	−7.4	−60.2	−5.2	−55.6
	0.001	−10.3	−64.8	−7.5	−60.0
	0.002	−15.1	−70.4	−11.6	−65.1
	expt				
NH_4^+/NH_3	0.0005	−80.5	−4.1	−79.0	−2.9
	0.001	−86.5	−5.6	−85.5	−4.1
	0.002	−94.3	−7.9	−94.1	−6.2
	expt	−84.9	−4.3	−84.9	−4.3
$MeNH_3^+/MeNH_2$	0.0005	−71.0	−3.1	−69.7	−2.3
	0.001	−76.5	−4.3	−75.6	−3.3
	0.002	−83.7	−6.3	−83.5	−5.2
	expt	−75.2	−4.6	−75.2	−4.6
$PhNH_3^+/PhNH_2$	0.0005	−65.7	−5.5	−62.6	−4.1
	0.001	−72.3	−7.6	−69.2	−5.8
	0.002	−81.3	−10.9	−78.6	−8.8
	expt	−73.5	−4.9	−73.5	−4.9

[a] Results are listed for two different wave functions with dielectric constant characteristic of water and using various isodensity contours (given in e/a_0^3). Experimental values (expt) are also given for comparison.

calculated with good accuracy. In the interest of brevity, only these two computational methods will be used to determine solvation energies in the remainder of this work.

Solution Phase Results

Solvation Energies. Determination of accurate solvation energies is a crucial aspect of pK_a calculations. SSC(V)PE results for solvation energies calculated with a dielectric constant characteristic of water are given in Table 4. For comparison, experimental aqueous solvation energies of neutral solutes are listed for[116] H_2O, MeOH, NH_3, and $MeNH_2$, for[117] PhOH and MeCOOH, and for[118] $PhNH_2$. Also, experimentally derived solvation energies of ionic solutes are listed for[119] OH^-, MeO^-, PhO^-, $HCOO^-$, $MeCOO^-$, NH_4^+, $MeNH_3^+$, and PhH_3^+. Unfortunately, virtually no experimental solvation energies are known in DMSO or MeCN for the solutes of interest here. For a given molecule and given contour value, the solvation energies calculated in all the solvents are found to be close to one another, simply because the solvent in dielectric continuum theory is characterized only by its dielectric constant, and each of these solvents is a high dielectric liquid. We note that the variation with dielectric constant ϵ in every case can be well described by the empirical scaling factor $(\epsilon - 1)/(\epsilon + C)$, where the constant C varies from about 0.00 to 1.11 depending on the particular molecule, contour, and wave function chosen. Otherwise, we tabulate and discuss here only the water results.

For a given solute with a given contour, the calculated SSC(V)PE solvation energy consistently decreases in magnitude in going from HF/6-31+G* to B3LYP/aug-cc-pVTZ. This difference is modest for neutral and cationic solutes, ranging from 0.2 to 3.5 kcal/mol, and is generally somewhat larger for anions, ranging from 3.3 to 6.7 kcal/mol.

Experimental results for solvation energies of neutral solutes are likely to be quite accurate, but those for ions may be open to some question. We adopt values for ions from a very recent analysis[119] that utilizes presumably accurate experimental values for solution phase pK_a's, solvation energies of neutrals, and gas phase proton affinities, together with a rough estimate of gas phase entropic contributions and the recently obtained value[86] of −264.0 kcal/mol for the proton solvation energy. If either or both of the latter two ingredients are incorrect, then the experimental solvation energies for ions must be shifted accordingly. However, the uncertainties are probably not large, so the experimental aqueous solvation energies quoted for ions can be accepted as reasonable estimates.

Examination of Table 4 shows that the experimental aqueous solvation energy of each neutral and cationic solute can be reproduced from dielectric continuum theory calculation by using a contour value somewhere in the range of 0.0005−0.002 e/a_0^3 with B3LYP/aug-cc-pVTZ wave functions. With HF/6-31+G* wave functions, several of the neutral solutes would require even smaller contour values (corresponding to even larger cavities). On the other hand, with either wave function each of the anionic solutes would require an even larger contour value (corresponding to an even smaller cavity) to reproduce the experimental solvation energy. The two most extreme cases here come with B3LYP/aug-cc-pVTZ wave functions, where we have determined that a contour value of 0.0114 e/a_0^3 would be required for OH^- and of 0.0161 e/a_0^3 would be required for MeO^- in order to reproduce experiment. Such values are far from the range 0.0005−0.002 e/a_0^3 that appears appropriate for neutral and cationic solutes. Also, it is clear that no single common contour value would lead to solvation energies in good agreement with experimental aqueous results for all the anions.

