SAMPL2 and continuum modeling

Anthony Nicholls · Stanislaw Wlodek ·
J. Andrew Grant

Abstract An account is given of our contributions to the SAMPL2 challenge for vacuum-water transfer energies. These contributions include different charge sets and radii used with Poisson–Boltzmann continuum theory applied to a single low-energy conformation. A rationale for this approach is given, including a summary of what we have learnt over previous SAMPL events. The results strongly suggest the need for new and repeated experimental measurements, both to clarify what appears to be experimental discrepancies in older measurements and to advance the field in a statistically sound manner.

Keywords Solvation · Free energy ·
Continuum dielectric

Introduction

The concept of the SAMPL challenges (SAMPL0 [1], SAMPL1 [2]) has been simple: Give contributors an opportunity to test their methods on previously unpublished data and to share the results of those tests with others using similar or diverse methods. This is the third such challenge and substantial progress can be seen from a procedure that

A. Nicholls · S. Wlodek (✉)
OpenEye Scientific Software, Inc, Santa Fe, NM 87508, USA
e-mail: stan@eyesopen.com

J. A. Grant
AstraZeneca Pharmaceuticals, Mereside, Macclesfield SK10
4TF, Cheshire, UK

is an approximation of the scientific method as handed down from Galileo, Bacon, al-Haytham and others. It is not the true scientific method because of the lack of new experimental data to feed the cycle of hypothesis generation, prediction, confirmation or refutation, followed by new hypotheses. A truly scientific approach would have a method make predictions of new observations, much as Einstein applied general relativity to predicting the bending of light around the sun before Eddington measured it. The best we can do is to predict values that are difficult to abstract from the literature. However, a more profound difference is the lack of experimental 'examination'. In a scientific field where different methods are vying for attention, experimentalists typically devise experiments to discern between theories. This examination is completely absent from the problem at hand, and indeed from essentially all of molecular modeling. There are no experimentalists queuing up to make measurements to prove the breakdown of continuum theory, or to illustrate the limits of all-atom simulations with current force-fields. There is neither the funding nor, in most cases, the interest from the analytical chemists. However, a more positive view is that substantial insights have been made with even such a limited application of the scientific method, and that the impact of new experiments would be substantial. With each successive SAMPL event the potential for dramatic progress, were this situation to improve, grows ever more evident.

We begin with a brief review of the accumulation of insights on Poisson-Boltzmann (PB) theory from SAMPL meetings as a prelude to our attempts this year. In this we will cover the issues of charge quality, radii parameterization and conformer selection. Although we should need to account for the change in the conformational landscape on solvation, experience has shown us that a single

conformation approach, where this conformation is chosen as the lowest energy conformation in vacuum, is currently more accurate [3]. In part this seems to work because states that lie higher in vacuum energy may be become better solvated, but such solvation seldom overcomes internal strain. While it might seem that this would at least suggest an increase in entropy on transference to solvent, i.e., because conformations are more similar in energy (landscape 'smoothing'), we will present a simple argument as to why polarization of the solute might explain why a single, 'prime', conformation continues to be a good approximation. We then turn to the data from SAMPL2 and how it illuminates our prior assumptions. The charge sets we have applied are AM1BCC v1.0 [4], MO6 [5] and those derived from high-level QM calculations (B3LYP at the cc-pVTZ basis set level) and the behavior of each had both expected and unexpected components. Although the MO6 charges performed best by standard measures we believe the evidence actually supports one of two hypotheses: (1) high-level QM charges really are better and there is a systematic experimental error in one class of compounds, or (2) there is a need for a reconsideration of the data from SAMPL1 because there remains a physical issue with the PB approach to some classes of compounds. In addition, there are clear examples where conformational sampling and even potentially conformational entropy are important, for instance in considering the solvation of glucose. Finally, the results from polysubstituted benzenes suggest a real need to consider solute-water Van der Waals interactions, solute polarization or both and clearly points to the importance of this class of compounds in future examinations of physical theories of solvation.

Methods

The methods used here have all been described previously. The PB solver ZAP [6] was used for all continuum calculations. ZAP uses a continuous dielectric function derived from atomic-centered Gaussians that has been shown to produce very similar small molecule solvation energies to those from discrete dielectric PB solvers, such as DelPhi [7, 8]. Differences appear for macromolecular electrostatics due to the dielectric description in concave regions, e.g., active sites of proteins, but for molecules of the type considered results are concordant and the advantages of using a differentiable dielectric are several-fold. A smoother dielectric is numerically more stable in finite difference solvers, such as ZAP. This means we can use coarser, hence faster, grids and yet get the same accuracy as other solvers. The physical dielectric cannot actually be discontinuous. The ZAP function may or may not be accurate but at least it is physically reasonable. And finally,

because we can calculate the derivative of the dielectric we can derive the gradient of the total energy with respect to an atomic radius. We put this to use in the optimization of radii types for a particular charge set. As described in our report from previous SAMPL meetings [3] we use a standard gradient-based optimizer to minimize the sum of squared differences between ZAP calculations and a set of benchmark solvation energies with respect to these radii types. These types are, for example, elemental or based on simple chemical typing, e.g., carbonyl oxygens. Several such sets of radii are described herein.

Conformations were generated using Omega v.2.2 [9] and minimized by the MMFF force field as implemented in Szybki v1.1 [10], both OpenEye programs. Typical settings for Omega were: SetFixRMS(0.0) to ensures conformations are not removed by RMSD (RMS distance between conformers), SetMaxConfs(0) to removes the limit on the number of conformations generated and SetEnergyWindow(25.0) to keeps all conformers within 25 kcal/mol of the lowest lying state using Omega's modified energy function. Omega works by torsional sampling of rotatable bonds although hydrogens are not considered in this process; rather they are added after the heavy atom positions are determined. As will be seen below, this had consequences because proton rotors could significantly affect solvation and were not handled well by Omega.

High-level quantum calculations were performed using the B3LYP density functional [11] at the triple-zeta cc-pVTZ level with Dunning's correlation consistent basis set as implemented in Gaussian 03 [12], with full coordinate minimization. Atomic charges were obtained using standard linear fitting to the electrostatic potential around each molecule, with sample points defined by four extended shells using Merz-Kollman radii and without constraining any charge moments [13]. As in SAMPL1, not all calculations finished before the submission deadline. In SAMPL1 this led to an interesting effect—essentially removing some of the more difficult molecules from the dataset. SAMPL2 submissions were largely complete, however, reflecting the less poly-functional and less flexible nature of the set.

AM1BCC v1.0 charges were derived from the implementation of the method of Bayly et al. [4], available within the collections of OpenEye tools known as QuacPac [14]. One significant difference in the OpenEye approach to that of Bayly et al. is that we do not take the extra step of finding an extended conformation to avoid the possibility of intramolecular charge–charge interactions. The latter can lead to over-polarized charges that are inappropriate when applied to extended conformations. However, there is little evidence suggesting these charges are not appropriate for the conformations for which they are calculated. In fact the opposite may be true.

MO6 charges were calculated as described in Ellingson et al. [15].

Methods development

Much of the development of the methods applied to the SAMPL events arose from the analysis of transfer energies of a set first provided to us by Robert Rizzo. The 'Rizzo' set contained about two hundred small molecules of limited flexibility and size (median heavy atom count of six), yet clearly demonstrated to us the advantages of using more physical charges, i.e., ones that better reproduce measurable quantities, such as the molecular dipole. The root mean square error (RMSE) over the Rizzo set is around 2.1 kcal/mol for what have become known as 'Gasteiger' charges, i.e., charges based on simple chemical functionalities and electronegativity equalization, and slightly less for force-field charges, for instance those from MMFF. In comparison, AM1BCC v1.0 charges achieve an error of 1.3 kcal/mol. This is without any adjustment of radii, merely using those from Bondi [16] that are based on crystal-contact distances. Although impressive, this accuracy does not come close to that seen in reports of methods that rely on extensive 'atom typing' to adapt charges and radii to experimental results. Atom, or chemical typing is a common method in modeling of specifying a characteristic of an element based on its apparent bonding pattern. For instance, an *sp2* carbon has, in some circumstances, different properties than an *sp3* carbon. Methods such as the SM6 charging and solvation method has over fifty chemical parameters [17] and further examples of highly parameterized methods are given in Table 1. Typical parameters include radii, area terms, additive constants, etc. The only parameter applied in the aforementioned ZAP calculations is a single area term meant to reflect the non-polar contribution to transfer, i.e., the energy that it would take to transfer the same molecule without partial charges. The dependence of the RMSE to the area term is weak, and a useful estimate can be made by independent means [18]. Typical values are between 0 and 10 calories per square Ångstrom of accessible surface area, as defined by the locus of the center of a sphere the size of a water molecule rolled over the surface of a molecule. For example, the optimum value when using MMFF charges is 10 cal/Å^2, while for AM1BCC charge set it is approximately 6 cal/Å^2. As the addition of parameters can always be used to reduce the RMSE of a method against a known dataset, we investigated the utility of optimizing a limited number of radii types by the method described above. It soon became clear that a few, mostly small, adjustments to the canonical Bondi radii were enough to reduce the RMSE to within the range seen by these methods but with far fewer parameters.

