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Review

Predicting pK_a in Implicit Solvents: Current Status and Future Directions*

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Computational prediction of condensed phase acidity is a topic of much interest in the field today. We introduce the methods available for predicting gas phase acidity and pK_as in aqueous and non-aqueous solvents including high-level electronic structure methods, empirical linear free energy relationships (LFERs), implicit solvent methods, explicit solvent statistical free energy methods, and hybrid implicit–explicit approaches. The focus of this paper is on implicit solvent methods, and we review recent developments including new electronic structure methods, cluster-continuum schemes for calculating ionic solvation free energies, as well as address issues relating to the choice of proton solvation free energy to use with implicit solvation models, and whether thermodynamic cycles are necessary for the computation of pK_as. A comparison of the scope and accuracy of implicit solvent methods with *ab initio* molecular dynamics free energy methods is also presented. The present status of the theory and future directions are outlined.

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Introduction

The reader of this journal is familiar with the concept of pK_a, defined as the negative logarithmic of the acid dissociation constant, $K_a = [H^+][X^-]/[HX]$

$$pK_a = -\log_{10} K_a \quad (1)$$

It provides a direct measure of the thermodynamic feasibility of a proton transfer reaction that is found in many processes occurring in nature and in the chemical laboratory. The associated thermodynamic driving force is directly related to the difference in pK_as of the donor (HD) and acceptor (HA).

$$\Delta G = 2.303RT(pK_a(HD) - pK_a(HA)) \quad (2)$$

The pK_a also offers a measure of the stability of the base relative to its conjugate acid, and understanding the factors that influence this stability could provide chemists with new strategies to manipulate synthesis[1] and/or gain insights into the mechanism of important biochemical reactions.[2] For example, racemases and epimerises are a class of enzymes[3] that catalyse the stereochemical inversion of α-amino acids and peptides (Fig. 1) through the heterolytic cleavage of very stable α-CH bonds (pK_as ~24[4]). Richard and co-workers have developed NMR methods to determine the aqueous pK_as of biologically important carbon acids, and gained new insights into the catalytic efficiency of these enzymes.[5] More recently, Kass and co-workers determined the pK_as of a series of acyclic polyols that involve extended hydrogen-bonding networks, and discovered that this has a profound influence on the pK_as of these oxygen-centred acids.[2b] This finding has direct relevance to enzyme catalysis (e.g. oxyanion hole formation),[2a] and the concept has been exploited in the design of new organic superbases,[6] Brønsted acid catalysts, and anionic receptors.[7]

Predicting pK_as is also of interest to other fields such as structural biology and drug development. X-ray crystallography can reveal precise three-dimensional positions of most atoms in a protein; however, hydrogen atoms are usually

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*The author, Junming Ho, is the winner of the 2012 Cornforth Medal awarded by the RACI.

L D

Fig. 1. Racemases are enzymes that catalyse the stereochemical inversion of L-amino acids by the abstraction and reprotonation of the α-CH proton.

unresolved because of their low electron density, and knowledge of the protonation states of titratable residues is often essential for elucidating the mechanism of enzyme catalysis. In addition, conformational preferences of proteins and enzymes are dependent on protonation states of residues, which could in turn affect their activity.[8] In drug design, it is also desirable to know the pK_a values of any ionisable groups within a given test compound as this knowledge may be important for improving potency against the drug target, and for modulating physical and pharmacological properties such as solubility, bioavailability, and distribution.[9]

Experimental determination of pK_a is straightforward as long as there is only one titratable group involved. Ullman and Bombarda have pointed out that for polyprotic acids containing four or more ionisable groups, it is not possible to obtain all microscopic pK_as from the titration curve.[10] For very weak or strong acids (p$K_a > 16$ or < 0) there are also difficulties in measuring their *aqueous* acidity because of the levelling effect of the solvent;[11] however, many synthetically and biologically important compounds such as amides and peptides have pK_as that are typically in the range of 20 or higher.[2c] While ^{1}H NMR spectroscopic methods have been developed to estimate the aqueous pK_as of compounds of these types,[4,5d,12] there are sometimes practical difficulties because of the time required to observe hydrogen–deuterium exchange, and/or solubility and stability issues.

In this context, computational chemistry offers a valuable alternative to quantitative pK_a studies. The methods available include linear free energy relationships (LFERs) and quantitative structure–property relationships (QSPRs), high-level electronic structure theory methods, implicit solvent methods, explicit solvent statistical mechanical free energy methods as well as hybrid quantum mechanical/molecular mechanical (QM/MM) procedures. The choice of method often depends on the system of interest. Implicit solvent methods are very popular in terms of computational cost and accuracy, and are the method of choice for small to medium-sized acids.[13] In a recent review, Alongi and Shields presented a detailed summary of the various implicit solvent methods that have been successful in the aqueous pK_a prediction of small monoprotic acids.[13c] Ho and Coote have also published an extensive methodological study to define the theoretical benchmarks for implicit solvent prediction of aqueous pK_as of common organic and inorganic acids,[14] and a 'how-to' tutorial review for performing implicit solvent pK_a calculations.[15]

On the basis of these studies, the average accuracy of these methods for *general* pK_a prediction in the aqueous phase is estimated to be about ± 2 units, and there is active ongoing research towards improving this level of accuracy. There is also interest towards extending implicit solvent methods to model temperature effects, and more complex systems such as multivalent transition metal ions, zwitterions, and polyprotic acids in aqueous and non-aqueous solvents. Notable developments include new quantum chemical algorithms to facilitate the computation of gas phase energetics of large systems and new cluster-continuum schemes for calculating ionic solvation free energies and pK_as of polyprotic acids. Some of these recent developments have also raised important methodological questions concerning the accuracy, scope, and correct usage of implicit solvation models. For example, (a) are thermodynamic cycles necessary for the computation of pK_as and (b) are implicit solvation models designed to predict *real* or *intrinsic* solvation free energies, and which proton solvation free energy should be used in conjunction with particular implicit solvation models?

The purpose of this review is to present and clarify these issues, explain the present status of the theory, and to provide an accessible overview of the spectrum of methods available for predicting gas phase and condensed phase pK_as. This paper is laid out as follows: We begin by reviewing recent developments starting with gas phase electronic structure calculations, LFER and QSPR methods, followed by implicit solvent methods. We devote the last section to explicit solvent statistical free energy methods, which are likely to become increasingly important in the future. The accuracy, scope, and predictive power of each method are explained, and future directions are outlined.

Gas Phase Acidities

Gas phase acidities are relatively straightforward to compute because of the absence of environmental effects. The gas phase acidity corresponds to the Gibbs free energy change of the deprotonation reaction.

$$\Delta G^{\circ}_{\text{gas}} = G^{\circ}(\text{H}^+) + G^{\circ}(\text{A}^-) - G^{\circ}(\text{HA}) \tag{3}$$

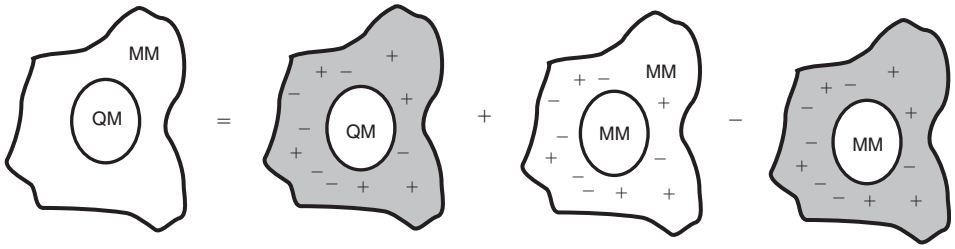
This Gibbs free energy change can in turn be expressed in terms of difference in electronic energies, and the thermal contribution to the free energy of each species (Eqn 4). The electronic contribution is generally evaluated using high level correlated wave function theory (WFT) or benchmarked density functional theory (DFT) methods, whereas the thermal contribution and the molecular geometry on which these computations are based, are typically obtained using small basis set Hartree Fock (HF) or DFT (e.g. B3LYP) calculations in conjunction with statistical mechanical equations derived from the ideal gas, rigid-rotor harmonic oscillator approximation with the application of appropriate scale factors.[16] The gas phase free energy of the proton G_{298} is $-26.3\,\text{kJ mol}^{-1}$ based on values of $6.197\,\text{kJ mol}^{-1}$ and $108.947\,\text{J mol}^{-1}\,\text{K}^{-1}$ for its enthalpy and entropy respectively.[17]

$$\begin{aligned}\Delta G^{\circ}_{\text{gas}} = {} & E(\text{A}^-) - E(\text{HA}) + G_{\text{corr}}(\text{H}^+) \\ & + G_{\text{corr}}(\text{A}^-) - G_{\text{corr}}(\text{HA})\end{aligned} \tag{4}$$

The treatment of conformationally flexible species, including the strategies for efficiently searching the conformational space, has been discussed in a recent tutorial review.[15]

Composite Methods

The coupled cluster CCSD(T) method[18] represents the 'gold standard' in *ab initio* quantum chemistry, and is widely used as the benchmark for new theoretical procedures. This level of theory can predict thermochemical properties to within $5\,\text{kJ mol}^{-1}$ of experiment (this level of accuracy is known as 'chemical accuracy'), and is the method of choice for systems that do not possess significant multireference character, as is the case for most closed shell species. Unfortunately, the



Scheme 1. Schematic representation of a two-layer ONIOM-EE method for quantum mechanical/molecular mechanical (QM/MM) calculations.

computational cost of this method scales steeply with the size of the system and is therefore limited to small molecular systems composed of very few heavy (or non-hydrogen) atoms.