Analogous observations have led previous workers in the field to postulate detailed empirical rules for determining different cavity sizes for particular kinds of solutes, which then allows dielectric continuum model calculation to reproduce the experimental solvation energies. Our own predilection is in the opposite direction, whence we would prefer to minimize all parameterization. With an isodensity cavity prescription, this means that we would like to prescribe a single universal contour value to cover all situations. The obvious consequence is that we must give up the possibility that applying dielectric continuum theory alone to bare solutes will exactly reproduce the experimental aqueous solvation energies of neutrals and cations, or of even coming anywhere close to the experimental aqueous solvation energies of most small anions having highly localized charge such as are considered here. Nevertheless, we find below that even such a highly constrained dielectric continuum theory can prove to be very useful for the problem at hand.

Acidity in Solution. We are now finally to the point of being able to put together all the necessary ingredients to determine pK_a in solution. Values calculated from contours in the range 0.0005−0.002 e/a_0^3 are summarized in Table 5. Experimental values are also listed there for water in water,[2] the remaining

TABLE 5: Calculated pK_a Values from the SSC(V)PE Method[a]

		HF/6-31+G*			B3LYP/aug-cc-pVTZ		
acid/base	contour	water	DMSO	MeCN	water	DMSO	MeCN
H_2O/OH^-	0.0005	41.8	38.9	50.7	39.3	36.3	48.1
	0.001	38.4	35.4	47.3	35.6	32.7	44.5
	0.002	35.2	32.3	44.1	32.6	29.7	41.5
	expt	15.7	31.2		15.7	31.2	
$MeOH/MeO^-$	0.0005	39.0	36.0	47.8	36.3	33.3	45.1
	0.001	36.3	33.4	45.2	33.6	30.7	42.5
	0.002	33.9	31.0	42.8	31.4	28.5	40.3
	expt	15.5	29.0		15.5	29.0	
$PhOH/PhO^-$	0.0005	23.1	20.0	31.8	21.2	18.1	29.9
	0.001	21.8	18.7	30.5	19.7	16.7	28.4
	0.002	21.0	18.0	29.8	18.9	15.9	27.6
	expt	10.0	18.0	27.2	10.0	18.0	27.2
$HCOOH/HCOO^-$	0.0005	12.4	9.3	21.1	11.7	8.6	20.4
	0.001	11.3	8.2	20.0	10.3	7.2	19.0
	0.002	11.0	7.9	19.7	9.8	6.8	18.5
	expt	3.8			3.8		
$MeCOOH/MeCOO^-$	0.0005	15.7	12.7	24.5	15.4	12.4	24.1
	0.001	14.2	11.2	23.0	13.6	10.6	22.4
	0.002	13.4	10.4	22.1	12.6	9.6	21.4
	expt	4.8	12.3	22.3	4.8	12.3	22.3
$PhCOOH/PhCOO^-$	0.0005	13.8	10.8	22.6	13.5	10.5	22.2
	0.001	12.6	9.6	21.4	12.0	9.0	20.8
	0.002	12.0	9.0	20.8	11.3	8.3	20.1
	expt	4.2	11.1	20.7	4.2	11.1	20.7
NH_4^+/NH_3	0.0005	7.9	4.0	15.2	5.2	1.3	12.5
	0.001	11.2	7.3	18.5	9.0	5.1	16.3
	0.002	15.2	11.3	22.4	13.8	9.9	21.0
	expt	9.2	10.5	16.5	9.2	10.5	16.5
$MeNH_3^+/MeNH_2$	0.0005	10.0	6.2	17.4	7.2	3.3	14.5
	0.001	13.2	9.3	20.5	10.7	6.8	18.0
	0.002	17.0	13.2	24.3	15.1	11.2	22.4
	expt	10.7	11.0	18.4	10.7	11.0	18.4
$PhNH_3^+/PhNH_2$	0.0005	1.0	−2.8	8.4	−2.3	−6.1	5.1
	0.001	4.3	0.4	11.6	1.3	−2.6	8.6
	0.002	8.4	4.6	15.7	6.0	2.1	13.2
	expt	4.9	3.6	10.6	4.9	3.6	10.6

[a] Results are listed for two different wave functions with dielectric constants characteristic of water, DMSO, and MeCN solvents, and using various isodensity contours (given in e/a_0^3). Experimental values (expt) are also given for comparison.

solutes in water,[120] eight of the solutes in DMSO,[121] and six of the solutes in MeCN.[122,123] The value listed for $MeNH_3^+/MeNH_2$ in DMSO is here estimated as that for $EtNH_3^+/EtNH_2$ in DMSO, based on the observation that these two systems are known to have essentially the same experimental pK_a's both in water[120] and in MeCN.[122]

In water, absolute pK_a values for alcohols and carboxylic acids are calculated to be much higher than experiment, whereas for the amines they are comparable to experiment. In DSMO and MeCN, absolute pK_a values are calculated to be comparable to experiment for all systems considered. However, even in DSMO and MeCN the contour value that would lead to exact reproduction of experiment varies somewhat from one system to the next, and is sometimes a little outside the range of 0.0005−0.002 e/a_0^3. This may or may not be significant, since the proton solvation free energies are less certain in these cases and the calculated pK_a values may therefore be subject to some unknown uniform shift in each of the nonaqueous solvents.