Table 1 Table of the reported efficacy of various methods along with the size of the dataset tested and the number of parameters used in each method

Group	# parameters	# data points	RMSE (kcal/mol)
Cramer [17]	52	273	0.68
Levy [29]	40	93	0.76
Sitkoff [30]	24	65	0.64
Abagyan [31]	78	315	0.72
ZAP	9	201	0.76

In most cases the reported RMSE, i.e., root mean squared error, is calculated on the training set. Levy et al. report on a test set

Figure 1 shows the effect of such parameterization on agreement with experiment.

This first set of radii adjusted to standard AM1BCC charges (ZAP9, so named for the eight radii plus the one non-polar term, Table 2, column two) became our standard approach in SAMPL0, a set of seventeen small molecules provided by Peter Guthrie in 2006. ZAP9 has a non-polar term of 6.3 cal/Å^2, and two chemical typings, one for oxygen and one for nitrogen. The chemical typing for oxygen increases the radii for carbonyl oxygens from 1.52 to 1.76 Å. The nitrogen chemical typing was for secondary and tertiary nitrogens. It has been known for some time that nitrogens are a difficult species for transfer energy prediction, as exemplified by the classic 'methylamine' problem [19, 20]. Adding a methyl group to ammonia would seem likely to make methylamine less soluble, given methyl is a classic hydrophobic group. Yet actually methylamine is more soluble than ammonia (−4.56 kcal/mol vs. −4.29 kcal/mol). Addition of further methyl groups, to get *N*-methylamine and *N*,*N*-dimethylamine, does decrease the solvation energy (−4.29 and −3.23 kcal/mol, respectively), but not as much as either all-atom simulations or PB theory would predict. pKa prediction models have similar struggles with certain nitrogens [21]. Various solutions have been suggested for this problem, such as considering the discrete hydrogen bonding energetics of water [21] or adjusting VdW parameters [22]. The PB solution is to adjust the radii of secondary and tertiary nitrogens, making them smaller so as to increase their solvation relative to primary nitrogens.

The results of the PB and all-atom simulation on SAMPL0 are illustrated in Fig. 2 and are described in detail in our SAMPL0 report [1]. In short, over 17 compounds both methods did reasonably well with all-atom simulations performing better (RMSE of 1.33 kcal/mol compare to 1.87 kcal/mol for PB). However, the performance of neither method was as good as might have been expected from prior work. This was in part because the molecules were larger and more functionalized than those attempted before and also in part because of the parameterization of our methods to those prior cases. Even with
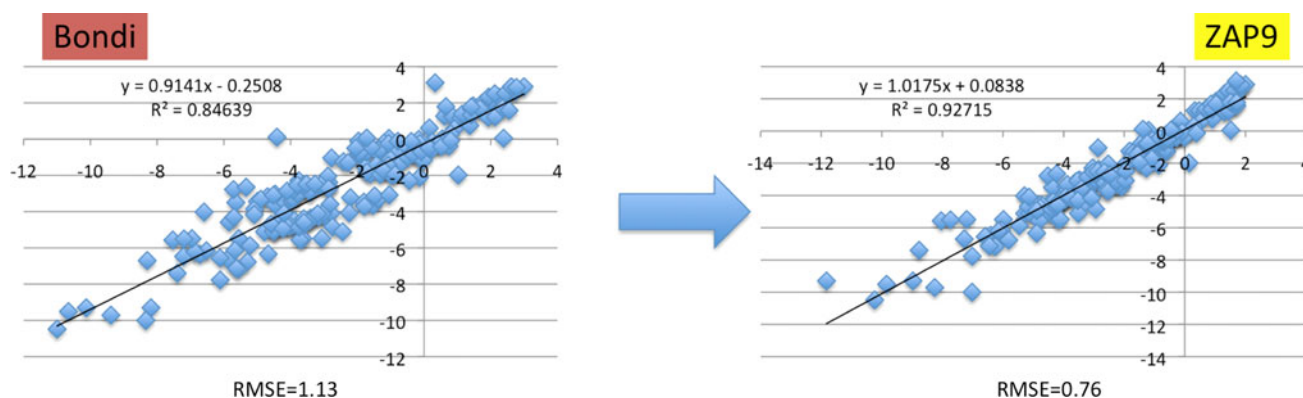
Fig. 1 The effect of radii optimization on the Rizzo set of vacuum-water transfer energies. Experimental energies in kcal/mol are on the x-axis and PB predicted energies on the y-axis. The 95% error bounds for the RMSE using Bondi radii are {1.01, 1.23} kcal/mol and for ZAP9 {0.83, 0.68} kcal/mol

Table 2 Table of radii used for various charge schemes

Radii in Å	Bondi	ZAP9	ZAP10	ZAP7	MO6-7	MO6-11
C	1.7	1.87	1.64	1.64		1.80
H	1.2	1.1	1.14	1.14	0.84	0.82
H on 2ndry N	1.2		0.6			
N	1.55				1.60	1.66
N Secondary	1.55	1.40				1.36
N Tertiary	1.55	1.40	1.2			1.36
O	1.52					1.50
O Carbonyl	1.52	1.76	1.83	1.83	2.16	2.17
O=S, O=P, O=N	1.52	1.52/1.76	1.83	1.52/1.83	2.16	2.17
O Ether	1.52		1.23			
S	1.8	2.15	1.93	1.93	1.71	1.71
P	1.8					
F	1.47	2.40	2.34	2.34	2.33	2.40
Cl	1.75	1.82				1.78
Br	1.85				1.49	1.53
I	1.98	2.65	2.65	2.65		
Surface area (cal/A^2)	10	6.3	5.7	5.7	8.3	7.4

Blank entries imply Bondi radii for that atom type. The entries "1.52/1.76" and "1.52/1.83" for doubly bonded oxygens other than carbonyl for ZAP9 and ZAP7 indicate both were used, as described in the text. Carbonyl oxygens for acetamide groups are all set to the Bondi radii for oxygen

all-atom simulations there was a component of parameterization to prior knowledge because the AM1BCC charges used had been adjusted to achieve better solvation energies. Alternate use of an AM1BCC v1.0 more similar to our implementation led to a much more similar RMSE (1.71 kcal/mol). PB faired poorly mainly because of the significant underestimation of the solvation of the two acetamide examples (circled in Fig. 2), *N,N*-dimethyl-benzamide and 4-methoxy-*N,N*-dimethyl-benzamide. The acetamide moiety has two atoms in close proximity that

ZAP9 chemically types, namely a carbonyl oxygen and a secondary nitrogen. However, the carbonyl oxygen parameterization makes the acetamide group less soluble, i.e., it contributes to the problem. We went back and looked at the two acetamide examples in the Rizzo set, and found both acetamide and *N*-methyl acetamide were significantly under predicted. As such, we removed the chemical typing for acetamide oxygens, i.e., allowed the radii to return to their Bondi elemental values, with results as shown in Table 3. For these four examples ZAP9 is still under predicting solvation, although the results are now not as extreme. We next considered the nitrogen parameterization—the reduction of the radii of secondary and primary nitrogens should work in our favor, i.e., make acetamide-like compounds more soluble. However, some simple test examples illustrated that reducing the radius of a buried nitrogen is often ineffective in increasing solvation [1]. For the smaller molecules in the Rizzo set the parameterization was effective, leading to up to a two kcal/mol increase in solvation, however, in the SAMPL0 examples the solvation energy was refractory to such changes. This strongly suggested the possibility that there is a physical effect not being well captured by PB of the order of a couple of kcal/mol per nitrogen center. This point will be reconsidered as we evaluate SAMPL2 and then reevaluate SAMPL1.

