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Symposium Report

The Role of Electrostatics in Chemistry

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This symposium, sponsored by the Computers in Chemistry Division of the American Chemical Society, featured a broad range of current activity devoted to the role and treatment of electrostatics in chemical structure and reactivity. The present report was written by the two organizers identified above.

Atomic charges and force fields

The symposium opened with several papers on the determination of atomic charges and the parameterization of electrostatic terms in molecular modeling. Varying degrees of sophistication were employed for the electrostatic terms.

Tom Halgren of Merck Research Laboratories (Rahway, N.J., USA) discussed some deficiencies of the MMFF94 force field and presented initial work on its reparameterization; for example when a proposed bond-increment scheme is used to determine simultaneous fits of multiple molecules to the molecular electrostatic potentials, the derived partial charges on the formaldiminium cation ($H_2CNH_2^+$) appear to be incorrect ($q_N = -1.13$ vs a presumably accurate value of -0.56 ± 0.02), For MMFF94 itself, solvation energies for alkanes are too hydrophobic ($+3.4$ kcal for methane vs an accurate value of $+2.0$), and too small heats of vaporization for butane, methanol, and *Z-N*-methylacetamide are observed. Incorrect preferences for hydrogen-bond directionality are also observed. A particularly significant problem appears to be a mis-estimate of the relative binding energies of the hydrogen bonded homodimers of *Z-N*-methylacetamide and a β-sheet conformation of the alanine dipeptide (quantum chemical calculations predict the former dimer is more strongly bound by 2–3 kcal whereas MMFF94, like many other commonly used force fields also examined, predicts it is more weakly bound by 3 kcal). The error was attributed to a deficiency of models in which the electrostatics are only represented nuclear-centered charges. It will be interesting to see if this interpretation can be confirmed by further analyses. In a related presentation, Jon Maple of Molecular Simulations Inc. (in a paper co-authored by Xianjun Kong, Marvin Waldman, and Carl Ewig) discussed the observation that if polarization (induction) is included explicitly in a force field, then the van der Waals interaction terms do not need to be so attractive. For example, the van der Waals contribution to the binding energy of $Cl^-(H_2O)$ is 5 kcal less in a model with explicit polarization. This presentation also showed examples of using a force field that includes both permanent atomic multipoles (through the quadrupole moment) and polarization (through induced dipoles). When both types of electrostatic terms are included, very substantial increases in the accuracies of intermolecular energies and geometries are obtained. This includes the directionalities of hydrogen bonds such as those with which Tom Halgren was concerned. The latter are now, for the first time, correctly predicted by a force field.

György Ferenczy of Gideon Richter, Ltd. (Budapest, Hungary) presented an algorithm for deriving a set of effective distributed multipoles. The application of effective multipoles leads to improved convergence in evaluating electrostatic interaction energies as compared to models with distributed multipoles coming from a multipole expansion. Furthermore a model with effective charges and dipoles leads to better reproduction of electrostatic interaction energies than models with only nuclear-centered charges.

Randall Shirts of Brigham Young University (Provo, Utah, USA) presented a comparison of class II and class III charge models as a function of conformation in alcohols and ethers. The class II model of Gasteiger yields connectivity-dependent but conformation-independent charges, whereas class III charges obtained by fitting calculated electrostatic potentials often show significant conformational dependence. The class II electronegativity equalization procedure of Rappé and Goddard predicts the conformational dependence of dipole moments more accurately than the absolute value of the dipole moment.

Michelle Francl of Bryn Mawr College (Bryn Mawr, Pa., USA) discussed the numerical stability of the electrostatic fitting process to obtain class III atomic partial charges. If the fitting points are too far away from the atoms in the molecule, the electrostatic potential can be predicted from a few multipole moments, and so it does not contain enough information to obtain meaningful values for all the atomic charges. As a consequence, if one places points externally at 1–3 × the van der Waals radius, one gets rank-deficient matrices in the fitting process, and the rank deficiency increases as the number of buried atoms increases; for example it is 2 for acetamide, 3 for phenol, 4 for adenine, and 5–6 for alanine dipeptide. In typical cases the electrostatic potential contains enough information to determine only 80% of the atomic charges in 10-atom molecules and only 70% of the atomic charges in 35-atom molecules. Yet there seems to be a bias in the field against placing fitting points inside the van der Waals radius.