This has motivated the development of composite procedures that approximate higher levels of theory by using various lower levels of theory. The advantage lies in the very significant savings in computational expense resulting from the lower level computations. Notable examples include the Gaussian-*n* (e.g. $n = 4$,[19] 3MP2-RAD[20]), CBS-X (e.g. X = QB3[21] and APNO[22]), ccCA-Y (e.g. Y = S4[23] and CC(2,3)[24]) and the MCCM/3[25] methods that have been developed to provide accurate estimates of reaction thermochemistry. The recently introduced ccCA-CC(2,3) procedure uses the completely renormalised coupled cluster method CR-CC(2,3)[26] in place of CCSD(T) and is designed to handle systems with significant multireference character that might be relevant for open shell species. This collection of composite methods allows the treatment of systems containing tens of heavy atoms. In several assessment studies,[15,17,27] composite procedures such as G3(MP2)-(+) and CBS-QB3 were found to deliver gas phase acidities of a broad range of neutral and ionic acids with an average error of ~5 kJ mol^{-1}. This level of accuracy can be further improved (in the kJ mol^{-1} range) using the Weizmann-*n* theories (e.g. $n = 3$[28] and 4[29]) but the increased computational expense restricts their application to systems composed of very few heavy atoms. For example, the W1w method was recently applied to predict the gas phase acidities of substituted methanes and methyl radicals (containing only two non-hydrogen atoms) which showed excellent agreement with available experimental data.[30]

There have been attempts to further broaden the scope of composite methods. Radom and co-workers have formulated cost-effective variants such as the G4(MP2)-6X,[31] W1X-1 and W1X-2,[32] and W3X[33] methods that retain a similar level of accuracy. The development of new quantum chemical algorithms has also helped to expand the scope of these procedures. For example, it is possible to employ explicitly correlated F12-type methods[34] (e.g. CCSD(T)-F12)[35] that include explicit two-electron terms to enable more rapid basis set convergence compared with conventional one-electron procedures, thus allowing the use of smaller and computationally less demanding basis sets. This approach has recently been used to extend the applicability of existing composite procedures (e.g. the W1-F12 and W2-F12 methods)[36] to larger polyacenes and nucleic acids containing up to 18 heavy atoms.

QM/MM Methods

Another commonly used approach for even larger molecular systems (composed of hundreds to thousands of heavy atoms that are common for biochemical systems) is to employ hybrid QM/MM procedures[37] by defining two or more layers within the structure that are treated at different levels of accuracy. Typically, the core layer is defined to capture the chemistry of the reaction, e.g. the site of deprotonation, and is modelled most accurately. The spectator region of the system constitutes the outer layer(s) and is usually treated with an inexpensive model chemistry such as molecular mechanics (e.g. AMBER[38] and CHARMM[39] force fields), semi-empirical method (e.g. PM6) or an inexpensive *ab initio* method (e.g. HF or DFT with a modest basis set). In QM/MM calculations, one can further take advantage of electronic embedding (e.g. the ONIOM-EE method)[40] by incorporating the partial charges of the MM layer into the quantum mechanical Hamiltonian, thereby providing a better description of the electrostatic interactions between the chemical environment and the core system (Scheme 1). Variants of this method that permit the polarisation of the MM layer, such as the Moving-Domain QM/MM approach,[41] have also been introduced. Accordingly, many different flavours of QM/MM methods have appeared in the literature depending on the choice of QM theory, MM force field, treatment of QM/MM boundary conditions, and whether electrostatic embedding is employed.

The ONIOM approximation[37a,42] is one example of this class of methods. This approach has been applied in conjunction with high-level composite procedures to yield so called multi-layer composite methods. Morokuma and co-workers developed the first of such methods, IMOIMO-G2MS[43] which utilised a simplified version of the G2 composite method for the core layer, and the ROMP2/6–31G(d) was used for the outer layer. Li and co-workers subsequently developed an analogous ONIOM-G3B3 procedure[44] to afford accurate estimates of related C–H and N–H bond dissociation enthalpies for ribonucleosides and deoxyribonucleosides. Coote and co-workers have also employed a similar strategy that uses the G3(MP2)-RAD composite procedure for the core layer and the MP2 with a large triple zeta basis set for the spectator layer to compute bond dissociation energies,[45] radical addition rate coefficients,[46] reduction potentials,[47] and pK_as.[1c] Most recently, Wilson and co-workers developed the ONIOM-ccCA method[48] that uses the ccCA composite procedure for the high layer and B3LYP/cc-PVTZ for the low layer, and applied this method for the computation of proton affinities of deoxyribonucleosides.[49]

QM/MM methods have also been applied to predict p*K*as of ionisable residues in proteins. For example, Jensen and co-workers developed multi-layer QM/MM methods that represent the protein environment using a hybrid effective fragment potential (EFP)[50]/classical force field approach.[51] When the QM region is treated at the MP2 level of theory, the authors verified that this approach can predict the pK_as of ionisable groups in the OMTKY3 protein to within 0.5 pK_a units.[52]

Cui and co-workers have also developed a free energy perturbation technique that employs DFT/CHARMM potential to predict pK_as of various proteins.[53] This class of methods will be revisited in the later sections of this paper in the context of explicit solvent approaches for pK_a prediction. It should also be mentioned that the development of *linear scaling* fully QM treatments of large molecular systems, e.g. by systematic fragmentation[54] and fragment molecular orbital methods,[55] is an active area of research, and the reader is referred to several insightful reviews[56] for a more detailed discussion on recent developments in this field.

DFT Methods

DFT methods are cost-effective alternatives to wave function methods.[57] These are also the preferred computational methods for transition metal chemistry.[57a] To date, a large number of DFT methods employing various levels of approximations have been developed. Perdew proposed a Jacob's ladder framework to classify DFT methods according to a hierarchy of density approximations, including those that employ the generalised gradient approximation (e.g. BP86[58]), meta-generalised gradient approximation (e.g. M06L[59]), hybrid generalised gradient approximation (e.g. B3LYP[60] and PBE1PBE[61]), and hybrid meta-generalised gradient approximation (e.g. BMK[62] and M062X[63]). Liptak and Shields have examined the use of various DFT methods for predicting the ΔH^o and ΔG^o for 17 deprotonation reactions, and found that the PBE1PBE and B3P86 functionals provided accuracies comparable to high level composite procedures.[64] This was also observed in a very recent assessment study that showed the PBE1PBE method produced very similar average errors compared with the G-*n* composite methods for a test set of 64 and 53 neutral bases and acids.[27c] However, DFT methods are also known to have several shortcomings, in particular their performance is known to be less consistent[65] and their error can only be estimated statistically by benchmarking against large sets of data. Burk et al. have found that the B3LYP when used in conjunction with the 6–311+G(d,p) basis set can predict gas phase acidities and basicities of 49 acids and 32 bases with an average accuracy of 10 kJ mol^{-1}; however, there are instances where the largest errors are in excess of 20 kJ mol^{-1}.[66] In another assessment study comparing the performance of various DFT (B3LYP, BMK, M05–2X, B97–1) and composite methods, the B97–1 method provided a mean absolute error of ~5 kJ mol^{-1} comparable to the accuracy of the more costly G3(MP2)-(+) procedure;[14,15] however, the corresponding error for cationic acids was much higher (>10 kJ mol^{-1}). While these results are likely to improve with the development of newer generation DFT methods (e.g. double-hybrid and dispersion corrected DFTs),[27c,63,67] it is generally recommended that some form of benchmarking be carried out to assess their performance for the particular class of acid being studied.

Condensed Phase Acidities

Whereas the development of powerful computer architectures and efficient quantum chemical algorithms has facilitated the calculation of accurate gas phase energies for a broad range of systems, the situation is less satisfactory in the solution phase primarily because of the absence of a framework, such as the variational principle, whereby solution phase energies can be systematically improved. For this reason, the development of theoretical procedures for chemically accurate solution phase thermochemistry remains one of the key challenges for modern computational chemistry. As noted in Eqn 2, an error of 5.7 kJ mol^{-1} in ΔG corresponds to one unit error in predicted pK_a at room temperature. Achieving this level of accuracy in *general* pK_a prediction remains difficult, although in many cases, it is possible to develop models or employ empirical corrections that can often provide very accurate estimates for selected classes of acids. Ultimately, the level of accuracy and the robustness of the model desired would also depend on the chemical problem that one is trying to solve, and this section reviews the methods available for solution phase pK_a predictions of varying accuracy, computational cost, and broadness of applicability. The main focus is on the prediction of *aqueous* pK_as of compounds at 25°C that are important in many biochemical and environmental processes and for which there is an abundance of experimental data for validating theoretical models. Acidity predictions of metal-containing species, and in non-aqueous solvents that are equally important in synthetic applications, are also highlighted in the relevant sections.