In the course of considering the residual errors of PB over the Rizzo and SAMPL0 sets we began to examine more closely the charges derived from AM1BCC. In particular, we extracted a useable database of vacuum dipole moments by microwave spectroscopy from McClellan's "Tables of Experimental Dipole Moments" [23]. These experiments are highly accurate, often to less than 1% of the absolute value. In comparing AM1BCC dipoles to experiment we noticed interesting some trends. AM1BCC is meant to mimic 6-31G* charges that form the basis of the AMBER force-field philosophy, i.e., such charges are
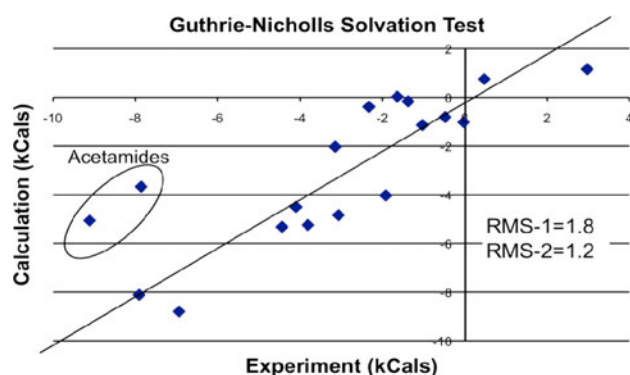
Fig. 2 Reprise of the SAMPL0 results of ZAP9 radii and PB. The acetamide outliers are indicated, as are the RMS errors with and without this pair of compounds. Axes are in kcal/mol

Table 3 Table illustrating the improvement in predicting solvation for molecules containing the acetamide group when the carbonyl oxygen is reset to its Bondi radius

Compound	Experiment	Zap9	Zap9/ Bondi carboxyl
Acetamide	−9.7	−8.2	−9.8
N-methylacetamide	−10	−7.0	−8.7
N,N-dimethyl-benzamide	−9.8	−5.6	−6.9
4-methoxy-N,N-dimethyl-benzamide	−11.0	−7.0	−8.2

known to be over-polarized by about 15% but this is considered a benefit because simulations in condensed phase are expected to polarize charges compared to vacuum. However, an examination of the Rizzo compounds using this reliable microwave data indicated that although 6-31G* charges might produce a 15% over-polarization *on average*, certain chemical types were either under over-polarized or over over-polarized. As AM1-BCC was parameterized to reproduce 6-31G* charges it largely follows these trends. An extensive examination concluded that correcting some of this variation consistently led to better prediction of solvation. As such, our next step was to consider whether charges more consistent with vacuum measurements would be better for PB. This has proven to be the case and was described in detail in our SAMPL1 report [3].

In brief, we first found that applying what we shall refer to as "high-quality" charges, i.e., those from QM calculations at the cc_pVTZ level or higher, improved results only when we reparameterize radii to these charges. This was performed over a subset of the Rizzo set leading to the radii description known as ZAP10. Subsequent application of ZAP10 radii and high-quality charges to the SAMPL0 set produced significantly better results (error ~1.3 kcal/

mol). The acetamide outliers were still under-predicted but less so than before. ZAP10 radii are listed in Table 2, column 3. The biggest difference between ZAP9 and ZAP10 was in the approach to the nitrogen issue. Rather than parameterize the radius of secondary nitrogens we adjusted the radius of their attached protons. These we gave an unphysical value of 0.58 Å. Although this seemed to work well for our training set, i.e., the subset of Rizzo we considered, this was to prove a disastrous choice, as described in our SAMPL1 report. In short, the unphysical radius for these protons lead to anomalous solvation in circumstances where one or more were in proximity to another polar group, e.g., a negative charge just outside the radius of a positively charged proton produces a causes a significant over-estimation of solvation.

Overall, SAMPL1 was a watershed event for those of us involved. There were significantly more contributions, many more molecules (fifty-six) and the molecules were large, polyfunctional and mostly flexible. The RMS errors for all methods were significantly higher than for SAMPL0 or for previous retrospective studies. PB performed better, in this instance, than simulations (2.44 kcal/mol for AM1BCC/ZAP9 compared to 3.53 kcal/mol for explicit water simulations over the same set of compounds). However, ZAP10 did not outperform the simpler ZAP9 (2.6 kcal/mol compared to 2.44 kcal/mol), largely due to the erroneous decision to parameterize secondary amine protons. If, retrospectively, we de-parameterized ZAP10, removing much of the chemical typing, to what we refer to as ZAP7 (Table 2, column 4) the end result was a remarkable RMS error of just 1.43 kcal/mol on some very difficult test cases. Even more remarkable was that ZAP7 contained no chemical adjustments for nitrogen at all. Our enthusiasm was tempered by the observation that high-quality charges were only calculated for about forty of the fifty-six compounds. Although the RMS error of ZAP9 with AM1BCC charges was 2.44 kcal/mol over the entire set of fifty-six it was only 1.9 kcal/mol over this same subset, i.e., failure to produce high-quality charges seemed to be an effective filter against some of the compounds with which we, and others, had the most difficulty.

Coming to SAMPL2, we felt confident of at least two approaches: ZAP9 with standard AM1BCC charges appeared both fast and reliable, and ZAP7 with high-quality charges and fewer parameters appeared a slower but slightly better method. The work with ZAP7 also seemed to suggest that the behavior of nitrogen might in fact not be as anomalous as first expected. For MO6 charges we decided to hedge our bets with respect to radii and made two sets. The first, MO6-7, was made similar to ZAP7, i.e., with a very parsimonious set of only six radii differing from Bondi and only one of these (oxygen)

having chemical typing. The non-polar area term for MO6-7 was 8.3 cal/$\mathring{A}^2$. For the second set, MO6-11 allowed more elemental types and the chemical typing of nitrogen along with a non-polar area term of 7.4 cal/$\mathring{A}^2$. Both sets of radii are detailed in Table 2, columns five and six. Finally, having a larger radius for carbonyl oxygens, with the exception for acetamide oxygens, is a characteristic that remains even in ZAP7. How should other oxygens be treated, e.g., those belonging to nitro, sulphonyl and phosphonyl groups? Existing data was inconclusive and so we saw SAMPL2 as an opportunity to test both approaches, i.e., whether it is better to treat doubly bonded oxygens as carbonyls or to treat them as acetamide oxygens. As such, we contributed two submissions each for our AM1BCC charges and for our high-quality QM charges.

We also felt confident in our single conformation approach, despite criticism that this was not accounting for conformational effects that clearly must have been present in many of the compounds in SAMPL0 and SAMPL1. The reason for this confidence was partly empirical and partly theoretical. The empirical component was that including multiple conformations never seemed to improve results. In addition, a report by Mobley and Dill using all atom-simulations suggested the effect is in general smaller than anticipated, although, in their hands, occasionally important [24]. Also in concurrence with our empirical findings, the authors found that if a single conformation was to be used the lowest lying vacuum conformation was preferred. The theoretical component involves the consideration of the effects of electronic polarization on solvation and is considered in some detail below.

Polarization can affect results in two ways and the first concerns partial charges. Most charging methods are conformationally independent, i.e., a single description is used for all conformations. As mentioned above, the AM1BCC method chooses an extended conformation to avoid the polarization AM1 exhibits when internal charge–charge interactions are present. And yet in these situations AM1 is attempting to describe the correct physics. Electrons do respond to the electrostatic field they find themselves in, whether the field is generated internally or externally. By choosing an extended conformation, Bayly and co-workers generate charges that are under-polarized compared to more compact conformers. In our transfer energy work we use the conformation that has the lowest vacuum energy, a state that often includes the type of interactions Bayly avoids. However, Bayly's approach can be appropriate for simulations, and for multi-conformer approaches in general, because over-polarized charges derived from compact forms lead to much greater solvation energies, when extended, than are seen experimentally. This was a component of our initial failure to get reasonable PB results with a multi-conformer approach, i.e., charges from compact forms predicted an unfolding from vacuum to water and gave solvation energies that were too large. Adjustment of the protocol to calculate AM1BCC charges for each conformation in situ substantially improved results.

The second reason polarization may favor a single conformation approach is to consider the energy landscape. There are two scenarios in which the single conformer *ansatz* will fail, one entropic and one (mostly) enthalpic. If there is a conformation that has a lower energy in solvent than the lowest lying vacuum conformation then we will under-predict solvation, i.e., by not considering the energy of transitioning to this lower state. Since the energy gained in 'unfolding', i.e., exposing more polar groups to external interactions, is mostly enthalpic, we so term this case. We have argued, with examples [3], that this is rare, i.e., the energy gained by 'unfolding' is normally not greater than the induced internal strain. However, we do see cases where the energy of the unfolded state is equivalent to the compact, low vacuum-energy state. This suggests the conformational landscape is flattened, i.e., there should be a favorable entropic term for solvation for some molecules. This is noted and quantified in the aforementioned work of Mobley and Dill [24] and is illustrated in Fig. 3a. But now consider what would happen if molecules are internally polarizable. In PB this is equivalent to an internal dielectric greater then one. Polarization has the effect of lowering the energy of internal interactions, i.e., states that have relatively lower energy in vacuum get lower still. As a consequence, the energy landscape will shift from Fig. 3a to b. Thus, internal polarization will tend to favor the single low-lying vacuum state in both phases.