The treatments discussed above involve nonpolarizable charge models. Jiabo Li of the University of Minnesota (Minneapolis, Minn., USA), in a paper co-authored by Tony Zhu and the two present reporters, discussed a new class IV charge model, called Charge Model 2 (CM2), that yields accurate partial charges by a bond-order-dependent mapping of Löwdin charges. This method yields more accurate dipole moments for test molecules than are obtained from the expectation value of the dipole moment operator for the same wave function from which the Löwdin charges are extracted. The class IV charges appear to be more accurate than class III charges, and they do not suffer instability problems for buried atoms. The class IV charges, when employed in polarizable form with a self-consistent reaction field, also lead to a more realistic treatment of solvation effects in phosphorus-containing compounds than was previously available. These changes have been used to parameterize several solvation models (SM5.42 models) with mean unsigned errors in the molar free energies of solvation of 0.4–0.6 kcal.

Yi-Ping Liu of Western Michigan University, in a paper co-authored by Bruce Berne (Columbia), compared two procedures for fitting parameters of force-field models with polarizable dipoles that are designed to account for many-body interactions. In the first method, called the cluster approach, potential function parameters are fit to reproduce the ab initio three-body energy of water trimers. In the second method, the electrostatic polarization response of a water monomer in the presence of a probe charge is used for parameterization. They found that parameters derived from fitting to the electrostatic polarization response can also reproduce the ab initio three-body energy of water trimers (except for bifurcated hydrogen-bonded ones). It is found, however, that the two methods explore different regions of the parameter space. In addition, they demonstrated numerically that a three-site model with point charges at the sites cannot describe the polarization response in uniform and nonuniform fields simultaneously with a single set of force-field parameters. They conclude that it is essential to go beyond such a model in order to obtain a transferable ab initio water potential.

New techniques and tools

Another subject of widespread interest at the symposium was the development of new algorithms for the treatment of electrostatic effects and new methods for using electrostatic potentials in computational modeling.

Carol Parish of Hobart & William Smith Colleges (Geneva, N.Y., USA), in a paper co-authored by W. Clark Still, discussed their generalized Born-surface area (GB/SA) continuum solvation model. Cavity and van der Waals interactions are modeled by differentiable solvent-accessible surface area terms. Electrostatics are treated by the generalized Born equation with a new solute descreening algorithm, in which a solute atom j of volume V_j at a distance r_{ij} from atom i reduces the solvation free energy of atom i by a term proportional to V_j/r_{ij}^4, which is the induction energy. The proportionality constants were parameterized, and a mean unsigned error of 0.9 kcal was obtained for molar aqueous solvation free energies. This may be compared to 0.5 kcal for the similar SM5.2PD/AM1 model of Hawkins, Cramer, and Truhlar. The difference is probably attributable, at least in part, to the fact that the GB/SA model has only three atomic surface tension coefficients, whereas the SM5.2PD/AM1 model has 12 such coefficients. Different test sets were also used.

Jiali Gao of SUNY (Buffalo, N.Y., USA) presented a model for aqueous solutions in which a solute is treated quantum mechanically by AM1, and the solvation is treated by diagonalizing a separate Fock operator for each solvent molecule, using QM/MM methods. This corresponds to a Hartree product wave function. In this model, a gas-phase water molecule has a charge of 1.86 D, and this increases to 2.29 D in solution, in good agreement with the experimentally observed increase in liquid water. The distribution of water dipoles has significant probability over a wide range from about 2.1 D to 2.5 D. This model gets around the problem of defining atomic polarizabilities, which is a critical issue in most previous polarizable-explicit-solvent models.