Next let us turn to consideration of relative pK_a values. It is useful to discuss these in terms of plots of experimental vs calculated pK_a, which are shown for 0.001 e/a_0^3 contour results in Figure 1. Square boxes are used for alcohols, circles for carboxylic acids, and diamonds for amines. Lines indicate the best linear regression fits to $pK_a(\text{expt}) \approx A \cdot pK_a(\text{calc}) + B$, with correlation coefficient r. Both HF/6-31+G* and B3LYP/aug-cc-pVTZ results show similar behavior and so will be discussed together.

In water, it appears that one linear regression can closely describe the alcohols ($A = 0.356, 0.371$; $B = 2.28, 2.73$; $r = 0.996, 0.996$), another the carboxylic acids ($A = 0.342, 0.300$; $B = -0.07, 0.68$; $r = 0.998, 0.992$), and yet another the amines ($A = 0.644, 0.597$; $B = 2.11, 4.09$; $r = 0.999, 0.996$), where the numerical results in parentheses are quoted first for HF/6-31+G* and then for B3LYP/aug-cc-pVTZ, both based on a contour value of 0.001 e/a_0^3. These calculated correlations may have useful predictive power for substituent effects on aqueous pK_a with various solutes sharing a common acidic functional group. However, when all solutes are taken simultaneously there are considerable deviations even from the best overall linear fits of calculation to experiment.

The DMSO and MeCN results are more encouraging. In each of these solvents a single linear regression with slope in the vicinity of unity fits all the solutes very closely. Thus, in these nonaqueous solvents the calculated results may have useful predictive power for both substituent effects and acidic functional group effects on pK_a.

Details of the linear regression fits to all solutes taken simultaneously are given in Table 6. It is most desirable to find a linear regression having correlation coefficient r of unity, since that should correspond to maximum predictive power. A secondary desire is to find a slope A of unity. Also, if A is near unity then the intercept B should be close to zero, but this is less important in view of the uncertainties in the proton solvation energies being used.

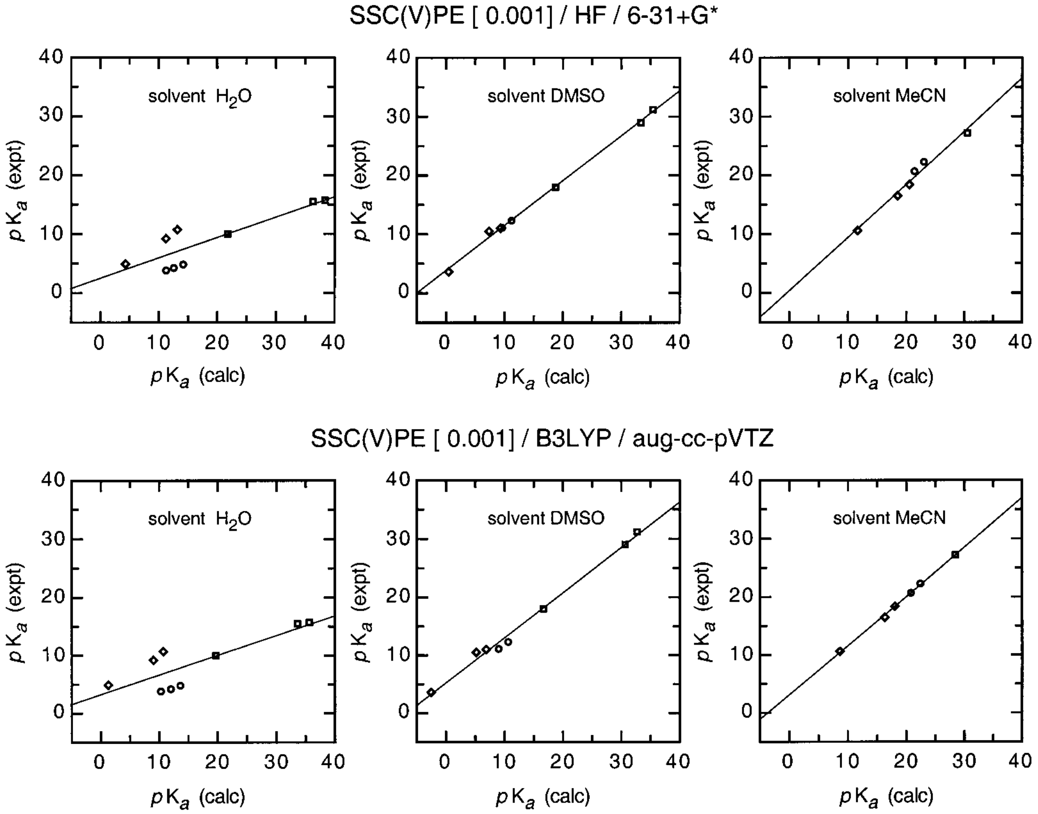

Figure 1. Experimental vs calculated pK_a values. Alcohols are shown with square boxes, carboxylic acids with circles, and ammonium ions with diamonds. Lines are drawn for the best linear regression fits.