This effect can be mimicked via the internal dielectric in PB. Care must be taken not to just change the dielectric without first also considering the consequences for external potentials and also solvation. The analytic forms for the electrostatics of a dipole in a sphere, a good model for many small molecules, tell us that changing the relative dielectric from 1.0 to 2.0 scales the external potential by 3/4 ("Appendix A"). This produces a quandary- if we have a vacuum-derived charged set do we scale charges by (4/3) to main the correct external potentials? If so the solvation must go up by (16/9). The effect of switching the dielectric is to reduce the solvation by a (3/4) ("Appendix A"), so the net effect would be to increase solvation by (4/3). As such, we can either get a polarizable model that has correct external potentials or solvation but not both, unless we also adjust radii. For a dipole in a sphere an increase of about 15% to the *solvated* radius, i.e., the radius in water but not the radius in vacuum, brings the solvation energy back into line.

There are several advantages to such a solvated radii *ansatz*. First, when using a continuous dielectric function

Fig. 3 a An illustrative graph where a set of conformations of a molecule are ranked from *left* to *right* by their force-field energy in vacuum, lowest on the *left* (*diamonds*). When each conformer is transferred to water the solvation compensates for internal strain (e.g., unmet hydrogen bonds in the vacuum become hydrated). Thus, the molecule goes from a low entropy state to a high entropy state. **b** A similar graph to **a** except now a polarization term has been added and adjustments have been made such the solvation of each conformation remains the same. Now both vacuum and water have low entropy
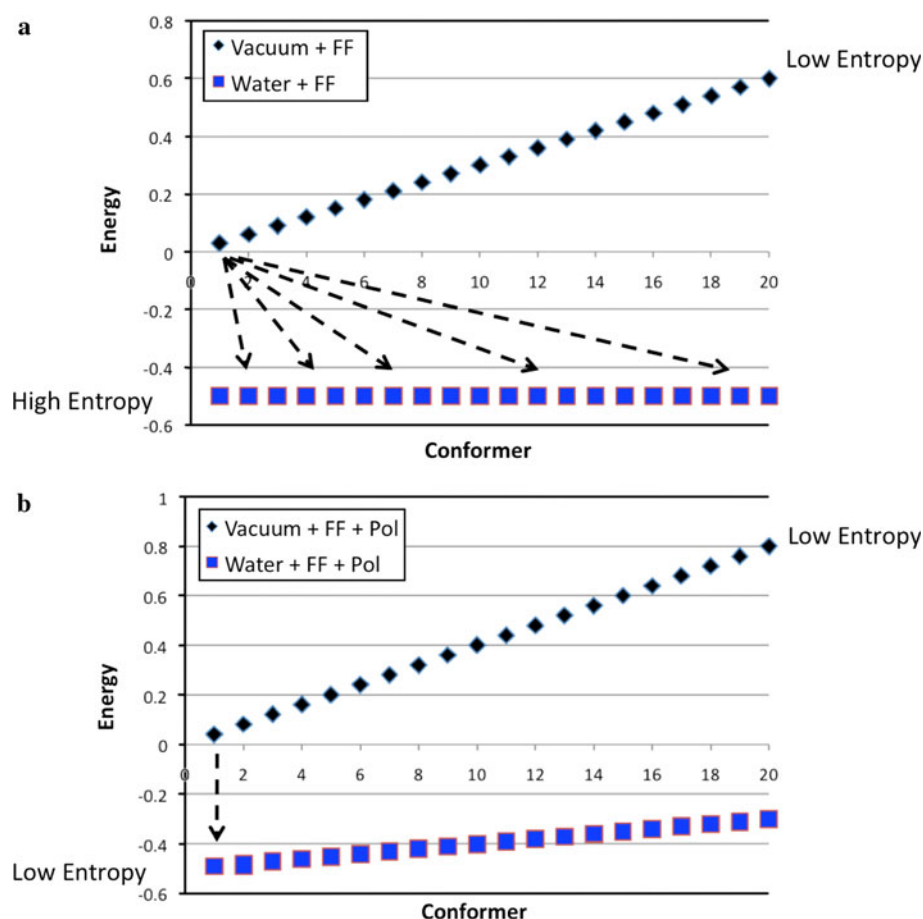
such as in ZAP the dielectric function switches from internal (low) dielectric to external (high) dielectric (water) over a finite distance. This switch cannot begin at the VdW surface. If it did then effectively water is being pushed further away from the solute charges and solvation is decreased- yet we know standard radii are effective in PB. Thus, the transition zone has to straddle the VdW radii. ZAP does this and has excellent agreement with hard sphere or molecular surface dielectric descriptions. However, on the inner side of the VdW surface the dielectric is higher than that of the bulk of the solute. It is disconcerting in a physical model to have a dielectric approaching that of water inside the molecule. This is not an issue for the continuous dielectric model in vacuum—it is easy to imagine the dielectric just inside the molecule being closer to that of vacuum. The solvated radius does away with this concern. The 15% adjustment is sufficient in ZAP such that the molecular dielectric at the VdW boundary is essentially equal to that of the rest of the molecule. A second advantage is that a connection can be made to the early work of Honig and Rashin on the solvation of ions [25]. Here they recommended an increase in ionic radii of 7%. Their suggestion was to apply this to both the vacuum and solvated form. If instead the increase were concentrated

purely in the solvated phase their recommendation would have been for an increase of 15%.

The application of an internal dielectric, charge correction and solvated radius to an example from SAMPL1 is shown for compound 20 from the SAMPL1 event in Fig 4a and b. In this case multi-conformer PB substantially over-predicts solvation due to the enthalpic case, i.e., there is a lower lying extended conformation. Application of polarization theory substantially reduces the gap between theory and experiment. Also note the general unflattening of the solvated energy landscape.

SAMPL2 results

Table 4 lists the RMS error for our six submissions, with the suspect cyanuric acid result excluded. At first glance the results were as expected, i.e., both MO6 and high-quality QM charges performed better than AM1BCC. However, the magnitude of the errors seemed surprising. From SAMPL1 we had expected an RMS error of around 2 kcal/mol for ZAP9 and perhaps around 1.5 kcal/mol for high-quality charges and ZAP7, yet SAMPL2 results where significantly higher. This struck us as odd because SAMPL2 seemed to