Eric Glendening of Indiana State University (Terre Haute, Ind., USA) discussed natural energy decomposition analysis (NEDA) for evaluating electrical and charge transfer effects in molecular calculations. He asked questions like; Why is $Ba^{2+}(H_2O)_2$ bent? Why is $(H_2O)_3$ more stable than one would predict from pairwise effects? NEDA decomposes an interaction energy as

$$\Delta E = EL + CT + CR$$

where EL is the electrostatic interaction, CT is a charge transfer component, and CR represents core repulsion; the method may be thought as of as an improved version of Morokuma's older energy decomposition analysis where each fragment is represented by a fully localized wave function, expressed in a natural bond orbital (NBO) basis. A NEDA analysis of $Li^+(H_2O)$ illustrates the method. One finds a charge transfer of 0.006 e from a nonbonding orbital on O to the 2s orbital of Li^+ which is the dominant term in a total charge transfer stabilization of CT = −6 kcal; this is added to EL = −48 kcal and CR = −18 kcal for a total interaction energy of −72 kcal. The CT and CR are large in magnitude only at Li–O distances less than 1 Å greater than the bond length, whereas the EL interaction is long ranged. NEDA is in the General Atomic and Molecular Electronic Structure System (GAMESS computer program package) as of the March-18-97 version, if one adds the NBO 4.0 module available from Frank Weinhold. Why is $Ba^+(H_2O)_2$ bent? Primarily due to EL terms. What causes the 2.5 kcal three-body effect in $(H_2O)_3$? In the NBO-based analysis it is all from CT. However if one bases the NEDA analysis on natural localized molecular orbitals, the effect shows up in ES (in a question from the floor, Keiji Morokuma asked how one can resolve this nonuniqueness – Glendening replied that there is no definitive way to do this, but he prefers the former method because it leads to a simpler picture for many systems).

Peter Politzer of the University of New Orleans (New Orleans, La., USA) showed that the energy of a molecule can be written exactly as a summation over atomic terms (no cross-terms), each of which involves only the electrostatic potential at the nucleus and its derivative with respect to nuclear charge. One can use Hartree-Fock theory to evaluate the electrostatic potential at the nuclei (since this is a one-electron property, Hartree-Fock is more accurate for the property than for total energies) and then use these formulas to obtain more accurate energies than are obtained from the expectation values of the Hartree-Fock Hamiltonian with its corresponding wave function! Politzer also developed correlations between minima in the radial electrostatic potentials of halide ions and their crystal radii and the lattice energies of their salts. Next he showed that the minimum in the electrostatic potential along a straight line between two nuclei in a molecule may be used to define covalent radii. He obtained very reasonable values: 0.415, 0.758, 0.719, 0.682, 0.696, 1.05, 1.01, 0.97, and 1.00 Å for H, C, N, O, F, Si, P, S, and Cl, respectively. This works much better than using minima of the electron density. Finally, Politzer compared the square of the magnitude of the minimum in the electrostatic potential along the straight-line bond path with the bond dissociation energy and found a strong correlation exists over a wide variety of different bond types.

Modesto Orozco of the University of Barcelona (Barcelona, Spain) discussed the role of the electrostatic potential of DNA in drug design. He recommends B3LYP, B3P86, and B3PW91 DFT methods as a reasonable way to obtain accurate electrostatic potentials at reasonable cost. Orozco then studied the use of perturbation theory to solve the Hartree-Fock equations for the polarization energy of a molecule by a set of point charges. He showed that the popular HF/6-31G* method is inadequate to represent the polarization effect in cation interactions with aromatics. In several cases with perturbations in the range 0.1–2 kcal, he found that perturbation theory agrees with full solution of the SCF equations within 0.1–0.2 kcal.

Lionel Carreira of the University of Georgia (Athens, Ga., USA) discussed the SPARC (SPARC Performs Analytical Reasoning about Chemistry) computational approach to structure, electrostatics, and thermodynamics. He treats acid/base sites as parent functionalities (e.g., ammonia, formic acid) that are perturbed by surrounding substitution. The perturbations include those from monofunctional spectroscopic dipoles for inductive and electrostatic effects, augmented by the refractive index as a descriptor for molecular polarizability, Taft-Abraham α,β parameters corrected for steric effects to describe hydrogen bonding, and additional parameters for valence bond resonance. Over a very large test set, he predicts pK_as with an RMS error of 0.4 log units, and he illustrated two cases where accurate speciations for multiple titrating sites were predicted.