Linear Free Energy Relationships (LFERs)

There are several approaches to calculating a condensed phase pK_a, ranging from phenomenological or theoretically guided LFERs or QSPRs[68] correlating pK_as with computed and/or experimental observables (Y_i) to direct calculations of pK_as. One of the earliest versions of the LFER method was presented by Hammett's studies of substituent effects,[69] and the resulting Hammett constants that came from these studies formed the basis for many early attempts to estimate the pK_as of organic acids.

$$\mathrm{p}K_a = a_0 + a_1 Y_1 + a_2 Y_2 + \cdots + a_n Y_n \qquad (5)$$

In more recent implementations of LFERs (or QSPRs), computed properties are often obtained by quantum mechanical calculations. Calculated or measured properties that may be correlated with pK_as include geometrical parameters (e.g. bond lengths),[70] atomic charges,[71] ionisation energies and electron affinities,[72] molecular electrostatic potential,[73] proton transfer barriers,[74] quantum chemical topology (QCT) descriptors,[75] as well as the energies of frontier molecular orbitals,[76] and these quantities may be regressed on experimental solution phase pK_as in order to develop a predictive equation. The resulting equation often provides insights into the origin of the acidity of the molecule, and new strategies may be designed to manipulate the acid–base properties of these compounds. Klamt[77] and others[78] have also directly computed solution-phase deprotonation energies (ΔE) using dielectric continuum models (neglecting zero-point vibrational energy and thermal contributions), and fitted these energies to experimental pK_as according to Eqn 6 in aqueous and non-aqueous solvents. Related approaches that introduce empirical corrections to obtain good fits between experimental and calculated pK_as have also been reported.[79]

$$\mathrm{p}K_a = a\frac{\Delta E}{RT\ln(10)} + b \qquad (6)$$

LFER and QSPR approaches are appealing because they allow for very rapid and often moderately accurate evaluation of pK_a values, which is especially important in pharmaceutical

applications such as high-throughput screening of large databases of drug candidates. The shortlisted candidates may then be reexamined using more rigorous models. However, the empirical nature of this approach means that it may be difficult to estimate errors associated with these models, particularly when they are applied on compounds outside of the training set. Such approaches are also impractical in situations where there is limited accurate experimental data needed to derive the predictive model, as is the case for certain acid functionalities (e.g. radical species) and solvent systems.

To calculate pK_as directly, typically only the chemically important portion of the system, e.g. the solute and the first solvent shell, are treated explicitly by quantum mechanics (QM). The rest of the system is treated by molecular mechanics (MM), which is essentially a QM/MM approach where in this case the MM subsystem is the solvent. It is common to find in the literature studies that base the QM/MM calculation on a single solvent configuration; however, this is likely to introduce significant sampling errors since deprotonation energies are likely to be very sensitive to the distribution of solvent molecules. This is an example that is best treated by an explicit solvent method where molecular dynamics (MD) or Monte Carlo (MC) methods are used to ensemble average the solvent. In this context, implicit solvation models are advantageous because methods based on classical electrostatics usually replace discrete solvent molecules by a dielectric continuum, so that the solvent and the ensemble averaged over all solvent configurations both become implicit, and this greatly accelerates phase-space sampling.

Implicit Solvent Methods

Thermodynamic Cycles

In QM-continuum treatments, the solution phase free energy change (ΔG_{soln}) is usually expressed as a sum of terms based on a thermodynamic cycle and examples of different thermodynamic cycles used for predicting pK_as are shown in Scheme 2. These terms can be further categorised into a gas phase (ΔG_{gas}) and solvation ($\Delta\Delta G_S$) contribution, where the latter is evaluated using implicit solvation models.

$$\Delta G_{soln} = \Delta G_{gas} + \sum \Delta G_S(\text{products}) - \sum \Delta G_S(\text{reactants}) \quad (7a)$$

$$\Delta G_{soln} = \Delta G_{gas} + \Delta\Delta G_S \quad (7b)$$

Expressed in these terms, thermodynamic cycles can often offer very good results through the judicious choice of level of theory for the calculation of ΔG_{gas} and the solvation model for calculation of solvation free energies. The task of finding an optimal combination of solute geometry, electronic structure method, implicit solvation model and cavity definition, and proton solvation free energy has been the subject of previous investigations,[14,80] but the number of procedures continue to grow as newer generation solvation models are introduced, or when refinements are made to the proton solvation free energy. In the following sections, we highlight prominent examples of thermodynamic cycles that have been successful in pK_a prediction. The issue of whether thermodynamic cycles are necessary for computing pK_as is also addressed.

Finally, when combining solution phase and gas phase thermodynamic quantities, one needs to pay close attention to the standard states. Gas phase energies are calculated with respect to a standard state of 1 bar (~1 atm) and denoted with a '°' superscript) whereas the corresponding standard state for solution phase and pure solvents are 1 molal (~1 mol L^{-1} for aqueous solution and denoted with a '*' superscript) and the concentration of that solvent (55 mol L^{-1} for pure water) respectively. Solvation free energies predicted by implicit models also differ from conventional values where the standard state is 1 mol L^{-1} in both gas and solution phase. The derivation of the corrections needed to convert between various standard states has been presented elsewhere.[81]

Implicit Solvation Models

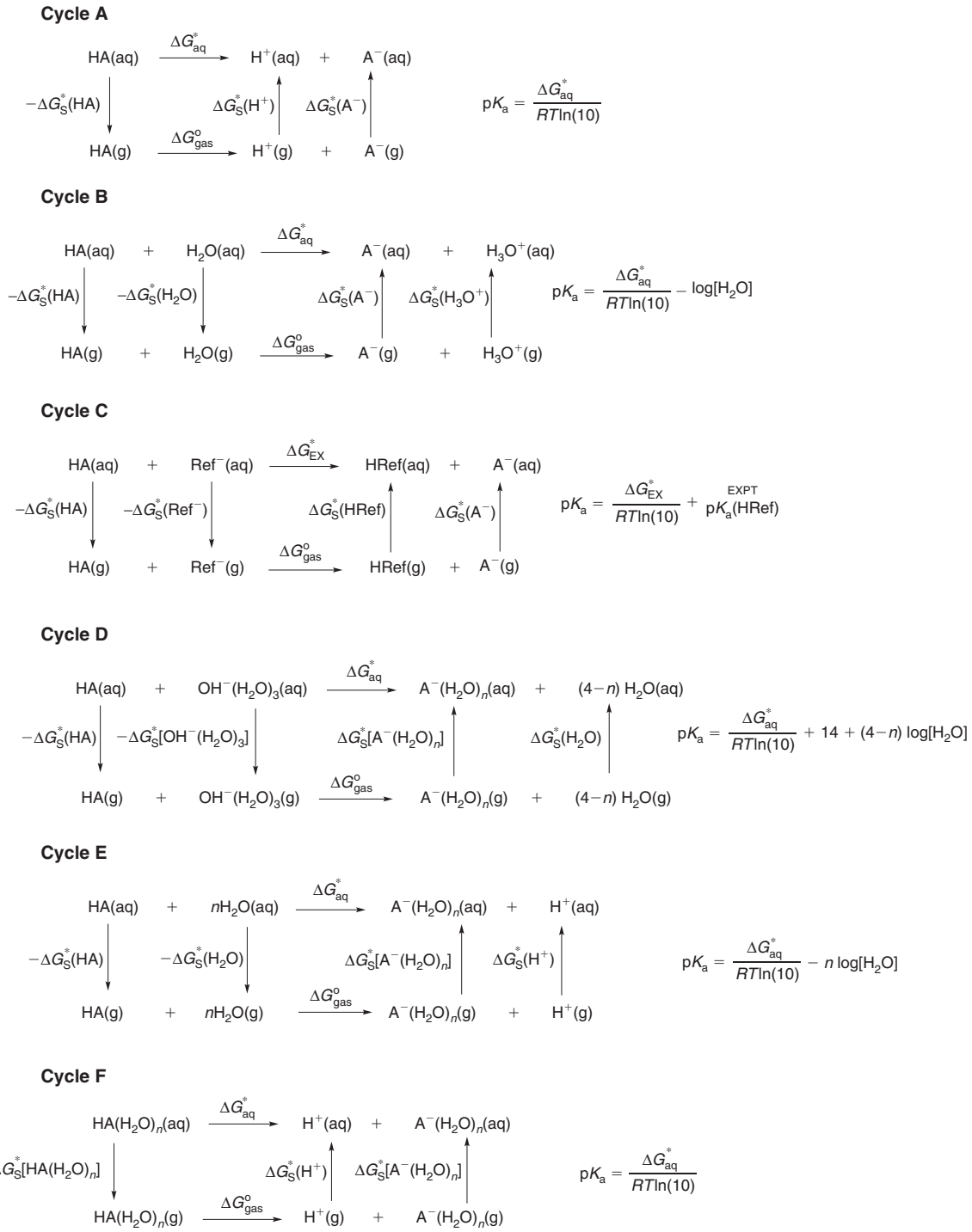
Implicit solvation models[82] (also commonly known as continuum solvent models) have been designed to make accurate predictions of solvation free energies in aqueous and non-aqueous solvents. The solvent reaction field used to compute the electrostatic contributions (ΔG_{elec}) in these models is determined either by numerical solution of the non-homogeneous Poisson equation (NPE)[83] or by the generalized Born approximation (GB).[84] The electrostatic contribution to the solvation free energy is the difference between the electronic energy of the polarised solute in the presence of the solvent field $\langle \psi^{pol} | H + \frac{1}{2} V | \psi^{pol} \rangle$, and the gas phase electronic energy (E_{gas}). Typically, these models also contain a non-electrostatic term that assigns contributions due to cavitation, dispersion, and/or solvent–structural effects.

$$\Delta G^*_S = \Delta G_{elec} + \Delta G_{cav} + \Delta G_{dis\text{-}rep} \quad (8a)$$

$$\Delta G^*_S = \left\langle \phi^{pol} \middle| H + \frac{1}{2} V \middle| \phi^{pol} \right\rangle + \Delta G_{cav} + \Delta G_{dis\text{-}rep} - E_{gas} \quad (8b)$$

Examples of implicit solvation models include the polarisable continuum model (PCM) family of methods (e.g. IEF-PCM,[85] CPCM,[86] and IPCM),[87] the SMx series (e.g. x = 8,[88] D[89]), the IEF-MST model,[90] SMVLE[91] and SS(V)PE (+FESR) models,[92] PB/Jaguar model,[93] and the COSMO[94] and COSMO-RS[94b,95] methods. In these models, both electrostatic and non-electrostatic terms depend on atom-based parameters that have been optimised at a pre-determined level of theory (usually HF or DFT) to reproduce experimental properties, such as solvation free energies. The groups of Cramer and Truhlar have compiled an extensive dataset of 3037 experimental solvation free energies and transfer free energies for 790 neutral and monovalent ionic solutes in aqueous and non-aqueous solvents for this purpose.[96]

