MOLECULAR SIMULATIONS TO STUDY THERMODYNAMICS OF
POLYETHYLENE OXIDE SOLUTIONS

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For The Degree
Of
Doctor Of Philosophy

By

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Abstract

Polyethylene oxide oligomers are intrinsic to Corexit oil dispersants used in response to the Deepwater Horizon accident at the Macondo well in the Gulf of Mexico (2010). PEO chains are fragments of nonionic surfactants used. Versatile PEO oligomers also exhibit thermodynamically interesting and complicated closed loop phase diagrams.

Oil spill dispersants are produced in bulk and stockpiled near the potential oil spill locations for several years. Effective thermophysical modeling of these dispersants should assist the application of lab-scale results to ocean-scales. Construction of reliable thermophysical models demands molecular-scale structural and phase behavior data. Fully defensible molecular-scale theory of such complex materials will be challenging. This thesis is an initial step toward that challenge.

We study here telechelic, primarily methyl-capped, PEO oligomers but we also anticipated variations in capping groups and chain lengths. End-to-end distance distributions of aqueous single PEO chain solutions provide more information on conformations than conventional radius of gyration distributions. Closed loop phase diagram of these polymers is often attributed on hydrophobic attractions present in these polymers. End-to-end distance distributions, obtained here, confirm those interactions in an experimentally accessible context. Indeed those interactions can be targetted by neutron scattering experiments to gather experimental data on these polymer solutions. Simulation results below on these PEO solutions thus identify direct experimental observation of hydrophobic interactions.
The only available molecular scale theory of hydrophobic interactions — the so-called Pratt-Chandler theory — has never been tested with direct numerical simulation results for the hard-sphere solute cases on which the theory was founded. Second virial coefficient calculations of Ar-sized hard spheres are obtained here for the first time, and directly compared with the results of the PC theory. The required calculations and extensive cavity search was never before attempted for this purpose, and this work provides world’s best data on Ar-sized cavity pair distribution functions in water at several temperatures.

The Flory-Huggins model is a universally used molecular-model of the phase behavior of polymer solutions. It has been experimentally established that the Flory-Huggins interaction parameter ($\chi$) is operationally concentration dependent for PEO (aq) systems, in direct contradiction to the statistical thermodynamic justification of that theory. In the research below, we develop the more general theory for the concentration dependence of the Flory-Huggins $\chi$ parameter. Our theory also provides the osmotic pressure of these solutions, a point that has not been noted before, and this additional information should be valuable in a much broader context. We then carry-out molecular simulations of PEO(aq) solutions to evaluate the more general theory. Our analysis and results identify an unexpected phase separation for $\text{CH}_3(\text{CH}_2-\text{O-CH}_2)_m\text{CH}_3$ ($m=11$) with coexisting oligomer volume fractions $(1 - \varphi) \approx (0.21, 0.91)$ at $T = 300$ K and $p = 1$ atm. Direct observation of the coexistence of these two phases then supports the correctness of the analysis for the systems studied.
MOLECULAR SIMULATIONS TO STUDY THERMODYNAMICS OF
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A DISSERTATION

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Chapter 1

Background

1.1 Oil Spill

The Deepwater Horizon accident of April 2010 is the underlying motivation for this research. After the disastrous oil spill we decided to study these PEO polymers in context to dispersants used in oil spill remediation. The Macondo well blowout gushed millions of gallons of crude oil into the Gulf of Mexico affecting all Gulf coast states. Swamps, supporting diverse flora and fauna, were layered with brown oil. Birds, fish and others were threatened by this spill.

The extreme pressures and the inaccessible location made troubleshooting operations technologically challenging and complicated. Several ideas were tried to cap the well to shut down the flow of oil. Capping with a big dome failed due to hydrate formations 5000 ft below sea level. Dumping junk and mud into the blowout pipe did not withstand the high pressure of the oil flow but capping with a hat and collecting oil onto the surface was partially successfully. Use of chemical dispersants at the surface and directly at the well-head was effective in reducing visible oil at the surface. Ultimately, after 87 days and estimated 4.9 million barrels of total oil discharge, British Petroleum (BP) installed a new blowout preventer to shut down the flow of oil completely.
British Petroleum tried several containment techniques to deal with oil which escaped to the surface thereby preventing some of it from reaching shore. Controlled burning was tried at initial stages of spill but later ruled out due to the size of spill. Containment booms — floating barriers used to concentrate surface oil — were ineffective in the ocean conditions of the Gulf of Mexico but were useful in calm water conditions of lakes and swamps. The oil spill dispersants functioned effectively for this spill. BP not only sprayed several millions of gallons of dispersant materials at the surface but also pumped it directly into the blowout location 5000 ft below sea level. Although, not designed for deep sea applications, natural currents and flow of oil improved their efficiency.