Bill Jorgensen of Yale University (New Haven, Conn., USA) presented two applications of a linear response approach to calculating molar free energies of solvation and free energies of binding. [Refs. – Warshel A, et al. (1992) Protein Eng 5: 215; Åqvist J, et al. (1994) Protein Eng 7: 385; Carlson HA, Jorgensen WL (1995) J Phys Chem 99: 10667]. In this approach, using hydration as an example, one assumes that

$$\Delta G_{\text{hyd}} = c_1\langle U_{\text{elec}}\rangle + c_2\langle U_{\text{vdw}}\rangle + c_3 A$$

where c_1, c_2, and c_3 are parameters, $\langle U_{\text{elec}}\rangle$ and $\langle U_{\text{vdw}}\rangle$ are the electrostatic and van der Waals interaction energies between the solute and the solvent averaged over a simulation, and A is the solvent-accessible surface area. In linear response theory, c_1 should equal 0.5. Jorgensen parameterized the model for a small training set in water with HF/6-31G* atomic charges and obtained $c_1 = 0.389$, $c_2 = 0.331$, $c_3 = 0.014$ kcal/Å^2, and a mean unsigned error of 0.73 kcal. Using OPLS-AA charges reduced the mean unsigned error to 0.65 kcal. A good correlation with different coefficients was also found for log $P_{\text{CHCl}_3/\text{H}_2\text{O}}$, where P is a partition coefficient, except for dimethylamine and trimethylamine; in these cases Jorgensen questioned the reliability of the experimental values due to possible protonation in water. Curiously, $\langle U_{\text{elec}}\rangle$ for acetamide dropped from −30 kcal in water to −5.5 in $CHCl_3$. Finally, Jorgensen demonstrated using this approach to predict relative binding free energies for a series of thrombin inhibitors (averaging now over thrombin/substrate interactions) and was able to obtain an average error of 0.8 kcal over seven data points. Clearly the linear-response method is a promising algorithm. As compared to free energy perturbation (FEP) theory it has the following advantages:

1. It yields absolute free energies without annihilating the solute by successive mutations.
2. It is fast – only one Monte Carlo or molecular dynamics run is required rather than a series of perturbation steps; with 500 water molecules one obtains good convergence in ~7 h on a 200 MHz PC.
3. It is easily applied to large solutes; there is less statistical noise for large differences as compared to the many windows needed for FEP.

But there are also disadvantages, chief among which are:

1. There is no rigorous justification.
2. One needs to reparameterize c_1, c_2, and c_3 for each new solvent.

Anthony Nicholls of OpenEye Scientific Software (Sante Fe, N.M., USA), discussed grid-based solution techniques for the Poisson equation in a nonhomogeneous medium such as is used to model electrostatic effects in small molecules and proteins. He showed that the numerical solutions converge much faster when the unrealistic model of a discontinuous dielectric constant is modeled more realistically with a gaussian switching function that changes over a range of about 1–1.5 Å.

Eugene Stefanovich of the University of Utah (Salt Lake City, Utah, USA), in a paper co-authored with Thanh Truong, proposed a method for incorporating a Madelung potential in quantum mechanical calculations of adsorbates and absorbates on and in solid lattices by the embedded cluster method. First the Madelung potential is converted to Ewald form. This potential is then represented by a set of discrete charges on the surface of the embedded cluster. After this all matrix elements of the Madelung potential between embedded cluster orbitals are evaluated using the discrete charges. The method is accurate and fast. It is particularly useful for zeolites where it is hard to define physical truncated lattices.

Electrostatic effects in small molecules

B. Govinda Rao of Vertex Pharmaceuticals, Inc. (Cambridge, Mass., USA), in a paper co-authored by Mark A. Murcko and U. Chandra Singh, discussed the effect of electrostatics on the free energy difference between a peptide and its ester analog acting as enzyme inhibitors for HIV protease. The amide was treated most accurately with unscaled HF/6-31G* charges, but the ester was treated better by scaling down the HF/6-31G* charges. Rao pointed out that this ad hoc treatment of electrostatics is limited to cases where one knows the answer beforehand, and that more study is needed to see if more general rules can be developed.