The majority of implicit solvation models (except the SMD, SM8, and COSMO-RS models) have been designed to predict *aqueous* solvation free energies at *room temperature*. There have been attempts[97] to reparameterise existing implicit models for non-aqueous solvents. This is generally achieved by applying an optimised scale factor (f) to the atomic radii, which in turn affects the electrostatic, cavitation, and van der Waals contributions to the solvation free energy. The value of 1.2 is recommended for aqueous solvent in most implicit solvation models.[82a,95b,98] Orozco and co-workers have parameterised the MST model in this fashion to predict solvation free energies of neutral solutes in non-aqueous solvents.[90b,99] Pliego and Riveros have also reported the first reparameterisation of the PCM model to calculate anionic solvation free



Scheme 2. Different thermodynamic cycles used in implicit solvent pK_a predictions. '*' denotes that the thermodynamic quantities are calculated with respect to a standard state of 1 mol L^{-1} for aqueous solutions, and 55 mol L^{-1} for pure water.

energies in DMSO,[100] and applied these energies to compute the pK_as of 41 organic acids in this solvent.[101] Later, Fu et al. adopted a similar approach to calculate solvation free energies of neutral and anionic compounds in DMSO, and successfully applied these energies in a cluster-continuum scheme to reliably predict the pK_as of a broad range of organic acids in this solvent.[102] Attempts to parameterise the PCM model for metal ions,[97a] and other solvents such as formamide,[97b] methanol,[97b] nitrobenzene,[103] and acetonitrile[104] have also been reported.

The SM8T[105] and the COSMO-RS models can further predict solvation free energies at temperatures other than 25°C. In several recent studies, the former model was used to model the temperature dependency of aqueous amine basicity,[106] amino acids,[107] and HCl acidity[108] that showed very good correlations with experiment. The COSMO-RS model has also been applied to study the temperature dependence of aqueous solubilities of solid carboxylic acids,[109] vapour pressure of nitrogen-rich explosive materials,[110] and generate temperature-dependent Arrhenius plots to derive kinetic

activation parameters of radical addition reactions in non-aqueous solvents.[46]

For small rigid solutes, their solvation free energies are often computed from a single-point calculation on either the gas phase or solution phase optimised geometry. For floppy and conformationally flexible systems, solvation free energy calculations usually entail carrying out separate conformational searches in both gas and solution phase to identify the key conformers, and their contribution to the solvation free energy is evaluated through a Boltzmann average (Eqn 9).[111] In a recent study, molecular dynamics simulations employing explicit molecular mechanical force fields for the solute and solvent were used to sample the conformational space for a test set of 20 neutral drug compounds. The study found that implicit solvation calculations based on the single-conformation approach provide an accurate estimate of solvation free energies for rigid molecules but perform poorly for flexible species and highlights the need for a multiconformation treatment.[112]

$$\langle G_{\text{gas}} \rangle = RT \ln \left[\sum_{i}^{N\text{conf}} \exp\left(-\frac{G^{i}_{\text{gas}}}{RT} \right) \right] \tag{9a}$$

$$\langle G_{\text{soln}} \rangle = RT \ln \left[\sum_{i}^{N\text{conf}} \exp\left(-\frac{G^{i}_{\text{soln}}}{RT} \right) \right] \tag{9b}$$

$$\Delta G_{\text{S}} = \langle G_{\text{soln}} \rangle - \langle G_{\text{gas}} \rangle \tag{9c}$$

Generally, the accuracy of implicit solvation models is $\sim$5 kJ mol^{-1} for *typical* neutral solutes, whereas monovalent ionic species have larger uncertainties of 15 kJ mol^{-1} or higher. By typical, we mean solutes that bear similar structural features and/or functionalities to those in the training set used to parameterise these models. In a similar way to MM biomolecular force field development, the atom-based parameters (e.g. atomic radii to construct molecular cavity and the atom–atom potential parameters to compute dispersion–repulsion interactions) are in principle transferable to other chemical systems containing similar functional groups. As discussed elsewhere,[113] because of the semi-empirical nature of implicit solvation models it is also crucial that the user understands their parameterisation boundaries so that these models may be applied in an optimal manner. In the following sections, we elaborate on several subtle points concerning the design and implementation of implicit solvent models, implications for pK_a predictions, and draw on recent examples from the literature to illustrate the predictive power and scope of these models.

Real versus Intrinsic Solvation Energies

In calculating free energies of solvation for ionic species (with charge $\pm z$), a distinction is made between *intrinsic* (or *absolute*) free energy of solvation (ΔG_{S}) and the *real* free energy of solvation (α), where the latter includes the contribution associated with the surface potential (χ) of the solvent.

$$a(A^{\pm z}) = \Delta G_{\text{S}}(A^{\pm z}) \pm z\chi \tag{10}$$

The surface potential is not amenable to direct measurement, and various estimates of this value for water (50,[114] 25,[115] $-$18,[116] 140,[117] and 550 mV[118]) have been reported. This raises the interesting question as to whether implicit solvation models are designed to predict intrinsic or real solvation free energies. As noted above, implicit solvation models have been parameterised to reproduce experimental solvation free energies. However, experimental data for ionic species are usually obtained *indirectly* since partition coefficients/vapour pressures are not directly measurable for these species. Instead, ionic solvation free energies are commonly derived from a combination of experimental pK_as, gas phase reaction energies, and a solvation free energy of the proton.[119] Accordingly, it boils down to which proton solvation free energy, $\alpha(\text{H}^+)$ or $\Delta G^*_{\text{S}}(\text{H}^+)$, was used to derive the experimental data. As discussed in more detail below, this remains an open question, but from a practical point of view, the contribution from the surface potential always cancel out in a chemically balanced equation involving *a single phase*, and the choice of real or intrinsic solvation free energies should not matter so long that they are used consistently for all reacting species and products.

Proton Solvation Free Energy

An implication from the above analysis for pK_a computations (e.g. cycles A, E, and F in Scheme 2) is that one should employ an implicit solvation model that is based on a consistent $\Delta G^*_{\text{S}}(\text{H}^+)$.[80a] As noted elsewhere,[120] this is analogous to using a consistent value for the absolute reduction potential of the standard hydrogen electrode (SHE), since its value also directly depends on $\Delta G^*_{\text{S}}(\text{H}^+)$. Table 1 provides an overview of several popular implicit solvation models used in aqueous calculations, the $\Delta G^*_{\text{S}}(\text{H}^+)$ upon which they are based, and examples of the levels of theory for which they have been most extensively benchmarked. The uncertainty associated with the presently accepted value of -1112.5 kJ mol^{-1} has been estimated to be no less than 10 kJ mol^{-1},[121] with more recent work suggesting even larger uncertainties.[122] This value was determined using the cluster-pair approximation,[121a,123] and is thought to represent the intrinsic solvation free energy since the ion–water clusters ($n \leq 6$) used to determine $\Delta G^*_{\text{S}}(\text{H}^+)$ are too small for the surface potential to develop.[124] However, this remains a controversial subject.[125] The corresponding values in methanol, acetonitrile, and DMSO have also been determined using the same method to be -1102.5, -1089.5, and -1143.5 kJ mol^{-1}, respectively.[120a] Other estimates of the proton solvation free energies in aqueous and non-aqueous solvents have also been reported and the data is summarised in Table 2.

It has recently been pointed out that the value of $\Delta G^*_{\text{S}}(\text{H}^+)$ also depends on the statistical mechanical formalism used to treat the electron, as this directly affects the formation free energy of the proton $\Delta G^{\circ}_{\text{f}}(\text{H}^+)$ that the cluster-pair approximation uses to determine $\Delta G^*_{\text{S}}(\text{H}^+)$.[124b] The values shown in Tables 1 and 2 are based on the Boltzmann electron convention; however, electrons and protons are fermions and applying the Fermi–Dirac formalism positively shifts the $\Delta G^*_{\text{S}}(\text{H}^+)$ of -1112.5 kJ mol^{-1} by 3.6 kJ mol^{-1} to yield a value of -1108.9 kJ mol^{-1} in water.[124b] This is particularly relevant for electron transfer and proton-coupled electron transfer reactions where one should adopt a consistent $\Delta G^*_{\text{S}}(\text{H}^+)$ and half potential of the standard hydrogen electrode (E_{SHE}) that is based on the same electron convention.