These surfactant mixtures break the large oil droplets into smaller droplets, creating oil-in-water emulsions that can carry oil deep into the ocean. A silver lining in this disaster was that this spill happened in Gulf of Mexico where wide range of oil-eating bacteria are present. Bacteria such as nematode and protozoa in sub-sea levels colonize on these emulsion droplets and use oil, as well as dispersant materials (FIG. 1.1), as a source of energy, breaking large organic compounds into smaller degradable fractions. The entire process usually takes approximately 4-6 weeks after initial application, depending on concentration of the bacteria. The application of dispersants is time sensitive and dispersants are most effective if applied within 48-72 hours after initial spill otherwise oil spreading over a larger area decreases dispersant efficacy.

1.1.1 Dispersants

Corexit EC9527A and Corexit 9500 were the dispersants used in response to this oil spill. Corexit EC9527A consists of 2-butoxy ethanol (a known carcinogen), small concentration of propylene alcohol and NALCO’s proprietary sulphonate surfactant. Debate over toxicity issues centered on 2-butoxy ethanol and use of less toxic
substitutes to corexit EC9527A. Corexit 9500 is a mixture of sorbitan, butanedioic acid, and hydrogenated light petroleum distillates with dioctyl sodium sulfosuccinate (Aerosol OT).

FIG. 1.2 is a cartoon of these dispersants showing nonionic tween surfactants with their polyethylene oxide chain backbone. Corexits — Environment Protection Agency (EPA) approved oil spill dispersants — were developed in 1980’s and used prominently in the Exxon Valdez oil spill and deepwater horizon oil spill. Although not designed for deep sea applications, approximately 0.8 million gallons of these chemical dispersants were applied directly into the well-head location. As stated earlier, due to presence of potential carcinogenic materials these dispersants were questioned for their toxicity but non-ionic, food grade emulsifiers (Tween and Span surfactants) were excluded from this debate. We might not use these Corexits dispersants in future spills but we will definitely use nonionic surfactants present in these materials.

Oil spill dispersants undergo demanding effectiveness approval processes and
successful dispersant materials are often produced in a bulk and stockpiled near potential oil spill locations for several years. We believe that effective thermo-physical modeling of these dispersants materials is necessary to transform lab-scale results into ocean-scale applications. We need to understand phase behavior and configurations of these dispersants in polar and non-polar solvents to develop full defensible molecular level theory. This thesis would be a initial step towards molecular-scale understanding of structure and phase behavior of dispersants. Results discussed in this thesis will motivate researchers to develop molecular level theory that can be utilized in developing novel oil spill dispersants. We selected polyethylene oxide (PEO) oligomers as models and perform molecular simulations. The main reason behind selecting this polymer is because it is intrinsic to non-ionic part of oil spill dispersant (Fig. 1.2). These polymers show interesting closed-loop phase behavior in water and experimentalist often struggle to explain concentration dependence of Flory-Huggins interaction parameter for these polymers. In this thesis, we used molecular simulations to answer some of these experimentally challenging questions. Accurate phase behavior and structural analysis of these polymers will affect designing of next-generation oil spill dispersants. There are several other reasons for choosing this polymer for this study and they are discussed in the next section.