Jean-Louis Rivail of the Université Henri Poincaré (Nancy, France) discussed the role of solvation in chemical reaction rates. He pointed out that when solute-solvent coupling is strong, nonequilibrium electrostatic effects may be important. He attempted to model these effects by a QM/MM formalism with the TIP3P force field for aqueous solvent and a DFT treatment of the solute. He found that the electric field in the relaxation of a nonequilibrium conformation of HOD...OH^- equilibrates on a time scale of 0.6 ps, which is more than an order of magnitude faster than the computed dielectric relaxation time of 8.0–8.5 ps. This may indicate a solvent cage effect. He also considered the reaction $Br_2 + C_2H_4 \rightarrow Br^- + C_2H_4Br^+$, which shows strong solvent effects on the rate. His simulation in water showed that the reaction rate is 0.44 times the rate calculated for equilibrium solvation of the gas-phase saddle point.

Dennis Dougherty of Caltech (Pasadena, Calif., USA) described cation-π interactions between aromatic rings and small cations (e.g., Na^+ or $NH_4{}^+$). These interactions are quite strong and can even be used for the molecular recognition of cations by organic hosts in aqueous media. In biological systems, the interaction is used in many protein systems, including acetylcholine binding sites, potassium channels, *S*-adenosylmethionine binding sites, and steroid biosynthesis. Dougherty found that the strength of binding in the gas phase (as measured by correlated ab initio calculations) could be correlated linearly ($R^2 = 0.99$) with the electrostatic potential of the aromatic system at the cation binding site (measured without the cation present). Dougherty pointed out that one could invoke a charge-quadrupole formalism to describe this interaction, and, if one adopts such an approach, that one can envision tuning aromatic quadrupoles for π-stacking of aromatic systems. He showed that molecules containing both phenyl and perfluorophenyl functionality stack strongly because the two quadrupole moments are opposed, and strong interaction permits unique crystallization motifs having potential application in the generation of polyacetylenic materials.

John Shelley of Proctor & Gamble, in a paper co-authored by Michiel Sprik (Cambridge) and Michael Klein (University of Pennsylvania), discussed molecular dynamics simulations of electrostatic effects within interfaces of sodium octanoate micelles in water. To model the polarizability of the octanoate, each atomic or group site is augmented by two additional sites which can rotate around their parent site and which can assume equal and opposite charges. The interface between the water and the octanoate is very thin, about the width of a CH_2 group. The only difference between the nonpolarizable and polarizable models is that the polarizable model shows a shell of water between the Na + counterion distribution and the carboxylate head groups in better agreement with experiment. For the two systems studied, globular and columnar micelles, which result respectively from low (0.6 M) and high (3.0 M) concentrations of sodium octanoate, the net electrostatic potential drop through the interface is quite similar despite the fact that the contributions to this potential from the different types of charged species in the system differ considerably. The results were interpreted in terms of an effective charge density calculated from the true charge density and the divergence of the polarization, and this effective charge density shows a clear double layer at the interface.

Biopolymers

The final major theme of the symposium was the role of electrostatic effects in DNA and proteins.

Jerry Manning of Rutgers University (New Brunswick, N.J., USA) discussed solutions of polyelectrolytes, i.e., linear polymers with multiple charges, such as DNA and RNA with their phosphate groups. He defined a dimensionless parameter

$$\xi = \frac{q^2}{DkTb}$$

where D is the dielectric constant, q is the charge at each charged site, and b is the distance between charges on the polyion. Note that $\xi = 4.2$ for B-form DNA under physiological conditions. For $\xi > 1$, his extension of Debye-Hückel theory indicates that there is a stable equilibrium state at $\theta = 1 - 1/\xi$, where θ is the fraction of charges on the polyion that have condensed counterions. The presence of a second polymer chain influences both θ and the structure of the condensed layers. For two close polymers, θ tends to $1 - 1/2\xi$. The potential of mean force between the polymers shows a minimum at intermediate separations (~50 Å for DNA) due to an increase in the partition function of the condensed layer. This may be visualized as a merging of the two counterion sheaths into a single large-volume sheath surrounding both polymers (with a corresponding gain in entropy). This effect leads to clusters of polymers, but eventually it becomes more repulsive to add even more polymers to the cluster. It is important to note that these counterion effects would not be predicted by a mean-field theory like the Poisson-Boltzmann equation.