TABLE 6: Linear Regression Parameters for Experimental pK_a vs pK_a Calculated with the SSC(V)PE Method[a]

	HF/6-31+G*			B3LYP/aug-cc-pVTZ		
contour	water	DMSO	MeCN	water	DMSO	MeCN
			slope *A*			
0.0005	0.269	0.638	0.688	0.253	0.629	0.614
0.001	0.345	0.764	0.904	0.340	0.776	0.848
0.002	0.453	0.930	1.060	0.468	0.974	1.104
			intercept *B*			
0.0005	3.83	5.80	5.54	4.61	7.26	8.21
0.001	2.50	3.85	0.39	3.25	5.26	3.11
0.002	0.35	0.76	−4.59	0.88	1.80	−3.86
			correlation coefficient *r*			
0.0005	0.799	0.991	0.994	0.750	0.980	0.985
0.001	0.869	0.999	0.989	0.835	0.996	0.999
0.002	0.944	0.989	0.866	0.931	0.994	0.911

[a] Results are listed for two different wave functions with dielectric constants characteristic of water, DMSO, and MeCN solvents, and using various isodensity contours (given in e/a_0^3).

In water, contour values in the range of 0.005−0.002 e/a_0^3 lead to correlation coefficients and slopes both considerably less than unity. Better looking results could be obtained by going to higher contour values. For example, with B3LYP/aug-cc-pVTZ wave functions we find that a very good maximum *r* value of 0.996 is reached with a contour value of 0.00440 e/a_0^3, but the corresponding slope *A* is still only 0.636. The maximum value of *A* is only 0.704, reached with a contour value of 0.00865 e/a_0^3 that produces a corresponding *r* value of only 0.839.

In DMSO, contour values in the range of 0.005−0.002 e/a_0^3 can lead to excellent correlation coefficients and reasonably good slopes, although not necessarily both at the same time. For example, with B3LYP/aug-cc-pVTZ wave functions we find that an excellent maximum *r* value of 0.999 is reached with a contour value of 0.00140 e/a_0^3, with a corresponding slope of 0.867. A slope of 1.000 is reached with a contour value of 0.00217 e/a_0^3, with a good corresponding *r* value of 0.991.

In MeCN, contour values in the range of 0.005−0.002 e/a_0^3 can again lead to excellent correlation coefficients and reasonably good slopes, although again not necessarily both at the same time. For example, with B3LYP/aug-cc-pVTZ wave functions we find that an excellent maximum *r* value of 1.000 is reached with a contour value of 0.00094 e/a_0^3, with a corresponding slope of 0.821. A slope of 1.000 is reached with a contour value of 0.00142 e/a_0^3, with a good corresponding *r* value of 0.981.

The collection of solutes should obviously be enlarged before taking too seriously the detailed values of the numerical fitting results described here. However, it is very clear that an isodensity contour of about 0.001 e/a_0^3 leads to very good correlation coefficients near unity in DMSO and MeCN solvents. Use of the linear regression fits allows good overall results to be obtained in nonaqueous solvents with the simple HF/6-31+G* wave function using the 0.001 e/a_0^3 contour. In DMSO the mean unsigned pK_a error is 0.3 and the maximum error is 1.0 (for NH_4^+/NH_3), and in MeCN the mean unsigned pK_a error is 0.7 and the maximum error is 1.1 (for $MeCOOH/MeCOO^-$). Use of the linear regression fits also allows good overall results to be obtained in nonaqueous solvents with the more sophisticated B3LYP/aug-cc-pVTZ wave function using the 0.001 e/a_0^3 contour. In DMSO the mean unsigned pK_a error is 0.6 and the maximum error is 1.2 (for NH_4^+/NH_3 and $MeCOOH/MeCOO^-$), and in MeCN the mean unsigned pK_a error is 0.1 and the maximum error is 0.4 (for NH_4^+/NH_3). Considering the wide range of functional groups and substituents that have been treated, we believe it likely that useful predictive power has been achieved for pK_a in these two nonaqueous solvents.