Fig. 4 a A real example of the phenomenon illustrated in Fig. 3a with compound 20 from the SAMPL1 dataset. As states have higher vacuum energies (*left* to *right*) solvation compensates such that many conformations have the same transfer energy. This example also had (rare) conformations that when solvated lie lower than the vacuum ground state. **b** With an internal dielectric, scaled charges and a +15% solvated radius, such that each states transfer energy remains the same, the result is similar to that illustrated in Fig. 3b. Note the *left* to *right* trend and also the reduced gap between lowest vacuum state and lowest solvated
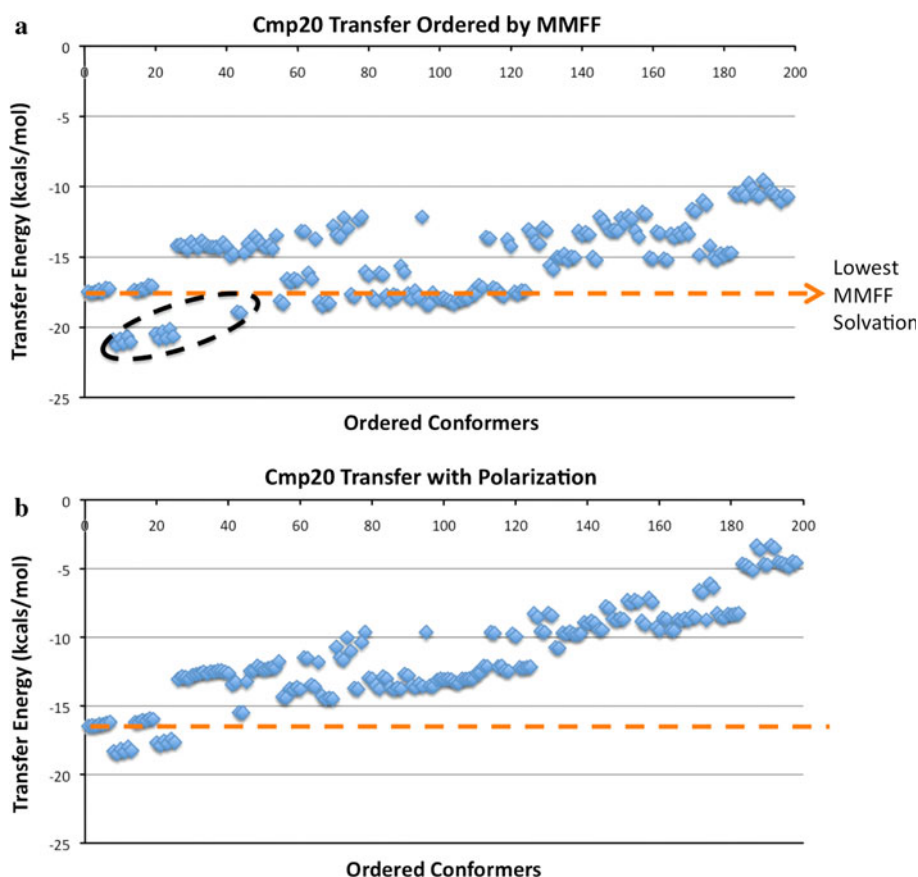
be a simpler exercise. Gone were the highly polar phosphamates, highly flexibly molecules and unusual chemical types and yet our average results were worse. As such, we also calculated the median unsigned error for each contribution, listed in the second column. Statistically speaking, a median is an estimate of the true mean that, while it converges more slowly, is insensitive to outliers. As can be seen, the median errors are much closer to expectations, although the values for high-quality QM charges still seemed too large. Investigation showed that in fact the unsigned error for the compound immediately below the median was significantly lower (values in parenthesis). It was clear there must be structure in the results that should be examined further. Figure 5 shows the absolute errors as frequencies binned in 1.0 kcal/mol tranches and smoothed to show the general form.

As previous parameterizations have used the RMSE as the performance metric, i.e., removing any bias, we would expect the frequency distribution to be weighted towards zero, with some Gaussian decay. While the MO6-11 results roughly have this form, Fig. 5 tells us is that both AM1BCC (ZAP9) and the high-quality charges (ZAP7) have a class of outliers. This is most pronounced for the ZAP7 where there is a clear separation into 'understood' and 'not-understood' molecules. Most of the rest of this

section will consider these poorly understood molecules. We would also point out that, while the statistics at this point are not strong, the results seem to point towards doubly bonded oxygens (sulfonyl-, phosphonyl- and nitro-) being typed as carbonyls.

Sugars

The worst prediction among the sugars was for glucose. The experimental result is a surprising −25.5 kcal/mol. Our submission using high-quality charges gave −20.5 kcal/mol. A 5 kcal/mol error is far larger than we would have expected. However, at least in part this result came from the aforementioned problem with Omega and protons. Shown in Fig. 6 are two 'protonic' conformations of glucose. There are many more but these two have relevance to the work at hand. The structure at left was used in the challenge. The structure at right is actually a lower vacuum energy structure (by MMFF) and so should have been used. It has a solvation energy of −22.0 kcal/mol, still an outlier but less so. In addition, the high-quality QM charges were for the incorrect conformation, i.e., may not have been sufficiently internally polarized. For example, high-quality QM charges for acetic acid with the hydroxyl proton making an internal hydrogen bond predict a

Table 4 Table of overall results from SAMPL2 for our six contributions

Method (Charges/radii)	RMSE (kcal/mol)	Median unsigned (kcal/mol)
AM1BCC/Zap9	3.45	1.9
AM1BCC/Zap9_SNP	3.32	1.78
HighQuality QM/Zap7	2.96	1.96 (1.51)
HighQuality QM/Zap7_SNP	3.0	2.44 (1.37)
MO6/MO6_7	3.08	2.0
MO6/MO6_11	2.81	1.6
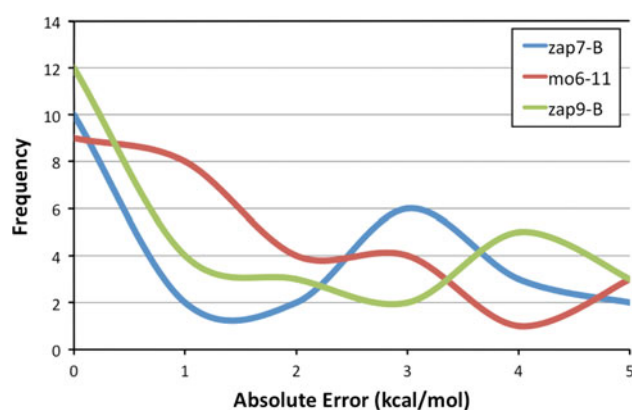
Fig. 5 The frequency of absolute errors for each of our three methods, i.e., ZAP9 and AM1BCC charges, MO6 charges with an expanded radii set and ZAP7 with high quality QM derived charges. The lines are smoothed frequency estimates binned at 1 kcal/mol ranges, i.e., {0, 1} kcal/mol, {1, 2} kcal/mol, with the frequencies assigned to the lower value on the abscissa

solvation of −6.3 kcal/mol with PB and standard radii, compared to the experimental value of −6.7 kcal/mol. Charges calculated with the proton maximally distant from the acceptor oxygen and applied to the internally hydrogen-bonded state gives −5.1 kcal/mol. Similar results are seen for other carboxylic acids. While the correct charges would not make up a 3.5 kcal/mol difference it would certainly decrease the error. A similar mistake was not made for xylose and the resultant error was about 2.8 kcal/mol, i.e., consistent with conformation corrected glucose. Glycerol then appears an odd outlier, i.e., PB *over-predicts* the solvation by 2.4 kcal/mol (experimental value of −8.3 kcal/mol, PB gives −10.7 kcal/mol). However, after the SAMPL2 event Guthrie presented an alternate possible value for glycerol of −13.43 kcal/mol giving a consistent PB error of −2.73 kcal/mol.

The source of this residual error for sugars still seems surprising. Alcohols and esters are well predicted by PB in the Rizzo set and so why these molecules are under-predicted remains an issue. Certainly one feature may be conformational entropy of the proton positions.

Uracils

The six uracil compounds (Fig. 7) represent the largest class within the SAMPL2 challenge and statistically over-weight the RMSE. Table 5 lists the individual and average errors over this subset. The lower average errors of the MO6-11 approach for the uracils essentially accounts for all of the lower overall error of this method. Meanwhile an average error of 4.6 kcal/mol badly skews the overall RMSE for ZAP7. In our opinion, we believe these experimental results may be in error.

Some of this reasoning is presented in the Geballe et al. overview of SAMPL2 [26]. Essentially we examined the collection of compounds from SAMPL1 and to our surprise found two examples of substituted uracils. One example is shown in Fig. 8 for a substituted chlorouracil. And yet, the ZAP7 results for these compounds were very accurate. For the example shown we are within experimental error (−11.1 kcal/mol for both theory and experiment). Yet, according to the experimental results in SAMPL2, the removal of the t-butyl group results in a 6.7 kcal/mol shift in solvation. The non-polar contribution from a t-butyl group is unlikely to be more than 2 kcal/mol (transfer energy of butane is +2 kcal/mol, for isobutene +2.3 kcal/mol) and is probably more like 1 kcal/mol (e.g., transfer energy of butyraldehyde −3.18 kcal/mol and octotanal is −2.29 kcal/mol). In fact ZAP7 predicts a reasonable 1.7 kcal/mol difference. It is true that a primary proton is also removed when the t-butyl group is added which would suggest the difference might be higher than 2 kcal/mol. However, there are also known examples that do not support this being a significant factor, for instance pyrazine and methyl-pyrazine from the Rizzo set are −7.4 and −7.77 kcal/mol, respectively. Certainly it is hard to envision a scenario where such a loss of a primary proton is responsible for ∼5 kcal/mol of energy. Some methods, by other contributors, did well on the uracil set presented in SAMPL2. We checked against the list of contributors for SAMPL1 and found that those who contributed to both meeting and did well on SAMPL2 uracil set tended to do poorly on the SAMPL1 uracil set, precisely because their estimates for that latter event were systematically too solvated. The solvation difference in these methods between SAMPL1 and SAMPL2 results were small, in line with our estimates and thus tending to support our contention.