An interesting question that was asked in response to Manning's talk is, "Does the sheath of counterions around DNA have to be taken into consideration?" Manning's answer was that it depends on the property under consideration. Clearly it is important for the interesting effects in his talk. In contrast, though, in the talk by Shelley (see above), it was reported that for charged micelles the counterion sheath has little influence on quantum mechanically determined properties like the fractional atomic charges and polarizabilities, and Manning suspects that the same is true for polynucleotides – the condensed counterions are close, but not that close, to the atoms of the macro-ion. On the other hand, how can one know, unless, like Shelley, Sprik, and Klein, one does the computation?

Weitao Yang of Duke University (Durham, N.C., USA), in a paper co-authored by Taisung Lee and Darrin York, discussed divide-and-conquer numerical methods for MOPAC/COSMO calculations on proteins and DNA. Polarization of the solute by the solvent increases the solvation free energies of proteins by about 10%, but the value for DNA is only about 2%, in part because the solvation free energy for the polyion is dominated by the ionic terms.

Elizabeth Getzoff of the Scripps Research Institute (La Jolla, Calif., USA) discussed electrostatic tuning of protein function and specificity, focusing on how three-dimensional charge arrangements promote molecular recognition, diffusion, catalysis, protein conformational changes, and specificity of binding. In the case of copper-zinc superoxide dismutase, Getzoff used site-directed mutagenesis in conjunction with electrostatic potential calculations to demonstrate how the superoxide anion radical is drawn into the active site along a protein-generated "highway" of positive potential. Mutation of critical positively charged residues to neutral amino acids severely slowed down enzyme activity, and mutation to a negatively charged residue eliminated activity completely. Getzoff also emphasized the importance of arginine as an active site residue owing to its flexibility. In the case of sulfite reductase, she discussed how the guanidinium group of Arg moves to different locations depending on the nature of the bound substrate.

Donald Hilvert, also of Scripps Research Institute, discussed similar effects for the case of chorismate mutase, which catalyzes the first committed step in aromatic amino acid biosynthesis. In particular, Hilvert emphasized that favorable electrostatic interactions, rather than the entropic effects usually considered to be important for this reaction, can account for most of the large rate enhancements achieved by the natural enzyme. Catalysis, in this instance, is provided by the electrostatic complementarity being higher for the transition state structure, which is dissociative in character, than for the reactant geometry. Hilvert demonstrated some of the important electrostatic interactions in chorismate mutase by generating double-substitution mutagenic combinatorial libraries, analyzing them by genetic selection in vivo, and subjecting individual variants to detailed kinetic characterization in vitro. He emphasized that by computing electrostatic interactions in known enzymes, it should be possible to design tighter binding inhibitors and improved haptens for raising catalytic antibodies for desired reactions.

Minoru Saito of Real World Computing Partnership (Ibaraki, Japan) described protein simulations with long-range electrostatics using the particle-particle/particle-cell (PPPC) method that he developed for protein simulations without cutoffs in 1990. This method is based on Barnes and Hut's no-cutoff simulations of gravitational N-body systems (such as nebulae) published in 1986 in Nature, and it provides an interesting alternative to Greengard's cell-multipole method (based on Greengard and Rokhlin's fast multipole method, also published in 1986) that was proposed for molecular dynamics calculations around 1992. These methods for avoiding cutoffs have already had a tremendous impact on the field of molecular simulations. In Saito's presentation, he examined the effects of single-site mutations on unfolding free energies (with separate simulations on the complete protein and on small fragments of random structure incorporating the residue of interest) by assuming a standard relationship between protein melting temperature and the free energy for unfolding. For mutants of the protein RNAse H1, the derived changes in melting temperatures correlated extremely closely with experiment. In addition, pK_a shifts for titrating residues were well reproduced in RNAse H1 – in contrast with methods using electrostatic cutoffs in the simulation, where errors of 17 pK units were found.