Summary and Conclusion

The B3LYP/aug-cc-pVTZ method gives gas phase acidities in very good agreement with experiment for solutes that range over different substituents and different acidic functional groups. The more economical HF/6-31+G* method also does reasonably well for gas phase acidities, due to a partial cancellation of errors from neglect of electron correlation and inadequate basis set completeness. Nuclear motion contributions are significant. While somewhat systematic and predictable, for quantitative work they should be individually evaluated for each solute.

The SSC(V)PE method, which is based on dielectric continuum theory for long-range electrostatic interactions, is used here to evaluate solvation effects. Isodensity cavities based on contours in the range of 0.0005−0.002 e/a_0^3 are considered, based on previous experience with neutral solutes.

Aqueous solvation energies for neutral and cationic solutes are found to be in the neighborhood of experimental values, but for anions the values are much too small in magnitude. Consequently, absolute pK_a results calculated in water are much higher than experiment. Even so, some useful correlations with experiment are found. In fact a correlation coefficient near unity can be found that encompasses all the solutes considered here, but only for a rather large contour value (corresponding to small cavities) that we regard as nonphysical fitting. For a more reasonable contour value of about 0.001 e/a_0^3, good separate linear correlations can be found for substituent effects on pK_a of solutes sharing the same acidic functional group, but numerical values of the correlation parameters turn out to be somewhat different for different functional groups.

The situation is considerably better but still not perfect in the polar nonprotic solvents DMSO and MeCN. There, correlation coefficients of essentially unity and slopes of exactly unity can be achieved with contour values either in or very close to the range 0.005−0.002 e/a_0^3. For the particular contour value of 0.001 e/a_0^3, absolute pK_a values are in fair agreement with experiment, correlation coefficients are very close to unity, and slopes are in the vicinity of unity, with MeCN having slope closest to unity. Use of the linear correlations leads to good accounts of pK_a in each of the two nonaqueous solvents for all the solutes considered.

To summarize, dielectric continuum theory with an isodensity contour value near 0.001 e/a_0^3 gives the best account of pK_a in the most innocuous solvent MeCN, a fairly good account in the somewhat basic solvent DMSO, and the poorest account in the difficult solvent water. This indicates that dielectric continuum theory produces solvation energies of about the right magnitude, even for anions, in the two nonaqueous solvents without the need for special cavity parameterization. This further implies that long-range bulk dielectric effects on pK_a are probably being described well in all the solvents considered, and that in the nonaqueous solvents whatever is still missing is well correlated with what is being treated. The problem in water is undoubtedly that specific short-range effects, such as hydrogen bonding for example, make further important contributions. Dielectric continuum theory is not very well suited to describe such specific short-range solute−solvent interactions, and this is the reason that such extensive parameterization has been found necessary in other studies to get the simple model to work quantitatively for this problem in water.

In conclusion, the present study has established that dielectric continuum theory can properly account for long-range electrostatic contributions from bulk dielectric to pK_a without adjusting the isodensity contour from values near 0.001 e/a_0^3 that have previously been found appropriate for other situations. Our view is that the most satisfactory general approach to the pK_a problem should not artificially distort the cavity to force dielectric continuum theory by itself to reproduce other things that it is ill-suited to describe, such as the strong solute−solvent interactions characteristic of hydrogen bonding with ionic solutes in water. A better way is keep a cavity that is related to the physical solute−solvent interface, and complete the picture by combining dielectric continuum theory with other complementary methods that are especially designed to account for specific short-range interactions. Such methods are now under investigation and will be reported in future work directed toward our goal of developing a simple computational approach to pK_a that will have predictive power, even in unusual situations where sufficient experimental data are not available for prior detailed parameterization.

Acknowledgment. The research described herein was supported by the Office of Basic Energy Sciences of the Department of Energy. This is Contribution No. NDRL-4372 from the Notre Dame Radiation Laboratory.