The Direct pK_a Calculation Method

Using the presently accepted value of $\Delta G^*_{\text{S}}(\text{H}^+)$ of -1112.5 kJ mol^{-1} the direct scheme (cycle A in Scheme 2) has been successful at predicting pK_as that are in very good agreement with experiment,[130] although in some cases, the solvation

Table 1. Examples of commonly used solvent models, the levels of theory which are applied, and the proton solvation free energy upon which the model is based

Solvent model	$\Delta G_S^*(H^+)$[A,B] [kJ mol^{-1}]	Level of theory	Ref.
(C)-PCM-UAHF	−1093.7	HF/6–31G(d) for neutrals and HF/6–31+G(d) for ions	[98b]
(C)-PCM-UAKS	−1112.5	B3LYP or PBE0/6–31+G(d)	[126]
SM6	−1105.8	MPW25/MIDI!6D or 6–31G(d) or 6–31+G(d)B3LYP/6–31+G(d,p)B3PW91/6–31+G(d,p) and any density functional theory method that can deliver a reasonably accurate electronic density for the solute of interest	[127]
SMD	−1112.5	Any electronic structure model delivering a reasonable continuous density distribution	[89]
SM8 and SM8AD	−1112.5	Hartree Fock (HF) theory and many local and hybrid density functionals with basis sets of up to minimally augmented polarised valence double-zeta quality	[88,128]
SS(V)PE+FESR	−1112.5	HF/6–31+G(d) and B3LYP/6–31+G(d)	[92]
COSMO-RS	—[C]	BP/TZVP // BP/TZVP[D]	

[A]'*' denotes a solvation free energy with a reference state of 1 mol L^{-1} in both gas and solution phase.
[B]Based on Boltzmann statistical treatment for the electron.
[C]The COSMO-RS model is parameterised to data for neutral solutes only.
[D]Based on the implementation in *Turbomole*.[129]

Table 2. Summary of various estimates of the solvation free energy of the proton ($\Delta G_S^*(H^+)$, kJ mol^{-1}) in aqueous and common non-aqueous solvents[A]

Solvent	$\Delta G_S^*(H^+)$	Method	Reference
Water	−1112.5 ± 10	CPA[B]	[121]
	−1110.2	CPA[B]	[122a]
	−1065.2	CCQ[C]	[125b]
	−1078.2	CCQ[C]	[133]
	−1056.5	CCQ[C]	[81b]
	−1115.9	CC[D]	[81b]
	−1111.3	CC[D]	[134]
	−1114.9	rCCC[F]	[135]
	−1098.9[I]	IWF[G]	[117a]
	−1133.8	NC[H]	[122a,136]
	−1128.0	NC[H]	[122a,137]
	−1118.4	NC[H]	[122a,138]
DMSO	−1131.9 ± 10	CPA[E]	[119b,121]
	−1143.5 ± 16	CPA[B]	[120a]
	−1127.9	rCCC[F]	[135]
	−1154.9[I]	IWF[G]	[117a]
Methanol	−1102.1 ± 10	CPA[E]	[121]
	−1102.5 ± 12	CPA[B]	[120a]
	−1061.1[I]	CCQ[C]	[125a]
	−1075.3	CC[D]	[139]
	−1121.9[I]	IWF	[117a]
Acetonitrile	−1066.1 ± 10	CPA[E]	[121]
	−1087.8 ± 12	CPA[B]	[120a]
	−1063.9	rCCC[F]	[135]
	−1081.9[I]	IWF[G]	[117a]

[A]Based on Boltzmann statistical treatment for the electron.
[B]Obtained using the cluster-pair approximation.
[C]Obtained using the cluster-continuum quasichemical theory (see cycle I, Scheme 3).
[D]Obtained using the cluster cycle method (see cycle II, Scheme 3).
[E]Obtained by adding the transfer free energy of the proton from water to solvent under the TATB assumption[140] to $\Delta G_S^*(H^+)$ of −1112.5 kJ mol^{-1}.
[F]The relaxed COSMO cluster–continuum (rCCC) model.
[G]Obtained using experimental estimates of the ionic work function.
[H]Determined using nanocalorimetry.
[I]Interpreted as the real proton solvation free energy.

model that was used may not be based on a consistent $\Delta G_S^*(H^+)$. There is also a growing number of studies[14,131] showing that the direct scheme can introduce mean absolute errors ranging from 2 to 7 units even for some common organic acids (e.g. amides and esters) in both aqueous and non-aqueous solvents. These errors are likely to originate from the calculated ionic solvation free energies and uncertainty in $\Delta G_S^*(H^+)$. In this light, the excellent agreement between directly calculated pK_as and experiment (<0.5 pK_a unit) often reported in the literature is likely to be a result of systematic, if not fortuitous, error cancellation.[132] As a good practice, we recommend pK_a predictions that utilise the proton solvation free energy (e.g. cycles A, E, and F in Scheme 2) should be accompanied by error bars that reflect the uncertainty of this energy (~± 10 kJ mol^{-1} or ± 2 units).

In other studies, the value of $\Delta G_S^*(H^+)$ has also been adjusted in order to provide the best fit with experimental pK_as in aqueous and non-aqueous solvents.[79e,141] This approach is essentially accounting for any systematic errors incurred by the electronic structure calculations and solvation model, and the resulting $\Delta G_S^*(H^+)$ may no longer be applicable in direct pK_a computations of other systems. A related approach is cycle B shown in Scheme 2. In this case, the experimental solvation free energies of hydronium ion and water are used in place of the proton; however, the solvation free energy of the former is also obtained indirectly from the $\Delta G_S^*(H^+)$,[119b,119c] and therefore carries similar uncertainty as $\Delta G_S^*(H^+)$.

Cluster–Continuum Solvation Free Energies

One of the difficulties associated with implicit solvent pK_a prediction is that computed *ionic* solvation free energies generally contain larger errors due in part to the inherent uncertainties associated with the experimental data, and also the difficulty of accounting for first shell solvent–solute interactions through the dielectric continuum representation of the solvent. The latter has been inferred from correlations between experimental pK_as and calculated free energies of dissociation in water (c.f. Eqn 6), where several independent studies[77a,79a,131c,142] determined slopes that are significantly lower than the

theoretical value of $1/RT\ln(10)$. By comparison, corresponding studies in organic solvents found slopes that are in better agreement,[77b,131c] and the general conclusion was that implicit solvation models are not able to fully account for specific ion–water interactions in the first solvation shell.

One approach for improving the accuracy of implicit solvation free energies is the addition of discrete solvent molecules so that first solvent shell interactions are treated explicitly. This idea has been explored since the late 1970s,[143] and has been separately referred to as discrete-continuum, supermolecule-reaction-field and semicontinuum methods. In systems with very high charge density or transition metal ions that contain vacant coordination site(s), explicit representation of first shell solvent effects becomes absolutely essential. This approach is also particularly relevant for species that undergo tautomeric transformations upon solvation, such as amino acids where the neutral tautomer is the only stationary point on the gas phase potential energy surface.[144]

Pratt and co-workers have developed a quasi-chemical theory of solvation[125b,145] which is essentially a two-layer approach whereby the first solvent shell is treated quantum mechanically, and the outer shell contributions are treated using dielectric continuum models. The authors successfully applied this approach to estimate the hydration free energies of the proton and other monovalent and divalent cations (including transition metal ions) that are in good agreement with experiment.[125b,146] A notable strength of this approach is the 'variational' framework where the optimal number of solvent molecules to be added is the one that minimises the quasichemical solvation free energy. Pliego and Riveros adopted a similar strategy called the cluster–continuum quasichemical theory (CCQ) for the calculation of solvation free energies of ionic species.[147] Specifically, explicit solvent molecules are added to the site(s) of the ion that carries the charge and solvent molecules are added incrementally to minimise the solvation free energy based on the thermodynamic cycle shown in Scheme 3 (cycle I).

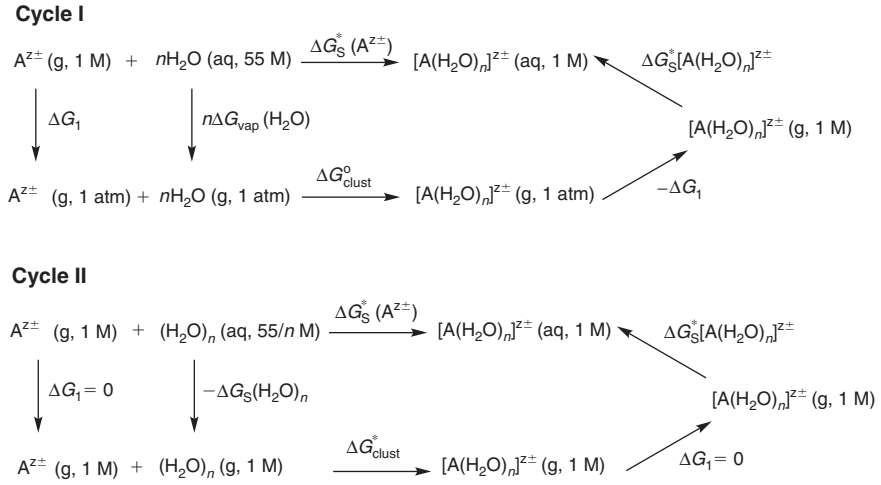
$$\Delta G_S^o(A^{z\pm}) = \Delta G_{clust}^o + \Delta G_S^o[A(H_2O)_n]^{z\pm} + n\Delta G_{vap} \qquad (11)$$

When implemented at the MP2/6–31+G(d,p) level of theory in conjunction with the IPCM model, the aqueous solvation free energies for monovalent ions are underestimated by $\sim$36 kJ mol^{-1}, due in part to the neglect of non-electrostatic contributions in the current implementation of this solvation model. Nonetheless, the errors are highly systematic compared with existing implicit solvation models, and the authors recommend adding a 36 kJ mol^{-1} correction to afford solvation free energies with mean absolute errors that are 3-fold smaller than those directly predicted by the PCM and SM5.42R models.[147] In a subsequent study, Fu et al. applied this approach for calculating solvation free energies of cations in DMSO and found a 4-fold reduction in error compared with direct PCM computations on the *bare* solute.[148] Tommaso and Leeuw have also used this approach and the COSMO model to predict solvation free energies of divalent Mg^{II} and Ca^{II} ions, and related bicarbonate species.[149] In other studies, the CCQ method was used in conjunction with PCM and SMD solvent models to calculate the ionic solvation free energies in non-aqueous solvents[150] such as methanol[125a] and DMSO.[151] More recently, this scheme was adapted by Krossing and co-workers, called the relaxed cluster-continuum COSMO (rCCC) model and applied to estimate the proton solvation free energies in water, DMSO and acetonitrile that agree well with available experimental values.[135]

