

## Chapter 1

# Structure and Reactivity in Aqueous Solution

### An Overview

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This introductory chapter provides a brief overview of the current state of the art in understanding and modeling structure and reactivity in aqueous solution. The contents of the chapters found in this book are discussed and areas where theory and experiment are working in tandem are highlighted.

Water is a remarkable substance. It covers two thirds of the Earth's surface, it makes up a large fraction of the total mass of biological organisms, it serves as the solvent in which essentially all biochemical reactions take place, and it's enthalpic and entropic characteristics repeatedly set it apart from other liquids (1). It is thus hardly surprising that chemists with an interest in the role that solvent plays in determining structure and reactivity devote themselves to aqueous solutions more than any other kind.

For theorists in particular this has been the case. Relative to modeling in the gas phase, it is only recently that theoretical techniques capable of simulating condensed phase chemistry have been developed. There are two complementary approaches which may be taken to modeling a solute embedded in a solvent. One is the quantum mechanical continuum approach (2-6) where the solvent is replaced by a continuous medium having the same dielectric constant as bulk liquid. This is a mean-field approach in which the solute polarizes the bulk medium, which back-polarizes the solute, etc.—a physical picture dating back to Onsager (7-9). In Chapter 2, the historical development of one such model is detailed by Tomasi, with special attention paid to algorithmic details. In addition, the present directions in which the model is expanding are detailed, including techniques to separate the continuum into fast and slow components for dynamical studies and methods for incorporating local anisotropy into the continuum model.

One significant drawback of any pure continuum approach is that the solvent bulk dielectric constant does not accurately describe the electric polarization field right up to the molecular "surface". Instead, the interaction of a solute with at least the first solvation shell is typically characterized by specific local energy components. One method which has been explored to address this is the assignment

of local surface tensions to specific regions of the molecular surface (10-13). Chapter 3 by Storer *et al.* describes continuum solvation models incorporating such local effects. In addition, it provides specific details of the algorithms required to accurately account for dielectric screening, an important effect whereby the interaction of one portion of the solute with the surrounding continuum is mediated by the intervention of remaining portions of the solute. Finally, this chapter presents an example of using Specific Range Parameters for the modeling of particular chemical reactions, in particular for the study of the effect of solvation on the Claisen rearrangement, a reaction that several other chapters in this symposium also discuss (*vide infra*).

The interaction energy of a set of charges with a surrounding dielectric medium may be found by solution of the Poisson equation (14-17). When the continuous charge density of a molecular solute is replaced by a collection of point charges, the solution of the Poisson equation becomes more facile; however, there are ambiguities involved in modeling a continuous charge density with point charges. There are also inherent ambiguities in defining the dielectric boundary between the solute and the solvent. In Chapter 4 Lim *et al.* discuss the use of calculated quantum mechanical densities for the evaluation of these quantities, and they present results for the solvation free energies of a number of ions and organic molecules. Tawa and Pratt present a similar Poisson equation derived formalism in Chapter 5, where they calculate the aqueous solvent-induced potential of mean force for the dissociation of sodium chloride and for nucleophilic substitution and addition reactions. Tawa and Pratt compare their calculations to other models where solvent has not been replaced by the mean-field continuum.

This alternative approach, i.e., representing the solvent in its discrete, molecular form, allows investigation of the microscopic details of solvation. It has been the case so far, though, that the number of solvent molecules that must be included to adequately model bulk solvation for a given solute is so large that a quantum mechanical treatment of the system has been prohibitively difficult. Instead, the solute-solvent and solvent-solvent interactions have been modeled classically using empirical force fields (18-24) or—very recently—a combination of such a force field with terms representing polarization of the water molecules. By using such a force field and following the trajectory of the system over time (25-28), it is possible to calculate dynamical properties or time-averaged equilibrium properties, or Monte Carlo methods (22,29) may be used to obtain equilibrium properties. Clementi and Corongiu discuss in Chapter 7 the step-by-step development of a force field that has been designed to reproduce numerous static and dynamical properties of flexible water over a sizable temperature range. Nyberg and Haymet analyze in Chapter 8 a more complete model for liquid water in which the force field permits dissociation (accompanied by ionization) of individual water molecules. They compare their results to other models with respect to predicting the pH of liquid water. Finally, in Chapter 22 Van Belle *et al.* present calculations with polarizable water molecules (*vide infra*).