There are two other possibilities that might cause calculations for this class of compounds to be inaccurate. First, uracil can tautomerize to the lactim structure as illustrated in Fig. 9. If the lactim were the more favorable structure in solvent then we would have been calculating the solvation energies for the wrong compounds. This would also agree with the SAMPL1 result where there are fewer or no tautomers for the substituted forms. However,
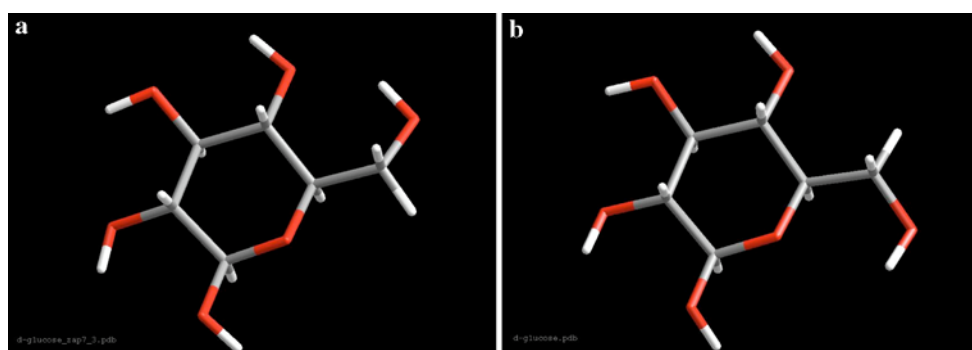
Fig. 6 **a**, **b** Conformations of glucose. On the *left* is the conformation used in SAMPL2 and on the *right* the lower vacuum energy conformation that ought to have been used
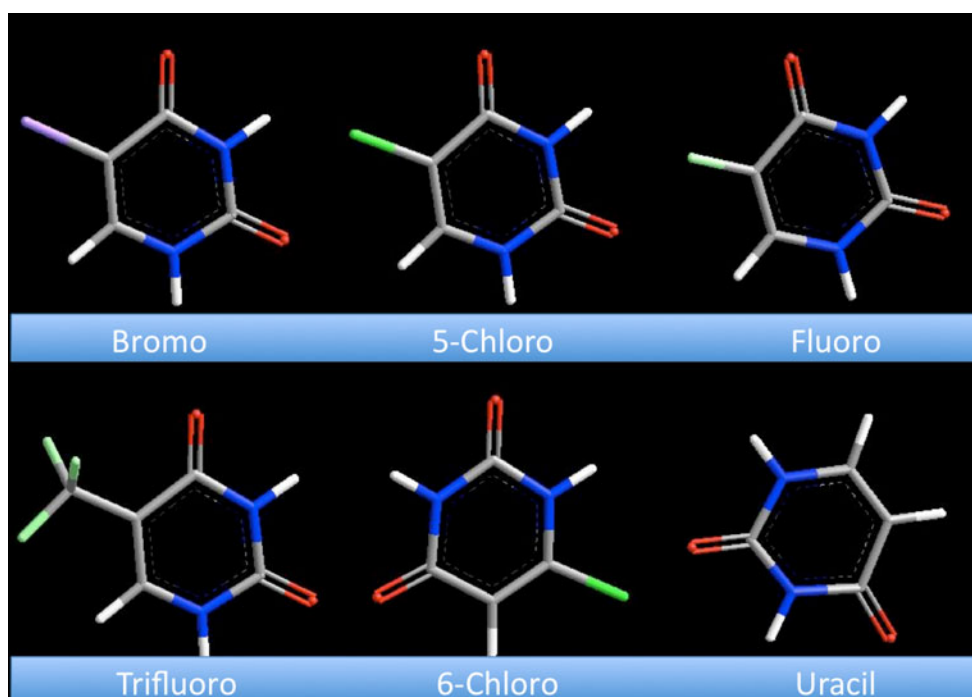

**Fig. 7** The halogenated uracils in SAMPL2

Table 5 The results over the six uracil compouds in SAMPL2 for both high quality QM charges and MO6 with the more extensive radii parameterization

Molecule	Experimental	HQ QM/ZAP7	MO6/MO6_11
5-trifluoromethyluracil	−15.46	−11.9	−16.8
6-chlorouracil	−15.83	−10.4	−12.7
Uracil	−16.59	−12.9	−15.8
5-fluorouracil	−16.92	−12.4	−17.0
5-chlorouracil	−17.74	−12.8	−16.3
5-bromouracil	−18.17	−12.6	−15.6
Average error		4.6 kcal/mol	1.5 kcal/mol

it is believed the lactam forms dominate in solution. As such the only possibility for systematic error is that the lactim structures dominate in vacuum. But if this were so we would expect the experimental results to consistently under predict the solvation, which is not seen.

The final possibility involves the behavior of secondary and tertiary nitrogens in PB. As noted above, we removed any specific parameterization for such nitrogens in ZAP7. In general, the estimation of the solvation energy of compounds containing secondary and tertiary nitrogen is difficult for most simulation methods, including PB. The typical anomalous behavior is that PB under predicts solvation by about 2 kcal/mol per nitrogen center. Since uracils have two

Fig. 8 One of the examples of a uracil analog from SAMPL1 (*left*), along with uracil (*right*)
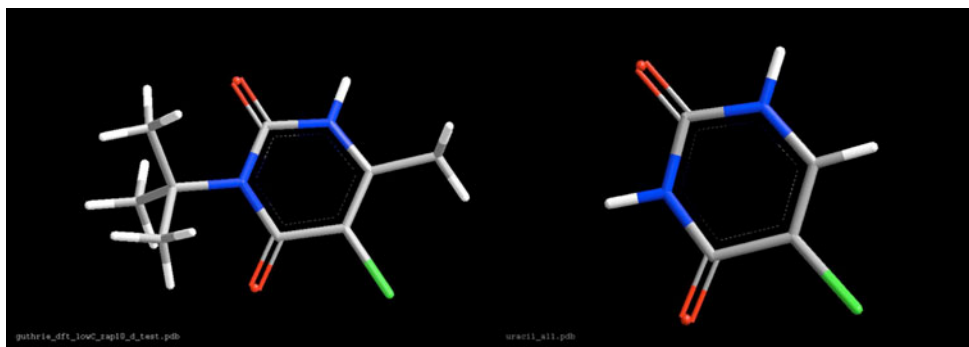
nitrogen centers this might imply a potential under estimation of about 4 kcal/mol, i.e., roughly what is seen. In support of this we note that caffeine with four nitrogens was also one of the worst outliers (experiment = −12.6 kcal/mol compared to −9.2 kcal/mol for ZAP7). However, there are several problems with this theory- first AM1BCC with parameterization for such atoms still underestimates the uracils by about 3 kcal/mol. Secondly, this would imply that the experimental results from SAMPL1 must be incorrect, i.e., they should be more solvated than theory suggests. Finally, the results from SAMPL1 and ZAP7 in general did very well for other compounds with secondary and tertiary nitrogens. Table 6 illustrates this for seventeen compounds that have one or more secondary or tertiary nitrogens (excluding aromatic nitrogens and those in nitro groups). The average absolute difference in solvation over these compounds is only 0.35 kcal/mol and exhibits no systematic over- or under-prediction. As SAMPL1 had more flexible molecules than SAMPL2 is was possible we had chosen conformations that were of higher energy than the lowest lying vacuum conformation and hence more solvated, i.e., perhaps we did well on compounds with secondary and tertiary nitrogens by accident in SAMPL1. We investigated this by a more thorough sampling of these compounds but found no compelling evidence to support this proposition.

Polychlorinated benzenes

The final category of outliers is the anomalous results for hexachloro-benzene and pentachloro-benzene. In general, chlorinated substituted compounds, whether benzene or not, are well predicted by PB. Table 7 shows the results for ZAP7 for some of the Rizzo set and for the two compounds

Fig. 9 Lactam to Lactim tautomerization of uracil

in SAMPL2. There is nothing to suggest many chlorines (e.g., carbon tetrachloride, hexachloroethane) are a problem for PB theory, nor when substituting in more limited measure to benzene (dichlorobenzene). In fact, hexachlorane, i.e., cyclohexane with six evenly spaced chlorine substitutions, has its solvation over-predicted by about 2 kcal/mol. What, then, accounts for the substantial under-prediction of hexachlorobenezene by 4.83 kcal/mol and pentachloronitrobenzene by 4.6 kcal/mol? With the uracil errors we have at least some suggestion of experimental oddity but these compounds are derived from the environmental literature where one assumes the transfer energies are well characterized.