Goddard and co-workers have adopted a modified cluster–continuum cycle where they used water clusters instead of separated water molecules (cycle II, Scheme 3) to calculate the aqueous solvation free energies for the proton and Cu^{II} ion.[81b] This method was originally proposed and utilised by Tawa et al.,[152] and was subsequently adopted by Mejas and Lago,[153] as well as Zhan and Dixon[134] to compute the aqueous solvation free energy of the proton and other ions.[154] This approach has also been shown to predict ionic solvation free energies in organic solvents that are in very good agreement with experiment.[155] In Goddard's study, the authors found in contrast to cycle I, the solvation free energy of the ions decreases monotonically with respect to the size of the water cluster, $(H_2O)_n$, and the final estimate was obtained by extrapolation to $n \to \infty$.

$$\Delta G_S^*(A^{z\pm}) = \Delta G_{clust}^* + \Delta G_S^*[A(H_2O)_n]^{z\pm} - \Delta G_S^*(H_2O)_n - RT\ln\left(\frac{[H_2O]}{n}\right) \qquad (12)$$

This approach afforded ionic solvation free energies that are within 8 kJ mol^{-1} of experimental values (at the B3LYP/6–311++G(d,p) level and using the COSMO solvent model),



Scheme 3. Two examples of thermodynamic cycles used to compute cluster–continuum solvation free energies.

which they attribute to the presence of similarly sized hydrogen-bonded clusters on both sides of the equation that gives rise to systematic cancellation of errors incurred by the solvation model and electronic structure calculations. The poorer performance of cycle A is interesting in light of Krossing's recent study,[135] where the latter used the G3 composite method instead of B3LYP for the gas phase calculations which might partly account for this difference. In a later study, Tommaso and Leeuw applied both cycles I and II to compute the solvation free energies for the purpose of calculating the pK_a and formation free energies of phosphate species in aqueous solution.[156] The cluster cycle II has also been used to examine the hydration free energies of lanthanide(III) ions,[157] monovalent anions and group 12 divalent cations.[158] While the scheme improves the accuracy of solvation free energies compared with direct computations by implicit solvation models on the bare solute, the *absolute* errors associated with divalent and trivalent ions are still too large for direct applications. Relative values are better reproduced due to error cancellation. In some cases, the studies found that the cluster–continuum solvation free energies did not necessarily decrease monotonically with the size of the water cluster, or that the converged value was still quite far off from experiment.[156,158] The differing success of the cluster–continuum method might originate from differences in the choice of electronic structure theory method, solvation model, and method used for generating the water clusters.

Cluster–continuum methods are also confronted with the practical difficulty arising from the rapidly increasing number of geometric degrees of freedom and number of configurations that may be important. Mullin and Gordon have employed the Monte Carlo method with simulated annealing and the effective fragment potential (EFP) water model to sample the conformational space of alanine–water clusters containing up to 49 water molecules.[159] da Silva et al. also employed molecular dynamics simulations to sample first solvent shell configurations that are subsequently reoptimised at the HF/6–31+G(d) level.[160] The authors applied the cluster–continuum scheme (cycle II, Scheme 3) but using only five explicit water molecules and the Poisson–Boltzmann solvent model (also at the HF level) to predict the solvation free energies of 60 ionic species with an average accuracy of $\sim$10 kJ mol^{-1}. This approach has recently been used to compute solvation free energies of cationic, zwitterionic, and anionic forms of 10 amino acids.[161]

We conclude this section by highlighting a subtle point concerning the computation of $\Delta G^*_S[A(H_2O)_n]^{z\pm}$ in Eqns 11 and 12. Most implicit solvation models have been parameterised to reproduce experimental solvation free energies of *rigid* ionic solutes; however, the floppy water and ion–water clusters employed in cluster–continuum models are likely to undergo significant changes in the internal (i.e. vibrational) partition function upon solvation, and the parameterised terms in implicit solvation models may not be able to account for these changes quantitatively.[81b] This might explain the partial success of the cluster cycle II which benefits from some cancellation of these errors. From the above studies, it is also clear that the performance of cluster–continuum schemes depend critically on the choice of electronic structure method, solvation model, geometry of water and ion–water clusters, and the method for generating these clusters. This is an area that will develop with further studies to establish the generality of these methods, and their compatibility with existing solvation models for the calculation of ionic solvation free energies.

Alternative Thermodynamic Cycles

In light of the shortcomings associated with the direct/absolute pK_a calculation method (cycles A and B in Scheme 2), several alternative thermodynamic cycles have been proposed. Cycle C represents the proton exchange scheme (or relative pK_a calculation method) and dispenses with the need for the proton solvation free energy, thereby eliminating a major source of uncertainty. Since the number of charged species is conserved across the reaction, there is also cancellation of the errors in the computed ionic solvation free energies. In addition, when an appropriate reference species is chosen, one can construct an isodesmic reaction to further reduce errors associated with the electronic structure calculations.

Tawa and co-workers employed this approach to compute the relative acidities of substituted imidazoles and showed that average deviations of $<$1 unit can be achieved provided that gas phase energies are obtained using benchmarked G-*n* or DFT methods.[162] Similarly, Shields and co-workers employed high-level composite procedures and the SM5.42R and CPCM solvent models to yield pK_as of six carboxylic acids that are accurate to 0.5 pK_a unit,[163] and Gutowski and Dixon applied the same strategy to compute pK_as of strong Brønsted acids (pK_as < -10) to within 2 pK_a units in nearly all cases.[131d] In another study, Namazian and Heidary have also applied the proton exchange scheme using acetic acid as the reference species, and was able to furnish pK_as of a wide range of carboxylic acids and several aliphatic alcohols with an average error of $<$1 unit at the HF/6–31G(d,p) level of theory.[164] This approach was subsequently applied by others to calculate the pK_as of amides and esters,[131a] diketenes,[165] diketopiperazines,[2d] selenic, selenenic and sulfinic acids,[166] large phenolic derivatives,[167] nitrous acid,[168] halofuranones,[169] alkanolamine and nucleotide bases,[170] pyridinium ions and radicals,[171] polyprotic histamine[132] oxicams,[172] amino acids,[27d] and metal-bound ligands.[173] The scheme has also been used to predict pK_as of synthetically important molecules (e.g. transition metal hydrides,[174] hydroquinones,[175] ylides,[176] thiols,[177] carbenes,[141g] chiral amides,[178] and phosphoric acids[1e]) in non-aqueous solvents such as DMSO.

Although the proton exchange scheme offers a straightforward means of improving the accuracy of directly computed pK_a values, its potential as a generally applicable pK_a calculation procedure is limited by the fact that its performance is also sensitive to the choice of reference acid, and the availability of an accurate pK_a value. In two recent studies, the proton exchange scheme was found to deliver average unsigned errors of 6 to 8 units for cationic C–H acids and maximum unsigned errors ranging from 3 to 5 units for carboxylic acids, irrespective of the solvent model employed.[14,131a] Seeing that the major source of error is likely to arise from solvation contributions, Ho and Coote developed a modified proton exchange scheme where aqueous ionic solvation free energies were computed using the cluster–continuum approach of Pliego and Riveros (cycle I Scheme 3). This approach exploits the fact that errors in IPCM cluster-continuum solvation free energies are systematic and relatively insensitive to the type of the ion,[147] and these errors would largely cancel in a proton exchange scheme. The authors have shown that using methanol as the reference species (HRef), this approach can provide an average accuracy of $\sim$2 pK_a units across a broad range of organic acids.[14] Smith and co-workers have also developed a similar approach for calculating the pK_as of various neutral and charged organic acids in DMSO,

acetonitrile, and THF with an average accuracy of ~1 unit.[150] These studies demonstrate the potential of this approach as a robust and generally applicable pK_a calculation procedure in aqueous and non-aqueous solvents.

In a similar spirit to cluster-continuum schemes for calculation of ionic solvation free energies, cycles D and E in Scheme 2 have been developed whereby explicit solvent molecules are included in the thermodynamic cycle for computing pK_as. The basis for these methods is that explicit solvation ought to account for specific solvent–solute interactions, and also decrease the dielectric continuum contribution to the variation of $\Delta\Delta G_S$ in ΔG_{soln}. As noted previously, explicit solvation is also essential in systems with very high charge density or transition metal ions containing vacant coordination site(s). Pliego and Riveros utilised cycle D in conjunction with the IPCM solvent model to obtain pK_a values that are accurate to within 2 units for a small test set of acids.[179] Most notably, they found that $\Delta\Delta G_S$ contribution in their cluster-continuum model does not exceed 40 kJ mol^{-1} whereas purely implicit solvent approaches contribute as much as 120 to 180 kJ mol^{-1}. This approach has also been applied in the pK_a prediction of the aqueous beryllium(II) ion,[180] large phenolic derivatives,[167a] and polyprotic citric acid[173c] with mean unsigned errors that are below 1 unit.

Kelly et al. have also proposed an implicit–explicit approach (cycle E).[142a] In particular, the authors found that addition of a single water molecule provided significant improvement over the direct method when used in conjunction with the SM6 solvation model. Klamt and co-workers examined a similar cluster–continuum approach using the COSMO-RS model,[181] and showed that regression of resulting free energies of dissociation with experimental aqueous pK_a values yield a slope that is closer to the theoretical value (c.f. Eqn 6). In a separate assessment study, the implicit–explicit approach was also found to improve the predicted pK_as of anionic carbon acids.[131a]

More recently, Marenich et al. applied a modified procedure (cycle F Scheme 2) whereby both the acid and its conjugate base are solvated by explicit solvent molecules, on a dataset of dicarboxylic acids in conjunction with various implicit solvation models. The study concluded that with conformer averaging, the thermodynamic cycle worked best with the SMD model to afford first and second dissociation constants with an average accuracy of less than 1 unit.[182] This scheme has also been applied to predict the hydrolysis constants of aquated transition metal ions (e.g. Cu^{II},[183] Mn^{II},[184] Fe^{II},[185] Al^{III},[186] and Fe^{III}[186b,187]) where explicit representation of first shell solvent molecules becomes essential. A similar approach has also been used to compute the aqueous pK_as of carboxylic acids,[188] neurotransmitters,[189] and triprotic aspartic acid,[190] where in the latter case, explicit solvation was necessary to stabilise the zwitterionic form of the acid.