Bo Jönsson of Lund University (Lund, Sweden) presented a Monte Carlo method for determining the chemical potential of charged particles modeled as charged spheres in a uniform dielectric medium. With this model, he calculated the binding of Ca^{2+} to small chelators and the calcium-binding proteins calbindin (75 residues, net charge −8), subtilisin, and calmodulin, and fragments thereof. When external monocharged salt concentrations were varied over 1 M in concentration, good agreement in binding constants was observed for the Monte Carlo approach, Poisson-Boltzmann modeling, and Debye-Hückel theory (provided an interior dielectric constant of 78.3 is chosen for the protein). However, when salts of higher charge were included, only the Monte Carlo method successfully predicted the correlation between doubly-charged ions. Calculations of pK_as for the basic residues in calbindin were also presented and compared to experimental values for both the apo and the calcium-binding form at different protein concentrations. The pK_a shifts were correctly reproduced, and the absolute differences between experimental and theoretical numbers were of the same magnitude as for calcium-binding shifts, although the relative differences were larger.

Norma Allewell of the University of Minnesota (Twin Cities, Minn., USA) and Michael Gilson of the Center for Advanced Research in Biotechnology (Rockeville, Md., USA) both discussed problems involving the use of the Poisson-Boltzmann equation to estimate pK_a values of ionizable residues in proteins. These differ from pK_a values in water because of three effects: desolvation, interaction with polar sites in the protein, and interaction with other ionized sites. Allewell used her calculations to show how a network of interacting ionizable groups allows nucleotide binding to aspartase transcarbamylase protein to be influenced by the binding of a substrate or inhibitor nucleotide very far away on the opposite side of the protein. Best agreement with experiment was achieved for an interior dielectric constant of 25 in the protein. Michael Gilson focused on the protonation states of a critical aspartyl dyad in HIV-1 protease. He found that for the free protein, the calculated pK_a values of the aspartyls are rather insensitive to the dielectric constant assigned to the molecular interior, and agree well with experiment. In contrast, when an inhibitor is bound to the protease, the computed results change by many log units when the dielectric constant is varied in the range 4–20. However, new experimental data on the variation of K_i with pH cast doubt upon previous experimental data on the aspartyl pK_as of the complex. As a consequence, it is currently impossible to determine the accuracy of the calculations for the complex.

Arieh Warshel of the University of Southern California (Los Angeles, Calif., USA) discussed the fact that the dielectric constant in semimicroscopic continuum models of proteins reflects protein reorganization effects that are not explicitly included in the given model. Warshel concludes that charge-charge interactions are damped out quickly in a protein because of the dipolar reorientation of the protein groups and water molecules, but since most protein models do not include the reorganization of the protein polar groups, the use of a large dielectric constant is phenomenologically required to rectify this inadequacy. Warshel demonstrated that the use of his linear-response approximation (LRA) treatment allows him to obtain accurate electrostatic energies in proteins while using a small "dielectric constant." This is due to the fact that his model takes into account the main contributions explicitly. Warshel demonstrated that his Semi-microscopic Protein-Dipoles-Langevin-Dipoles LRA treatment is applicable to a wide range of electrostatic properties in proteins, in particular pK_as, ligand binding, and redox potentials. He particularly focused on charge-charge interactions in proteins by taking the bacterial reaction center as a test case and demonstrating how the LRA treatment leads to reduction in the calculated charge-charge interaction free energies.

David Chatfield of Florida International University (Miami, Fla., USA), in a paper co-authored by Bernie Brooks and Attila Szabo (NIH), discussed motional parameters for staphylococcal nuclease calculated from an 18 ns MD simulation and measured with NMR, in light of the importance of electrostatic interactions in modulating the dynamics of protein backbone and sidechain motions. An exceptionally long equilibration period of 4 ns followed by an 11-ns period of stability characterized the simulation. The most significant conclusions were that a discrepancy between simulation and NMR suggest revisiting NMR-measured order parameters for alanine and leucine sidechain motions, and that the simulation's wide range of relaxation times for methyl rotations may be indicative of microstates not resolved on the NMR time scale.

Jeff Madura of the University of South Alabama (Mobile, Ala., USA) obtained good agreement with experiment for a Poisson-Boltzmann model of a 42-residue α-helix and a 66-residue globular protein. A key feature of this work was the application of a new method to compute the electrostatic component of the gradient for molecular degrees of freedom.

Conclusion

The symposium organizers were satisfied that the 3-day event provided a reasonable snapshot of the current status of activity in electrostatic modeling. Acknowledgment is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this conference.

Invitation to readers:

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