When an anomalous result is obtained in molecular modeling the last resort is to invoke polarization. And certainly, if one had to look at the SAMPL2 set and point to two compounds that might exhibit polarization issues it would be these two polychlorinated species. Other methods did badly on these molecules as well, e.g., all-atom simulations. The only attempts that were close were either a consequence of using poorer charge sets, e.g., giving the chlorines more of a partial charge than high-quality QM would suggest is appropriate, and Jay Ponder's polarizable Amoeba force-field [27]. This suggests that both all-atom simulations and PB may not be able to address the solvation of this type of molecule without including polarization.

There are other examples where PB fails similarly, for example the highly unpolarizable molecule tetrafluoromethane has a reported solvation energy of +3.1 kcal/mol, whereas ZAP9 gives about +0.4 kcal/mol, and the very polarizable bromoform has an experimental value of −1.98 kcal/mol, whereas ZAP9 predicts +1.0 kcal/mol. We have shown in unpublished work that these outliers can be partially addressed by adjusting the solute dielectric to that obtained from the molar refractive index of each compound. Figure 10 illustrates that if the dielectric is estimated for the SAMPL2 compounds, either by looking up the refractive index in the CRC handbook [28] or by interpolation from similar compounds, there is a slight, if unconvincing, trend in the error relative to relative dielectric (the correlation coefficient of 0.1987 is statistically better than
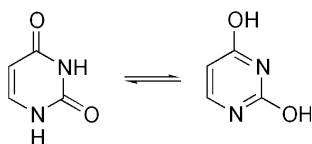
Table 6 Compounds containing a non-aromatic secondary or tertiary nitrogen not in a nitro group

SAMPL1 ID	Experiment (kcal/mol)	HQ-QM/ZAP7 (kcal/mol)	Number of secondary N	Number of tertiary N
7	−8.2	−8.2		1
8	−9.84	−11.7	1	1
9	−7.65	−9.5	2	
11	−3.51	−4.51		1
21	−1.45	−1.09		1
32	−9.13	−8.08	1	1
44	−3.64	−4.21		1
47	−8.43	−10.04	1	
48	−7.78	−5.81	1	
49	−14.7	−11.44		2
50	−10.22	−13.12	2	
51	−20.25	−18.11	2	
52	−11.14	−11.15	1	1
53	−6.68	−7.84	2	
56	−3.25	−5.22		1
57	−4.13	−4.67		1
63	−9.41	−8.08		2

The average absolute difference in solvation between experiment and prediction is 0.35 kcal/mol, i.e., showing no particular pattern to over- or under-predict

Table 7 Examples of polychlorinated compounds from previous studies and the predictions using high quality QM charges and ZAP7 radii

Molecule	Experiment (kcal/mol)	HQ QM/ZAP7 (kcal/mol)
Benzene	−0.87	−1.28
Chlorobenzene	−1.12	
Dichlorobenzene	−1.36	−1.21
1,4-dichlorobenzene	−1.01	
Carbon Tetrachloride	−1.07	−0.72
Hexachloroethane	−1.41	−1.8
Hexachlorane	−5.44	−7.4
Hexachlorobenzene	−2.33	1.5
Pentacholoronitrobenzene	−5.2	−0.6

the null model with a probability greater than 0.98). In addition, the assumption that the non-polar term is a constant for molecules that differ greatly from the polarizability of the alkanes is a long-standing flaw in the PBSA approach. Both these approaches may begin to address the issue with hexachlorobenezene and pentachloronitrobenzene. The good news is that there may be data for more such poly-substituted halogenated compounds in the environmental literature. If so, this would be invaluable in improving our understanding of solvation.

Discussion

SAMPL2 proved a most interesting event for several reasons. First, there were a significant number of contributors with a wider variety of approaches than before. The sharing of insights, especially to problem compounds, was illuminating and appreciated by all. Secondly, this was the first SAMPL where there was enough theoretical confidence to challenge some of the experimental results. In particular it was clear to all that cyanuric acid had to be incorrect and significant doubt was raised over glycerol that proved to be well founded. This is remarkable—to our knowledge we know of no instance where molecular modeling has previously successfully challenged experiment. And there remain, in our minds, some speculation concerning the uracil results. Whether the polychlorinated compounds are actually exemplars of physics we need to capture remains to be seen, but the possibilities are intriguing. Overall SAMPL2 results suggest theory ought to be in the position of suggesting compounds that should to be measured, e.g., we ought to be able to say if compounds are within the dynamic range of a physical technique and furthermore to select those that illuminate differences between theoretical approaches. Theory and experiment could actually supplement each other and drive towards a better understanding of solvation.

Of the specific things learnt from SAMPL2, the most important seemed to us to be the continuing reliability of high-quality charges. That these take substantial effort to calculate is a problem for the continuum method but likely also a problem for all-atom simulations. That PBSA, while such a simple theory, is competitive with the sampling and energetics of molecular dynamics remains remarkable. At each SAMPL we see evidence that the surface area term needs to be addressed for PB. It is unclear just how useful this will be as attempts to include a variable surface area term from molecular dynamics results have not proved very predictive. But, as described in our SAMPL1 paper, relatively non-polar molecules such as carbon tetraflouride and diiodomethane have such widely different surface tensions (6 mN/m vs. 51 mN/m respectively) we surely have to consider dispersive forces for highly polarizable or unpolarizable molecules. Not everything is an alkane, that much at least SAMPL has taught us!

We also continue to be surprised that a single low-energy conformation is sufficient for transfer energy estimation. Although proton position possibilities for the sugar molecules in SAMPL2 suggest its importance, there is no definitive pattern with respect to conformational sampling other than the consequence of getting caught in the wrong conformation, i.e., a higher energy conformation than would be seen in vacuum. This, again, is something that

Fig. 10 A graph of the errors
from ZAP7 and QM charges
versus a dielectric calculated
from the refractive index of the
compounds or from
extrapolation from similar
compounds. The R^2 of this
correlation is a weak 0.199, but
is still statistically significant to
the NULL model ($p < 0.02$)
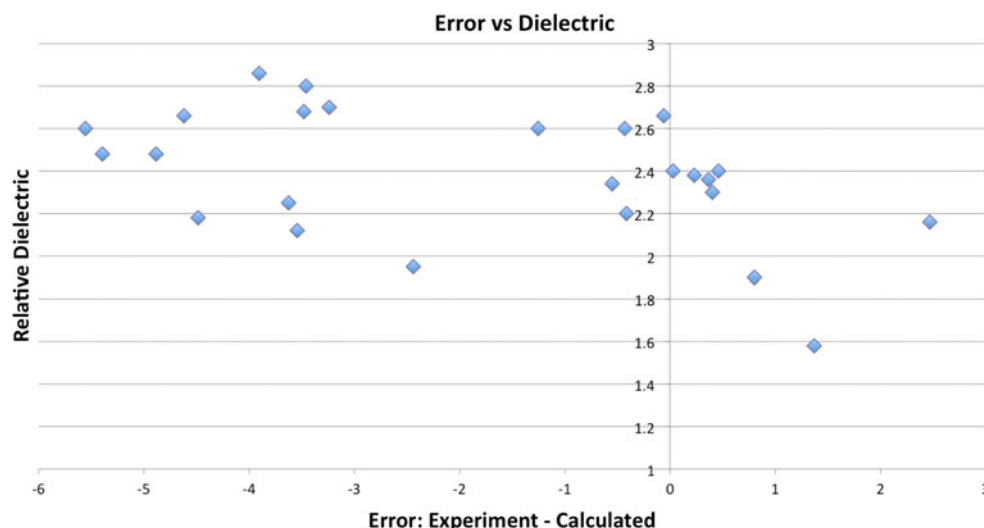
could be tested by a careful selection of compounds for prospective measurement. It could also be addressed by NMR techniques that accurately measure the preferred conformation in solution. An example where our approach accurately predicts a transfer energy but for the wrong solvated conformation would be invaluable.