References and Notes

(1) Bell, R. P. *The Proton in Chemistry*; Chapman and Hall: London, 1973.
(2) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley: New York, 1992.
(3) Smith, B. J.; Radom, L. *J. Phys. Chem.* **1991**, *95*, 10549.
(4) Smith, B. J.; Radom, L. *J. Am. Chem. Soc.* **1993**, *115*, 4885.
(5) Smith, B. J.; Radom, L. *Chem. Phys. Lett.* **1994**, *231*, 345.
(6) Ochterski, J.; Petersson, G. A.; Wiberg, K. B. *J. Am. Chem. Soc.* **1995**, *117*, 11299.
(7) Bagno, A.; Scorrano, G. *J. Phys. Chem.* **1996**, *100*, 1536.
(8) Martin, J. M. L.; Lee, T. J. *Chem. Phys. Lett.* **1996**, *258*, 136.
(9) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764.
(10) Peterson, K. A.; Xantheas, S. S.; Dixon, D. A.; Dunning, T. H., Jr. *J. Phys. Chem. A* **1998**, *102*, 2449.
(11) Hammerum, S. *Chem. Phys. Lett.* **1999**, *300*, 529.
(12) Burk, P.; Koppel, I. A.; Koppel, I.; Leito, I.; Travnikova, O. *Chem. Phys. Lett.* **2000**, *323*, 482.
(13) Seo, Y.; Kim, Y.; Kim, Y. *Chem. Phys. Lett.* **2001**, *340*, 186.
(14) Pokon, E. K.; Liptak, M. D.; Feldgus, S.; Shields, G. C. *J. Phys. Chem. A* **2001**, *105*, 10483.
(15) Jorgensen, W. L.; Briggs, J. M.; Gao, J. *J. Am. Chem. Soc.* **1987**, *109*, 6857.
(16) Rullmann, J. A. C.; van Duijnen, P. Th. *Mol. Phys.* **1988**, *63*, 451.
(17) Guissani, Y.; Guillot, B.; Bratos, S. *J. Chem. Phys.* **1988**, *88*, 5850.
(18) Jorgensen, W. L.; Briggs, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 4190.
(19) Tanaka, Y.; Shiratori, Y.; Nakagawa, S. *Chem. Phys. Lett.* **1990**, *169*, 513.
(20) Gao, J.; Li, N.; Freinforf, M. *J. Am. Chem. Soc.* **1996**, *118*, 4912.
(21) Figueirido, F.; Del Buono, G. S.; Levy, R. M. *J. Phys. Chem.* **1996**, *100*, 6389.
(22) Byun, K.; Mo, Y.; Gao, J. *J. Am. Chem. Soc.* **2001**, *123*, 3974.
(23) Rashin, A. A.; Rabinowitz, J. R.; Banfelder, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 4133.
(24) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8552.
(25) Lim, C.; Bashford, D.; Karplus, M. *J. Phys. Chem.* **1991**, *95*, 5610.
(26) Chen, J. L.; Noodleman, L.; Case, D. A.; Bashford, D. *J. Phys. Chem.* **1994**, *98*, 11059.
(27) Tawa, G. J.; Pratt, L. R. *J. Am. Chem. Soc.* **1995**, *117*, 1625.
(28) Andzelm, J.; Kölmel, C.; Klamt, A. *J. Chem. Phys.* **1995**, *103*, 9312.
(29) Peräkylä, M. *J. Org. Chem.* **1996**, *61*, 7420.
(30) Li, J.; Fisher, C. L.; Chen, J. L.; Bashford, D.; Noodleman, L. *Inorg. Chem.* **1996**, *35*, 4694.
(31) Richardson, W. H.; Peng, C.; Bashford, D.; Noodleman, L.; Case, D. A. *Int. J. Quantum Chem.* **1997**, *61*, 207.
(32) Kallies, B.; Mitzner, R. *J. Phys. Chem. B* **1997**, *101*, 2959.
(33) Topol, I. A.; Tawa, G. J.; Burt, S. K.; Rashin, A. A. *J. Phys. Chem. A* **1997**, *101*, 10075.

(34) Shapley, W. A.; Bacskay, G. B.; Warr, G. G. *J. Phys. Chem. B* **1998**, *102*, 1938.

(35) Jayaram, B.; Liu, Y.; Beveridge, D. L. *J. Chem. Phys.* **1998**, *109*, 1465.

(36) Peräkylä, M. *J. Am. Chem. Soc.* **1998**, *120*, 12895.

(37) Schüürmann, G.; Cossi, M.; Barone, V.; Tomasi, J. *J. Phys. Chem. A* **1998**, *102*, 6706.

(38) Schüürmann, G. *J. Chem. Phys.* **1998**, *109*, 9523.

(39) Kubicki, J. D. *J. Phys. Chem. A* **1999**, *103*, 903.

(40) Peräkylä, M. *Phys. Chem. Chem. Phys.* **1999**, *1*, 5643.

(41) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **1999**, *103*, 11194.

(42) Lee, I.; Kim, C. K.; Han, I. S.; Lee, H. W.; Kim, W. K.; Kim, Y. B. *J. Phys. Chem. B* **1999**, *103*, 7302.

(43) Lee, I.; Kim, C. K.; Lee, I. Y.; Kim, C. K. *J. Phys. Chem. A* **2000**, *104*, 6332.

(44) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **2000**, *104*, 2402.

(45) Chen, I.-J.; MacKerell, Jr., A. D. *Theor. Chem. Acc.* **2000**, *103*, 483.

(46) Topol, I. A.; Tawa, G. J.; Caldwell, R. A.; Eissenstat, M. A.; Burt, S. K. *J. Phys. Chem. A* **2000**, *104*, 9619.

(47) Zhan, C.-G.; Zheng, F. *J. Am. Chem. Soc.* **2001**, *123*, 2835.