Interestingly, a recent assessment study found that the error incurred by the implicit–explicit method (cycle E) increases monotonically with the number of added water molecules when the CPCM-UAKS and CPCM-UAHF models were used.[14] By comparison, the errors were relatively stable for the SM6 model, consistent with an earlier study by Kelly et al.[142a] As noted before, one explanation of this behaviour is that many implicit solvation models do not account for changes in the internal partition function of a hydrogen bonded solute induced by the presence of solvent and these effects are likely to become important as the size of the ion-cluster increases. The more stable performance shown by the SM6 model is presumably because the model has been parameterised to reproduce solvation free energies of ion–water clusters in place of bare ions for cases where implicit solvation models are expected to be inadequate.[127] Accordingly, it is important to note that the success of the implicit–explicit method may also depend on the choice of implicit solvation model.

Hybrid discrete–continuum schemes are not yet broadly applicable because the rules for automating the number of water molecules to add, where they should be added, and their compatibility with particular implicit solvation models are not always obvious. The optimal number of explicit solvent molecules reported in many studies was determined empirically through minimising the deviation with experimental data. Moreover, cycles E and F also utilise the absolute solvation free energy of the proton, which introduces additional uncertainty to the computed pK_as. We envisage that future implementations of these methods might employ molecular dynamics or Monte Carlo simulations to provide a systematic way for sampling solute–solvent configurations.

Avoiding the Thermodynamic Cycle

There is growing interest towards QM-continuum approaches that directly compute solution phase reaction free energies without using a thermodynamic cycle.[186a,191] This is partly motivated by the fact that thermodynamic cycle based methods usually require relatively costly electronic structure calculations for gas phase energies, as well as the difficulties associated with modelling solution phase species that do not have stationary points in the gas phase.[113b] This approach also circumvents the cumulative errors that arise from summing the independent energy terms in a thermodynamic cycle.

One approach would be to approximate the solution phase free energy in Eqn 7 from the potential of mean force (PMF),[192] that is the solution phase free energy surface where the unaveraged degrees of freedom are the internal degrees of freedom of the solute. This corresponds to the sum of the first three terms in Eqn 8b, i.e. $\langle \phi^{pol}|H+\frac{1}{2}V|\phi^{pol}\rangle$ plus non-electrostatic terms. This is analogous to approximating ΔG in Eqn 4 with ΔE, as is sometimes used in gas phase computations, and the implicit assumption is that zero-point vibrational energy and thermal contributions to the free energy associated with these degrees of freedom mostly cancel in the reaction energy. As noted previously, this approach has been used to compute solution phase reaction energies that are correlated with experimental pK_as (Eqn 6), and a common finding is that this often yields a slope that deviates from the theoretical value of $1/RT\ln(10)$, especially for aqueous solvents.[142,181] The deviations might reflect the level of theory at which the PMF was evaluated, and/or inaccuracies associated with the implicit solvation model.

It has recently been questioned as to whether the ideal gas rigid rotor harmonic oscillator molecular partition functions could be used to compute the solution-phase thermal corrections ($G_{corr,soln}$) for assembling a solution-phase free energy (c.f. Eqn 4).[113b]

$$G_{soln} = \left\langle \phi^{pol}\middle| H+\frac{1}{2}V\middle|\phi^{pol}\right\rangle + G_{nes} + G_{corr,soln} \qquad (13a)$$

$$\Delta G^*_S = G_{soln} - G_{gas} \qquad (13b)$$

Cramer and Truhlar have clarified that the translational partition function in the gas phase becomes the liberational free energy in solution,[193] and that the dependence of rotational partition functions on the molecular principal moments of

inertia makes them very insensitive to the small changes in solute structure usually associated with solvation. In addition, the authors showed that in cases where solvent effects on vibrational modes are significant, including the vibrational contribution computed in the SMD solvent model (Eqn 13b) improves the accuracy of computed solvation free energies.[192] However, it is important to note that since implicit solvation models have been parameterised at relatively modest levels of theory, the solution phase free energies computed in this manner might not be amenable to systematic improvement through the use of higher levels of theory.

In this context, Frau and co-workers have employed solution phase free energies obtained using Eqn 13a in conjunction with an *isodesmic* scheme (at the HF, B3LYP and CBS-QB3 levels of theory) to compute solution phase reaction energies (using the CPCM-UAHF/UAKS models). For a dataset of C–H acids and pyridine bases, the authors obtained pK_as (at all three levels of theory) that are comparable with the proton exchange scheme,[191d,191e] signifying the ability of this approach to largely cancel any errors incurred by this approximation and the lower levels of theory that was used to evaluate the PMF. This approach has also been used to predict the aqueous pK_a values of triprotic nitriloacetic acid[194] and Cu^{II} complexes.[195] A related defined-sector explicit solvent cluster continuum (DSES-CC) model[196] has also recently been introduced, relying only on solution phase computation and the use of a sector model for optimising the placement of explicit solvent molecules to yield highly accurate pK_a values (error <1 pK_a unit) of various mono- and dicarboxylic acids.

Polyprotic Acids

In polyprotic systems, one needs to distinguish between so called *macroscopic* versus *microscopic* pK_a values. The difference is easily explained if one recasts the Henderson–Hasselbach equation in terms of the protonation occupancy (θ), which refers to the fraction of bound protons as a function of pH:

$$\theta(\mathrm{pH}) = \frac{1}{1 + 10^{(\mathrm{pH}-\mathrm{p}K_a)}} \qquad (14)$$

Accordingly, the pK_a of a titrating site is defined as the pH for which 50 % of the site is occupied by a proton, i.e. $\theta = 0.5$. In monoprotic acids, one measures only the degree of protonation associated with a single site, and the corresponding microscopic pK_a may be determined. On the other hand, polyprotic systems contain multiple (n) titrating sites and any of the 2^n microstates can contribute to θ, which is a macroscopic property. As such, the pK_a values determined using a titration curve for a polyprotic acid are macroscopic constants, which has contributions from multiple microstates. For simple polyprotic acids, such as sulfuric and phosphoric acid, the macroscopic and microscopic pK_as are related though Eqn 15 where m and n are the number of *indistinguishable* microstates associated with each protonation state.[197]

$$\mathrm{p}K_a^{\mathrm{Macro}} = \mathrm{p}K_a^{\mathrm{Micro}} + \log\left(\frac{n}{m}\right) \qquad (15)$$

The second term in Eqn 15 is essentially a statistical (entropic) correction and the resulting macroscopic pK_a can be directly compared with experiment. This correction should not be confused with the rotational symmetry number used to calculate the gas phase rotational partition functions, which corrects the number of symmetry allowed rotational energy levels associated with the point group of the molecule.[198] For polyprotic systems where the microstates are distinguishable (e.g. tautomers), then one should use Boltzmann averaged Gibbs free energy for computing the pK_a.[130e,172,199]

Accurate predictions of the pK_as of polyprotic systems pose a challenge for implicit solvent methods because of the presence of poly-charged ions with very large solvation free energies ($>1000\,\mathrm{kJ\,mol^{-1}}$). Hybrid cluster-continuum approaches have shown some degree of success towards the treatment of such species. As noted previously, the implicit–explicit method (cycle E in Scheme 2) was found to improve the accuracy of predicted pK_as for anionic carbon acids.[131a] Marenich et al. have also recently applied cycle F in conjunction with the SMD solvation model to afford very accurate pK_as of dicarboxylic acids,[182] and similar approaches have also been applied to predict hydrolysis constants associated with aquated multivalent metal ions.[184,185,187b] Toomaso and co-workers have applied cluster–continuum schemes (cycles I and II in Scheme 3) to compute ionic solvation free energies for computing the pK_as of ortho- and pyrophosphates.[156] Lee and McKee also examined the use of various cavity definitions (Pauling, UFF, UAKS, and Klamt) and the effect this has on predicting the pK_as of monoprotic, diprotic, and triprotic acids. The authors found that suitable combinations of electronic structure method and cavity definition can provide reasonable estimates for monoprotic and diprotic acids, but this approach fails for triprotic acids owing to the presence of highly charged trivalent anions.[80c] Other groups have also explored direct solution phase computations such as the defined-sector explicit solvent cluster continuum (DSES-CC) model,[196a] and the isodesmic scheme[191c,191e,194] to predict the pK_as of dicarboxylic acids and triprotic nitrilotriacetic and nitrilotripropionic acids.

Explicit Solvent Methods

Explicit solvent calculations of pK_as are comparatively scarce primarily because they entail significantly higher computational cost compared with implicit solvent approaches. Nonetheless, such methods are also based on a different theoretical framework that could potentially overcome some of the shortcomings and limitations associated with the latter approach. Most notably, the success of implicit solvent thermodynamic cycle based approaches relies heavily on the accuracy of implicit solvent predictions of solvation free energies, and this problem is further compounded by the fact the implicit solvation models have been parameterised to reproduce experimental solvation free energies, which have rather large uncertainties especially for charged species. In contrast, MD approaches model solute–solvent interactions explicitly, and solution phase free energy changes may be computed directly from the statistical mechanics formalism of condensed-phase simulations (c.f. methods that avoid using a thermodynamic cycle). The accuracy of these methods would in turn depend on the quality of the electronic structure theory method and/or MM force field, reaction coordinate, sampling method, and associated simulation parameters. This section introduces and reviews recent developments in DFT and QM/MM molecular dynamics simulations for calculating solution phase pK_as.