Nonequilibrium solvation can be critical for many processes, e.g., electron transfer (30) and spectroscopy (31). If the effects of solvation can be modeled as an extra, general coordinate on a solute potential energy surface, it becomes

straightforward to extend dynamical studies from the gas-phase into solution (32-35). Using an approach which permits the separation of equilibrium and nonequilibrium components of aqueous solvation, Garrett and Schenter examine in Chapter 9 the radical addition of hydrogen atoms to benzene. In particular, they use variational transition state theory (36) to calculate kinetic isotope effects (KIEs) and explore solvent-induced changes in the KIEs for deuterium and muonium. Ando and Hynes also adopt this generalized coordinate approach in Chapter 10, where they consider the aqueous ionization of hydrochloric acid. In particular, they assess the importance of nonequilibrium microsolvation in the proton transfer from HCl to a water molecule and the subsequent separation of the two ions. This same system is also studied by Rivail *et al.* in Chapter 11 using a quantum mechanical continuum model with either one or two explicit water molecules. In addition to providing this stimulating study which the reader may compare to the work of Ando and Hynes, Rivail *et al.* also explore the hydrolysis of formamide in aqueous solution, again focusing on the details of those specific water molecules that are not part of the bulk solvent but are instead involved in the reaction itself. A third subject addressed in this chapter is a comparison of the properties of an isolated water molecule, a water molecule in the water dimer, and water in the bulk.

These various methods for modeling aqueous solvation provide considerable flexibility to researchers probing specific chemical problems. One area of particular interest is understanding how aqueous solvation affects organic reactions (37,38). In Chapter 12, Bertrán *et al.* use various solvation models to study the effect of solvation on several organic reactions, paying particular attention to the location of the transition state along the solvated reaction coordinate and the degree to which nonequilibrium solvation effects must be included in solvation modeling.

Ultimately, some of the most interesting organic reactions occurring in aqueous media are those involving biological macromolecules. In this latter area, Warshel has explored many models for aqueous solvation (27,39) as it affects enzyme-mediated reactions. In Chapter 6, Warshel and Chu summarize their experience with numerous macroscopic (e.g., continuum), microscopic (e.g., discrete), and microscopic/macroscopic hybrid water models. In particular, they consider the balance between quantum and classical mechanics strategies and examine some of the algorithmic details of model implementation.

One possibility discussed by Warshel involves the replacement of explicit solvent molecules with pseudopotentials. Gordon and co-workers have also been active in this area (40)—their approach divides microsolvated clusters into a “solute” (potentially supermolecular) and a set of water molecules with which it interacts. The solute is treated quantum mechanically; the “spectator” region is modeled using pseudopotentials developed to accurately reproduce electrostatic, polarization, and exchange repulsion interactions in prototypical systems.

The marriage of quantum mechanical and classical mechanical treatments, where the former is applied to the solute and the latter to the solvent, is also a subject of much interest (27,41-44). In Chapter 15, Gao applies such a strategy to the Claisen rearrangement, already discussed in Chapter 3, and to the Menshutkin nucleophilic substitution reaction. In addition, Gao extends a classical water model

into the supercritical regime in order to examine the change in the potential of mean force for ion-pairing in sodium chloride. Tucker and Gibbons also consider supercritical water in Chapter 14, where they consider the hydrolysis of anisole in supercritical solvent. They illustrate that clustering of the solvent is an important phenomenon such that local dielectric constants may deviate significantly from the bulk value above the critical point.

The selectivity of biologically important reactions, like those mediated by enzymes, depends in part on the ability of macromolecules to recognize the structure of their often complicated substrates (45). As such, it is of considerable interest to examine how aqueous solvation affects conformational equilibria. Venanzi *et al.* consider this issue for a diuretic acylguanidine, amiloride, in Chapter 18. They additionally extend their studies into the regime of molecular recognition and present results for the hydrolysis of phenyl acetate in aqueous solution both as a free substrate and as a guest in a  $\beta$ -cyclodextrin host.

The contribution by Wilcox *et al.*, chapter 19, also considers molecular recognition, and it includes a description of their synthetic design of cyclic polyaromatic receptors capable of transporting hydrophobic substrates into aqueous solution. In particular, they provide microscopic and thermodynamic analyses of host-guest interactions and illustrate the synergy between synthesis, spectroscopy, and molecular modeling in their experimental design.

Gajewski and Brichford, in Chapter 16, also combine experimental data and statistical modeling in an examination of the effects of solvation on the Claisen rearrangement. Their combination of kinetic isotope effect measurements and factor analysis using a variety of solvent descriptors provides a unique perspective which may be compared to the theoretical modeling of Chapters 3 and 15. Severance and Jorgensen provide a fourth perspective on the effect of solvation on the Claisen rearrangement. In Chapter 17, they employ Monte Carlo statistical mechanics simulations (29) with a classical water model. In particular, they consider in detail the effects of multiple conformational minima for the reactant allyl vinyl ether and examine the microscopic solvation of the gas-phase reaction coordinate. Comparison of these four studies of the Claisen rearrangement gives rise to a detailed understanding of the reaction as it occurs in water and moreover serves to illustrate the individual strengths and weaknesses of the various methods employed. This comparison is summarized in Chapter 3.