(48) Bartberger, M. D.; Fukuto, J. M.; Houk, K. N. *Proc. Nat. Acad. Sci. U.S.A.* **2001**, *98*, 2194.

(49) Toth, A. M.; Liptak, M. D.; Phillips, D. L.; Shields, G. C. *J. Chem. Phys.* **2001**, *114*, 4595.

(50) Liptak, M. D.; Shields, G. *J. Am. Chem. Soc.* **2001**, *123*, 7314.

(51) Liptak, M. D.; Shields, G. *Int. J. Quantum Chem.* **2001**, *85*, 727.

(52) Jang, Y. H.; Sowers, L. C.; Çağin, T.; Goddard, W. A., III *J. Phys. Chem. A* **2001**, *105*, 271.

(53) In ref 52, a novel dielectric continuum procedure is used wherein the dielectric constant inside the cavity is taken to be some value ϵ_{QM} different from the usual value of 1. This is used only for evaluation of the reaction field energy; consistently using it also in calculation of the solute internal electronic energy would produce a huge shift in the result. One of the rationalizations given for this device is that the electronic structure calculation may not fully account for solute polarizability, but the empirical finding of a value $\epsilon_{QM} = 0.92$ that is less than unity belies that. In fact, it can be shown that for a high dielectric solvent this procedure effectively scales the reaction field contribution to the solvation energy by a factor of $1/\epsilon_{QM}$. Thus, this parameter plays the same role as an overall multiplicative scaling of the pK_a.

(54) Kubicki, J. D. *J. Phys. Chem. A* **2001**, *105*, 8756.

(55) Topol, I. A.; Nemukhin, A. V.; Dobrogorskaya, Y. A.; Burt, S. K. *J. Phys. Chem. B* **2001**, *105*, 11341.

(56) Klicić, J. J.; Friesner, R. A.; Liu, S.-Y.; Guida, W. C. *J. Phys. Chem. A* **2002**, *106*, 1327.

(57) Li, H.; Hains, A. W.; Everts, J. E.; Robertson, A. D.; Jensen, J. H. *J. Phys. Chem. B* **2002**, *106*, 3486.

(58) Florián, J.; Warshel, A. *J. Phys. Chem. B* **1997**, *101*, 5583.

(59) Kawata, M.; Ten-no, S.; Kato, S.; Hirata, F. *Chem. Phys.* **1996**, *203*, 53.

(60) Kawata, M.; Ten-no, S.; Kato, S.; Hirata, F. *J. Phys. Chem.* **1996**, *100*, 1111.

(61) Sato, H.; Hirata, F. *J. Phys. Chem. A* **1998**, *102*, 2603.

(62) Hirata, F.; Sato, H.; Ten-no, S.; Kato, S. In *Combined Quantum Mechanical and Molecular Mechanical Methods*; Gao, J., Thompson, M. A., Eds.; American Chemical Society: Washington, DC, 1998; p 188.

(63) Sato, H.; Hirata, F. *J. Phys. Chem. B* **1999**, *103*, 6596.

(64) Sakurai, M.; Furuki, T.; Inoue, Y. *J. Phys. Chem.* **1995**, *99*, 17789.

(65) Wiberg, K. B.; Castejon, H.; Keith, T. A. *J. Comput. Chem.* **1996**, *17*, 185.

(66) Brinck, T.; Larsen, A. G.; Madsen, K. M.; Daasbjerg, K. *J. Phys. Chem. B* **2000**, *104*, 9887.

(67) Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2001**, *3*, 1523.

(68) Maksić, Z. B.; Vianello, R. *J. Phys. Chem. A* **2002**, *106*, 419.

(69) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(70) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161.

(71) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210.

(72) Bader, R. F. W.; Henneker, W. H.; Cade, P. E. *J. Chem. Phys.* **1967**, *46*, 3341.

(73) Bentley, J. *J. Phys. Chem. A* **1998**, *102*, 6043.

(74) Bentley, J. *J. Phys. Chem. A* **2000**, *104*, 9630.

(75) Abraham, M. H.; Chadha, H. S.; Whiting, G. S.; Mitchell, R. C. *J. Pharm. Sci.* **1994**, *83*, 1085.

(76) Hirschfelder, J. O.; Curtiss, C. F.; Bird, R. B. *Molecular Theory of Gases and Liquids*; Wiley: New York, 1964.

(77) Davidson, N. *Statistical Mechanics*; McGraw-Hill: New York, 1962.

(78) Pitzer, K. S.; Gwinn, W. D. *J. Chem. Phys.* **1942**, *10*, 428.

(79) Benson, S. W. *J. Am. Chem. Soc.* **1958**, *80*, 5151.

(80) Cumming, J. B.; Kebarle, P. *Can. J. Chem.* **1978**, *56*, 1.