Ab initio *Molecular Dynamics*

A pre-requisite for classical molecular dynamics simulations is a potential energy function that is needed to evaluate the forces

acting on the nuclei to propagate the dynamics of the system. In purely classical simulations, empirical force fields such as CHARMM[39] and AMBER,[38a] typically assume a functional form of the potential energy, e.g. harmonic oscillator for bond stretches, bends, and torsion, which are parameterised to experimental data and/or *ab initio* calculations. However, there are inherent difficulties with modelling bond formation or cleavage using these functional forms, and a quantum mechanical description of the solute is usually needed for computing dissociation constants. Fully *ab initio*,[200] empirical valence bond models,[201] and hybrid QM/MM[53b,202] molecular dynamics simulations have been developed for this purpose; most notably, Car and Parrinello have pioneered the development of DFT-based molecular dynamics,[200a] which also permits the application of DFT calculations to much larger systems. In this framework, MD trajectories are generated from forces obtained from 'on the fly' electronic structure (DFT) calculations. The technical details concerning the theory and implementation of these techniques are outside the scope of this review, and the interested reader is referred to several reviews[203] on the subject for further details.

From a molecular dynamics perspective, QM-continuum methods are perceived as a *static* approach, where reaction free energy is evaluated from QM computations based only on several points in configuration space representing the most important conformers of the reactants, transition states, and products. On the other hand, many different configurations are sampled in MD simulations, and conformational effects are automatically incorporated into the ensemble-averaged free energy. The thermodynamic free energy difference of two states (A and B) is directly related to the ratio of the probabilities of finding the system in the respective states:

$$\Delta G_{BA} = -RT \ln\left(\frac{P_B}{P_A}\right) \tag{16}$$

The brute force approach to evaluating Eqn 16 is to count the number of configurations in the corresponding states during the course of the MD or Monte Carlo (MC) simulation. However, deprotonation (particularly for weak acids) is classified as a rare event, and occurs on a time scale that is many orders of magnitude longer than the time scale that can be followed by *ab initio* MD simulations. In such cases, special sampling techniques are usually required. On this note, the high computational cost associated with explicit solvent methods is not due to the cost of calculating the interaction energy between the solute and explicit solvent molecules, but rather the need to do so over a large number of configurations in order to obtain a converged ensemble average.

In an explicit solvent set-up, the acid is typically placed in a periodic box of explicit water molecules, where the latter may be simulated using MM force fields (e.g. SPC[204] and TIP5P[205]), or treated at the same QM level as the solute, as is the case for DFT molecular dynamics (DFTMD).[200a] Owing to the increased computational overhead, DFTMD simulations typically use 30 to 50 solvent molecules in a relatively small periodic cell (length L), and this introduces significant finite size errors due to spurious interactions with periodic images (solvation free energies of ions scale with cell volume $1/L^3$)[206] that will need to be corrected. A reaction coordinate (r) is chosen to represent the dissociation process, and constrained molecular dynamics[207] or metadynamics[208] simulations may be employed to enforce deprotonation, i.e. enhance sampling. A variety of reaction coordinates have been considered for pK_a calculations, including simple geometrical coordinates (e.g. bond lengths or bond angles),[209] coordination number,[207a,210] or non-bonded parameters in so-called 'alchemical transformations'.[211] Various methods, such as weighted histogram analysis method (WHAM)[212] and the blue-moon ensemble method,[213] may be used to extract the potential of mean force $W(r)$ from constrained MD or MC simulations, which is used for computing the dissociation constant (K_a) using Eqn 17[214]

$$f_{HA} = \frac{\int_0^{R_c} 4\pi r^2 \exp\left(-\frac{W(r)}{kT}\right) dr}{\int_0^{R_{max}} 4\pi r^2 \exp\left(-\frac{W(r)}{kT}\right) dr} \tag{17a}$$

$$K_a = \frac{(1 - f_{HA})^2}{f_{HA} c^o V} \tag{17b}$$

where f_{HA} is the fractional concentration of the acid HA, R_c is the dividing surface between reactants and products, c^o is the standard concentration, and V is the volume of the simulation cell.

Recent Applications

DFTMD methods employing distance constraints (e.g. the proton donor–acceptor distance) have been successfully employed to compute the pK_as of liquid water,[209b,209c] formic acid,[215] histidine,[216] and uranyl(VI) hydrate.[217] Sprik and co-workers have also developed and pioneered the use of coordination-constrained methods to compute solution phase pKas of a variety of acids, including liquid water,[207a] histidine,[218] carbonic acid,[219] pentoxyphosphoranes,[210] hydroxy-pyridones,[131b] silicic acid, and hydrated metal ions.[220] The advantage in the latter reaction coordinate lies in the ability to control the coordination of a species, and prevents ion recombination that would normally occur with simple distance constraints. Later, the same authors developed an 'alchemical' free energy method where a mapping potential is defined to evolve the deprotonation reaction by morphing the proton into a dummy atom.[211b] The authors further employed a proton exchange scheme analogous to cycle C in Scheme 2 to cancel the systematic errors associated with finite cell effects to afford pK_a values of a series of simple neutral, cationic, and zwitterionic organic and inorganic systems that are in good agreement with experiment.[221] A similar strategy has been used in the pK_a prediction of divalent hydrated ions[220b] and histidine.[216] More recently, MD simulations that employ QM/MM potentials have also been carried out,[209a,222] with the added advantage of reduced computational cost and consequently a larger simulation box which alleviates some of the errors associated with finite cell effects.

On the basis of these studies, it can be inferred that DFTMD methods are capable of predicting pK_as to within 2 units of experiment. This observation is interesting in light of the larger errors (average errors of 12 or more kJ mol^{-1})[27c] observed in the application of DFT methods for the calculation of gas phase acidities. Additionally, a recent QM/MM study also found that the use of HF or MP2 in the QM region does not affect the accuracy of pK_a appreciably.[209a] Quite possibly, there is cancellation of errors associated with the electronic structure calculations, free energy calculations, and simulation

parameters, and it is of interest to examine the performance of these methods more broadly in the future.

Implicit versus Explicit Methods

There are relatively few studies that directly compare the performance of implicit solvent and explicit solvent pK_a calculations,[131b] presumably because both methods generally employ different electronic structure calculation methods. Implicit solvent methods typically use high-level *ab initio* gas phase energies and solvation free energies evaluated at levels of theory that implicit solvation models have been parameterised, whereas *ab initio* MD normally use periodic DFT with plane wave basis set. Nonetheless, results from state-of-the-art calculations indicate that both approaches can predict pK_as with comparable accuracies, i.e. 1 to 2 pK_a units. A notable strength of explicit solvent methods is that they contain significantly fewer parameters compared with implicit solvation models, and do not necessarily rely on empirical parameterisation. In addition, they provide a systematic framework for modelling solvent effects, for example, by incorporating improved MM water models and/or improving the quantum mechanical description of the solute in QM/MM implementations. Implicit solvation methods also require further extension to deal with the effect of inhomogeneous environments or high concentrations. An example is the acidity of surfaces,[223] where a more detailed atomistic description of the solvent and environment is preferred. Its major drawback is the significantly higher computational overhead, and the more restricted choice of electronic structure method that may be applied, but we envisage that these methods will become more accessible with increasing computational power and the development of more efficient implementations.

While DFT molecular dynamics is a popular approach for explicit solvent calculations of pK_as, the reader should also note that other related techniques have also been developed, including fully first-principles fragment-molecular-orbital[200b] and constant-pH molecular dynamics[224] simulations, the 3D-reference interaction site model (3D-RISM),[225] as well as improved quantum mechanical based force fields for simulating the solvent, such as the effective fragment potential (EFP) model,[50,226] the XPOL,[227] and XP3P.[228] Molecular dynamics or Monte Carlo simulations may also be used in conjunction with statistical perturbation theory to compute absolute and relative solvation free energies for use in thermodynamic cycle based pK_a calculations.[229]

Concluding Remarks

The development of computationally efficient implicit solvation models has greatly facilitated the study of reactions in the condensed phase. Nowadays it is increasingly common to find pK_a studies that predict acidities to within a unit of experiment, but when one delves deeper into the details of implicit solvent methods for computing pK_as, it may appear that this level of accuracy exceeds what might otherwise be expected. As presented in this review, a myriad of theoretical procedures has emerged in the literature as a result of different combinations of thermodynamic cycle, electronic structure method, implicit solvation model, definition of atomic cavities, solvation free energy of the proton, number of explicit solvent molecules to include, and whether conformational ensembles were used. Many studies often present theoretical procedures that have been carefully calibrated to reproduce experimental data for a selected class of compounds with excellent accuracy; however, these procedures often need to be re-calibrated when they are applied to other classes of compounds, the reason being that the calibrated procedures work through optimal compensation of errors, and this often limits the scope of the method. Of course, the level of accuracy and broadness in applicability that is desired would also depend on the chemical problem that one is trying to solve. Nonetheless, the development of robust pK_a calculation procedures with broad applicability remains an area of active research. We have reviewed recent developments towards this direction, including a clarification of the values for the proton solvation free energy that are compatible with implicit solvation models, cluster-continuum schemes that improve the accuracy of calculated ionic solvation free energies and pK_as of polyprotic systems and newer schemes that directly compute deprotonation free energies in implicit solvents, thereby circumventing the additive errors associated with using the thermodynamic cycle.

Concurrently, there have been important advances in explicit solvent statistical mechanical free energy methods for the computation of pK_as, although the computational cost and complexity added by these methods mean that they have to offer a significant advantage in accuracy in order to be considered worthwhile. There is now a sizable literature employing DFTMD to predict the pK_as of small to medium-sized acids, and a survey of the literature shows that these methods exhibit comparable accuracies to implicit solvent methods. It is of interest to examine whether the performance of these methods can be systematically improved though the use of better levels of theory, and how they perform more broadly. We envisage that these problems will be revisited in the near future.

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