1.2 Polyethylene oxide

Polyethylene oxide (PEO) is a well known widely used polymer. This is the most widely studied synthetic polymer in biology and chemistry. PEO is also known as polyethylene glycol (PEG) or polyoxyethylene (POE) polymer based on molecular weight. PEO polymers are commercially available in variety of molecular weights ranging from 300-100,000,000 g/mol. Hydrophilicity and viscosity of ethoxylated surfactants increases with increase in ethoxylation. This technique is used
effectively in designing nonionic surfactants with particular hydrophobic lyophobic balance (HLB) for specific application. PEO polymers are available as branched and linear polymers. High purity, mono-disperse PEO polymers are difficult to produce and are expensive. Recently, it was observed that high purity PEO polymers are crystalline in nature when observed through X-ray diffractometer. PEO is soluble
in water, methanol, ethanol, dichloromethane, benzene and acetonitrile but insoluble in hexane and diethyl ether.\textsuperscript{[8]}

### 1.2.1 Production

PEO chain molecules are commercially produced by polymerization techniques. These reactions require an initiator and typically mono-functional methyl-ether or methoxy-polyethylene glycol is used.

\[
\text{HO-CH}_2\text{CH}_2\text{-OH} + (\text{CH}_2\text{OCH}_2)_n \xrightarrow{\text{acidic/basic catalyst}} \text{HO- (CH}_2\text{OCH}_2)_{n+1}\text{H} \quad (1.1)
\]

This reaction may be carried out with either acidic or basic catalyst and water, and ethylene glycol or ethylene glycol oligomer. Ethylene glycol is preferred as starting material with alkali catalysts to obtain polymers with low polydispersity. This reaction is exothermic and the alkali catalysts used are NaOH, KOH and Na\textsubscript{2}CO\textsubscript{3}.

### 1.2.2 Thermodynamics

PEO polymer solutions are thermodynamically interesting due to the common occurrence of close-loop phase diagrams that occur with aqueous PEO solutions, PEO in ionic liquids and polymer blends.\textsuperscript{[12[14]} Typically, PEO polymers are soluble at low temperatures but form a separate phase at higher temperatures, then become miscible again at yet higher temperatures (FIG. 1.4). A distinct polymer-rich phase is stable between a lower critical solution temperature (LCST) and upper critical solution temperature (UCST) which are molecular weight dependent for PEO polymers. Reasons for these close-loop phase diagrams have been debated, but include: (a) the size of the chain molecule and the effect on the entropy of mixing, (b) hydrogen bonding characteristics of water and (c) van der Waals attractions.\textsuperscript{[13[15[17]} Although, PEO polymers do participate in hydrogen bonds, some of the debate centers on whether they aggregate in the aqueous environment.\textsuperscript{[18]} At low temperatures, hydrogen bonds
and van der Waals attractions compete with each other. The demixing is dependent on temperature but as the temperature increases, favorable hydrogen bonds evidently become stronger and mixing dominates. This phase behavior of PEO polymers is exploited in designing non-ionic surfactants for a variety of applications and is typically characterized by determining the cloud point.\textsuperscript{10}

![Closed loop phase diagrams of aqueous solutions of PEO](image)

**Figure 1.4:** From Dormindontova,\textsuperscript{14} closed loop phase diagrams of aqueous solutions of PEO. Experimental data is represented by symbols and curves are calculated by theoretical models. The PEO polymerization number is shown near each curve.

### 1.2.3 Applications

PEO is a versatile polymer and has found applications in a wide range of industries. PEO is used in medicines, coatings, foods, surfactants, lubricants, cosmetics and batteries. PEO is a FDA-approved major ingredient of laxatives. It has some effect in preventing colon cancers in rats and mice.\textsuperscript{20} Nowadays, PEGylation of therapeutic proteins is a widely used technique in drug delivery systems. PEGylation is the process of attaching PEG polymers to proteins. This technique improves efficacy of proteins by enhancing their solubility and protecting them from enzymes.
(immunogenicity). PEO polymers are also approved as excipients in ointments, skin creams, film coatings, tablet binders and lubricants. PEO polymers are used as lubricants in aqueous and non-aqueous environments. They are part of non-ionic dispersants when attached to functional groups. The solubility of dispersants can be modified by changing the length of PEO polymers, a common technique used to alter the hydrophilic-lyophilic balance (HLB) of surfactants. Lithium polymer cells use a high molecular weight PEO material as a separator and electrolyte solvent due to its high temperature resistance and high viscosity. These batteries carry more energy (higher power density) compared to traditional Li-ion batteries. We study these polymers here because of their role in dispersant materials used in response to the Deepwater Horizon accident of 2010; but the structural understanding obtained here should also impact these other industries.