(81) Bailey, W. F.; Monahan, A. S. *J. Chem. Educ.* **1978**, *55*, 489.

(82) East, A. L. L.; Radom, L. *J. Chem. Phys.* **1997**, *106*, 6655.

(83) Ayala, P. Y.; Schlegel, H. B. *J. Chem. Phys.* **1998**, *108*, 2314.

(84) Ben-Naim, A. J. *J. Phys. Chem.* **1978**, *82*, 782.

(85) Reiss, H.; Heller, A. *J. Phys. Chem.* **1985**, *89*, 4207.

(86) Tissandier, M. D.; Cowen, K. A.; Feng, W. Y.; Gundlach, E.; Cohen, M. H.; Earhart, A. D.; Coe, J. V. *J. Phys. Chem. A* **1998**, *102*, 7787.

(87) Tuñón, I.; Silla, E.; Bertrán, J. *J. Phys. Chem.* **1993**, *97*, 5547.

(88) Tawa, G. J.; Topol, I. A.; Burt, S. K.; Caldwell. R. A.; Rashin, A. A. *J. Chem. Phys.* **1998**, *109*, 4852.

(89) Mejías, J. A.; Lago, S. *J. Chem. Phys.* **2000**, *113*, 7306.

(90) Zhan, C.-G.; Dixon, D. A. *J. Phys. Chem. A* **2001**, *105*, 11534.

(91) Marcus, Y.; Kamlet, M. J.; Taft, R. W. *J. Phys. Chem.* **1988**, *92*, 3613.

(92) Schurhammer, R.; Wipff, G. *J. Mol. Struct. (THEOCHEM)* **2000**, *500*, 139.

(93) Schurhammer, R.; Wipff, G. *J. Phys. Chem. A* **2000**, *104*, 11159.

(94) Dupuis, M.; Marquez, A.; Davidson, E. R. 1999 “HONDO 99”, a computer program based on HONDO 95.3. Quantum Chemistry Program Exchange (QCPE), Indiana University, Bloomington, IN 47405.

(95) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(96) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(97) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(98) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

(99) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294.

(100) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

(101) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007.

(102) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.

(103) Chipman, D. M. *J. Chem. Phys.* **2002**, *116*, 10129.

(104) Chipman, D. M. *J. Chem. Phys.* **1996**, *104*, 3276.

(105) Chipman, D. M. *J. Chem. Phys.* **1997**, *106*, 10194.

(106) Zhan, C.-G.; Bentley, J.; Chipman, D. M. *J. Chem. Phys.* **1998**, *108*, 177.

(107) Chipman, D. M. *J. Chem. Phys.* **1999**, *110*, 8012.

(108) Chipman, D. M. *J. Chem. Phys.* **2000**, *112*, 5558.

(109) Chipman, D. M. *Theor. Chem. Acc.* **2002**, *107*, 80.

(110) Chipman, D. M.; Dupuis, M. *Theor. Chem. Acc.* **2002**, *107*, 90.

(111) Zhan, C.-G.; Chipman, D. M. *J. Chem. Phys.* **1998**, *109*, 10543.

(112) Zhan, C.-G.; Chipman, D. M. *J. Chem. Phys.* **1999**, *110*, 1611.

(113) Lebedev, V. I.; Laikov, D. N. *Dokl. Math.* **1999**, *59*, 477.

(114) Bartmess, J. E. “Negative Ion Energetics Data” in *NIST Chemistry WebBook*, NIST Standard Reference Database Number 69; Linstrom, P. J., Mallard, W. G., Eds.; National Institute of Standards and Technology: Gaithersburg MD, 20899; July 2001 (http://webbook.nist.gov).

(115) Hunter, E. P.; Lias, S. G. “Proton Affinity Evaluation” in *NIST Chemistry WebBook*, NIST Standard Reference Database Number 69; Linstrom, P. J., Mallard, W. G., Eds.; National Institute of Standards and Technology: Gaithersburg MD, 20899; July 2001 (http://webbook.nist.gov).

(116) Ben-Naim, A.; Marcus, Y. *J. Chem. Phys.* **1984**, *81*, 2016.

(117) Cabani, S.; Gianni, P.; Mollica, V.; Lepori, L. *J. Sol. Chem.* **1981**, *10*, 563.

(118) Pearson, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 6109.

(119) Pliego, J. R., Jr.; Riveros, J. M. *Chem. Phys. Lett.* **2000**, *332*, 597.

(120) *CRC Handbook of Chemistry and Physics*, 82nd ed.; Lyde, D. R., Ed.; CRC Press: New York, 2001.

(121) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(122) Coetzee, J. F. *Prog. Phys. Org. Chem.* **1967**, *4*, 45.

(123) Kolthoff, I. M.; Chantooni, Jr., M. K.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23.