Conclusions

SAMPL2 proved an unexpectedly hard challenge for continuum methods for reasons we are only beginning to understand. It is clear, however, that this event is continuing to push both our understanding of solvation and our ability to predict it. A substantial subset was predicted as expected from our work on prior SAMPL events and within 1.0 kcal/mol. Of the outliers there is, we believe, some doubt over the largest subset, i.e., the substituted uracils, leaving only the sugars and the polychlorinated compounds with abnormally high solvation. The latter may be exemplars of the importance of polarization although it is too early to say for sure. Further measurements and more data should greatly illuminate the importance of polarization in solvation. In addition, there is enough consensus belief in the methods to now conclude that we ought to be able to assist experimentalists in their choice of technique with which to produce new data. Although such experiments are not common, the potential impact on the field of molecular modeling is profound. The prediction of protein–ligand binding cannot be considered tractable if we cannot predict solute–water interactions. When we can routinely calculate solvation energies to better than 1 kcal/mol accuracy, physical theory may, for the first time, begin to have an impact on such properties as ligand binding or solubility, i.e., areas of central importance to the pharmaceutical industry.

Appendix A

Potentials

The equation for the potential around a sphere with a point dipole at the center, in cgs units, is:

$$\phi_{\text{dipole}\_p\_\text{in}\_\text{sphere}\_r} = \frac{3\varepsilon_{\text{outside}}}{2\varepsilon_{\text{outside}} + \varepsilon_{\text{inside}}}$$
$$p\cos(\theta)/(4\pi\varepsilon_{\text{outside}}\varepsilon_0 R^2)$$

where ϕ is the potential, $\varepsilon_{\text{inside/outside}}$ is the relative dielectric inside/outside the sphere, ε_0 is the absolute permittivity in free space, p is the magnitude of the dipole and R is the distance to the center of the sphere and θ is the angle between the measurement point, the center of the sphere and the direction of the dipole. If we term $\phi(1:1)$ the potential when the internal dielectric is set to one and ϕ(1:2) the potential when the internal dielectric is set to two we have:

$$\phi_{\text{dipole}\_p\_\text{in}\_\text{sphere}\_r}(1:1) = p\cos(\theta)/(4\pi\varepsilon_0 R^2)$$

$$\phi_{\text{dipole}\_p\_\text{in}\_\text{sphere}\_r}(1:2) = \frac{3}{4}p\cos(\theta)/(4\pi\varepsilon_0 R^2)$$

$$\therefore \phi_{\text{dipole}\_p\_\text{in}\_\text{sphere}\_r}(1:2) = \frac{3}{4}\phi_{\text{dipole}\_p\_\text{in}\_\text{sphere}\_r}(1:1)$$

Solvation

The equation for the solvation of a dipole at the center of a sphere, again in cgs units, is:

$$G_{\text{dipole}\_p\_\text{in}\_\text{sphere}\_r} = -\frac{p^2}{4\pi\varepsilon_{\text{inside}}\varepsilon_0 r^3}\frac{(\varepsilon_{\text{outside}} - \varepsilon_{\text{inside}})}{(2\varepsilon_{\text{outside}} + \varepsilon_{\text{inside}})}$$

where the symbols are the same except r is the radius of the sphere. If we set $\Delta G_{1:80}$ to the transfer energy of a sphere that has a relative internal dielectric of one and $\Delta G_{1:2:80}$ to

the transfer energy of a sphere with a relative internal dielectric of two then we get the following:

$$G_{1:80}^{\text{dipole}-\text{transfer}} = -\frac{p^2}{1*4\pi\varepsilon_0 r^3}\left[\frac{(80-1)}{(160+1)}+\frac{1-1}{1+2}\right]$$

$$\approx -\frac{p^2}{8\pi\varepsilon_0 r^3}$$

$$G_{1:2:80}^{\text{dipole}-\text{transfer}} = -\frac{p^2}{2*4\pi\varepsilon_0 r^3}\left[\frac{(80-2)}{(160+2)}+\frac{2-1}{2+2}\right]$$

$$\approx -\frac{p^2}{8\pi\varepsilon_0 r^3}\left[\frac{1}{2}+\frac{1}{4}\right]$$

$$\therefore G_{1:2:80}^{\text{dipole}-\text{transfer}} \approx [3/4]G_{1:80}^{\text{dipole}-\text{transfer}}$$

In the second equation we are calculating the sum of two transfers: of the sphere from vacuum to a medium of dielectric two, then from this medium to a dielectric of eighty.

References

1. Nicholls A, Mobley DL, Guthrie JP, Chodera JD, Bayly CI, Cooper MD, Pande VS (2008) Predicting small-molecule solvation free energies: an informal blind test for computational chemistry. J Med Chem 51(4):769–779
2. Skillman AG, Nicholls A (2008) SAMPL2: statistical analysis of the modeling of proteins and ligands
3. Nicholls A, Wlodek S, Grant JA (2009) The SAMP1 solvation challenge: further lessons regarding the pitfalls of parametrization. J Phys Chem B 113(14):4521–4532
4. Jakalian A, Jack DB, Bayly CI (2002) Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation. J Comput Chem 23(16):1623–1641
5. Zhao Y, Truhlar DG (2006) A density functional that accounts for medium-range correlation energies in organic chemistry. Org Lett 8(25):5753–5755
6. Grant AJ, Pickup BT, Nicholls A (2001) A smooth permittivity function for Poisson–Boltzmann solvation methods. J Comp Chem 22:608–640
7. Gilson M, Rashin A, Fine R, Honig B (1985) On the calculation of electrostatic interactions in proteins. J Mol Biol 184:503–516
8. Nicholls A, Honig B (1991) A rapid finite difference algorithm, utilizing successive over-relaxation to solve the Poisson–Boltzmann equation. J Comp Chem 12(4):435–445
9. OMEGA http://www.eyesopen.com/products/applications/omega.html
10. SZYBKI http://www.eyesopen.com/products/applications/szybki.html
11. Hertwig RH, Koch W (1997) On the parameterization of the local correlation functional. What is Becke-3-LYP? Chem Phys Lett 268(5–6):345–351
12. Gaussian I. www.gaussian.com
13. Singh UC, Kollman PA (1994) An approach to computing electrostatic charges for molecules. J Comp Chem 5(2):129–145
14. QUACPAC http://www.eyesopen.com/products/applications/quacpac.html
15. Ellingson BA, Skillman AG, Nicholls A (2010) Analysis of SM8 and Zap TK calculations and their geometric sensitivity. JCAMD 24. doi:10.1007/s10822-010-9355-3
16. Bondi A (1964) J Phys Chem 64:441
17. Kelly CP, Cramer CJ, Truhlar DG (2005) SM6: a density functional theory continuum solvation model for calculating aqueous solvation free energies of neutrals, ions, and solute-water clusters. J Chem Theory Comput 1:1133–1152
18. Sharp KA, Nicholls A, Fine RF, Honig B (1991) Reconciling the magnitude of the microscopic and macroscopic hydrophobic effects. Science 252(5002):106–109
19. Jones FM, Arnett EM (1974) Prog Phys Org Chem 11:263–322
20. Ben-Naim A, Marcus Y (1984) J Chem Phys 81:2016–2027
21. Marten B, Kim K, Cortis C, Friesner RA, Murphy RB, Ringnalda MN, Sitkoff D, Honig B (1996) J Phys Chem 100:11775–11788
22. Rizzo RC, Jorgensen WL (1999) OPLS all-atom model for amines: resolution of the amine hydration problem. JACS 121:4827–4836
23. McClellan AL (1963) Tables of experimental dipole moments, 1st edn. W. H. Freeman and Co., New York
24. Mobley DL, Dill KA, Chodera JD (2008) Treating entropy and conformational changes in implicit solvent simulations of small molecules. J Phys Chem B 112(3):938–946
25. Rashin AA, Honig B (1985) Reevaluation of the Born model of ion hydration. J Phys Chem 89(26):5588–5593
26. Geballe M, Skillman AG, Nicholls A, Guthrie JP, Taylor PJ (2010) The SAMPL2 blind prediction challenge: introduction and overview. JCAMD 24. doi:10.1007/s10822-010-9350-8
27. Ren P, Ponder JW (2003) Polarizable atomic multipole water model for molecular mechanics simulation. J Phys Chem B 107:5933–5947
28. Lide DR (ed) (1998) CRC handbook of chemistry and physics, 79th edn. CRC Press, Boco Raton
29. Gallicchio E, Zhang LY, Levy RM (2002) The SGB/NP hydration free energy model based on the surface generalized born solvent reaction field and novel nonpolar hydration free energy estimators. J Comput Chem 23(5):517–529
30. Sitkoff D, Sharp K, Honig B (1994) Accurate calculation of hydration free energies using macroscopic solvent models. J Phys Chem 98:1978–1988
31. Bordner AJ, Cavasotto CN, Abagyan RA (2002) Accurate transferable model for water, n-Octanol and n-Hexadecane solvation free energies. J Phys Chem B 106:11009–11015