In Chapter 20, Breslow considers the effect of aqueous solvation on a different pericyclic process, the Diels-Alder reaction. This chapter discusses the experimental rates for several Diels-Alder reactions in the presence of various salts designed to tighten or disrupt internal water structure. In addition, other organic reactions and molecular recognition events are examined under the same conditions. Blokzijl and Engberts, in Chapter 21, offer additional experimental insights into aqueous acceleration of the Diels-Alder reaction by comparing inter- and intramolecular variants of the cycloaddition. They examine in detail the enthalpic and entropic components of the acceleration and identify both the reduction in hydrophobic surface area and the possibility of enhanced solute-solvent hydrogen bonding in the transition state as being critical to the observed rate accelerations.

As part of their explanation for aqueous acceleration of the Diels-Alder reaction, Breslow and Blokzijl and Engberts invoke the tendency of non-polar solutes to associate in order to minimize their exposed surface area in aqueous solution (46-48). In Chapter 22, Van Belle *et al.* examine this hydrophobic interaction in detail using a simulation model that includes the polarization of discrete water molecules. They examine in particular the potential of mean force for the association of two methane molecules in water and find no evidence for a solvent-separated minimum, in disagreement with several prior studies that did not account for polarizability of the water molecules. Another particularly interesting result of their study is the reduced dipole moment of water molecules within the first two solvation shells of the methane solutes. This result has important implications for the dielectric continuum models discussed elsewhere in this volume. In Chapter 23, Hermann examines the interaction of hydrocarbons in aqueous solution using a decomposition of the free energy of solvation into a cavity-surface-tension contribution and a contribution calculated from configurationally averaged solute-solvent interaction potentials. In addition, comparisons between explicit-solvent molecular dynamics calculations and the results from transferable fragment solvent-distribution functions are offered.

The hydrophobic effect manifests itself for situations other than hydrocarbon-water and hydrocarbon-hydrocarbon interactions. Importantly, it appears to play an important role in dictating the folding and higher-order structure of proteins (49,50). Understanding and predicting the structure and dynamics of proteins is of great interest. In Chapter 13, Gai *et al.* provide experimental details of the aqueous photophysics of 7-azaindole, a potentially useful surrogate chromophore for tryptophan which would permit the observation of short-time scale dynamics when incorporated into enzymes. Scheraga discusses in Chapter 24 theoretical approaches to predicting protein structure. In particular, continuum solvation techniques employing terms depending on either solvent shell volume or solvent-accessible surface area are presented; calculated and measured thermodynamic values are compared for the interaction of individual amino-acid residues and generic organic functionalities. Using molecular simulations, Ben-Naim also considers the interaction of specific protein residues in Chapter 25. This chapter concludes that solvent-induced attraction between hydrophilic groups can be stronger than that between hydrophobic groups, suggesting that surface tension models which are based on the positive values observed for hydrocarbons may be insufficiently flexible to model the solvation of more complex functional groups.

Chapter 26 describes the modeling of a different kind of biopolymer in water, namely DNA; Beveridge *et al.* describe a full nanosecond simulation of a dodecamer double helix in aqueous solution and analyze the effect of solvation and of complexation with a repressor-operator protein on the structural dynamics. They find a number of structures which exhibit metastability over periods of hundreds of picoseconds, suggesting that the dangers of short simulation times for biomolecular systems are significant. In Chapter 27 Pohorille and Wilson also explore a large biologically relevant system. They use molecular simulation to study the interaction of a model dipeptide with a glycerol 1-monoleate bilayer. The degree to which the dipeptide penetrates the interfacial region between the solvent and the bilayer is

explored, as are the differential dynamics of the dipeptide surrounded by water compared to inside the bilayer.

Finally, Chapter 28 provides an additional perspective on an interfacial system; Benjamin uses molecular simulation to analyze the dynamics of electron transfer from liquid water to an adjoining 1,2-dichloroethane phase. The overall relaxation dynamics in response to a photochemically induced electron transfer event are found to depend on each of the two solvents and their different respective time scales.

In summary, aqueous solvation plays an important role in diverse systems of great chemical importance. This volume attempts to provide as wide a perspective as possible (in a four-day symposium) in this regard. We have reached a stage where theory and experiment may be used in conjunction, complementing each other's strengths and weaknesses, so as to illuminate chemical phenomena at a greater level of detail than would be possible from either one alone. We sincerely hope that some of the examples of this synergy that are provided in this book will stimulate further collaborations in this regard.

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