1.3 Molecular simulations

Molecular simulations are computational techniques which can provide insights into experimentally inaccessible molecular-scale physical phenomena under equilibrium and non-equilibrium conditions. Advances in computational capabilities have made it possible to solve the high-dimensional equations which are at the heart of molecular simulations. Molecular simulations are often used as a first step in development of new theories, materials and experimental designs. These techniques reduce physical experiments required for these purposes. Molecular simulation methods are traditionally broken down into molecular dynamics (MD) and Monte Carlo (MC) methods. Modern methods blend these two approaches together in appropriate ways. That is true of the work here also and further discussion will follow.

Both MC and MD methods fundamentally require a description of the potential energy of a given molecular configuration, but calculations achieve that in a
vast variety of ways. *Ab initio* techniques solve Schrödinger’s equation in appropriate approximations, but with increasing system sizes the computationally difficulty becomes prohibitive.

Classical mechanical MD simulations with model force-fields are the workhorse technique for materials simulation and are central to the work that follows. These methods solve Newton’s equation of motion

$$m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i \quad (i = 1, 2, \ldots, N),$$

from an initial configuration, based on evaluation of the forces

$$\vec{F}_i = -\frac{\partial V_N}{\partial \vec{r}_i},$$

after adopting a model potential function $V_N(\vec{r}_1, \vec{r}_2, \ldots, \vec{r}_N)$.

All the results here utilize the classic molecular dynamics simulations package GROMACS unless otherwise specified. The potential energy model takes the form

$$V_N = \sum_{\text{bonds}} k_b (r_{ij} - r_0)^2 + \sum_{\text{angles}} k_\vartheta (\vartheta - \vartheta_0)^2$$

$$+ \sum_{\text{dihedrals}} k_\varphi [1 + \cos (n \varphi - \delta)] + \sum_{\text{improper}} k_\psi (\psi - \psi_0)^2$$

$$+ \sum_{i=1}^{N-1} \sum_{j>i}^N 4\varepsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_{i=1}^{N-1} \sum_{j>i}^N \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

The first four terms of Eq. (1.4) are intra-molecular (bonded) interactions. The last two terms, van der Waals and coulombic interactions, are non-bonded terms. The various bonded and non-bonded parameters required for these models, Eq. (1.4), are available with the published force fields. These force fields are approximate and partially based on experimental results.
The initial configuration for an MD simulation might be generated by randomly placing the molecules in the simulation cell. This randomly generated configuration will not have the lowest possible potential energy. We typically remedy this inopportune characteristic by initial energy minimization, after which genuine MD simulation is initiated. MD simulations generate trajectories of atoms over many steps of extension $\Delta t$. Velocity and position of an atom is produced by using the leapfrog algorithm after each step. It uses positions $\vec{r}_j$ at time $t$ and velocities $\vec{v}_j$ at time $t - \frac{1}{2}\Delta t$ and it updates position and velocities using the forces $\vec{F}_j(t)$ determined by the position at time $t$:

$$\vec{v}_j \left( t + \frac{1}{2}\Delta t \right) = \left( \frac{\vec{F}_j(t)}{m_j} \right) \Delta t + \vec{v}_j \left( t - \frac{1}{2}\Delta t \right)$$ \hspace{1cm} (1.5)$$

$$\vec{r}_j \left( t + \Delta t \right) = \vec{v}_j \left( t + \frac{1}{2}\Delta t \right) \Delta t + \vec{r}_j \left( t \right)$$ \hspace{1cm} (1.6)$$

Trajectories generated by these simulations are then analyzed to calculate mechanical properties of interest. We then consider the probability $p(q^N, p^N)$ that such a trajectory accesses a neighborhood of a particular phase point of the $N$ atoms, specified by the positions $q^N$ and momenta $p^N$. This probability can be written as the products of the probability density $f(q^N, p^N)$ and phase space volume $dq^N dp^N$. According to Boltzmann distribution, this probability is

$$p(q^N, p^N) \propto \exp \left( -\beta \mathcal{H} \right) dq^N dp^N,$$ \hspace{1cm} (1.7)$$

in terms of the the total energy, or Hamiltonian $\mathcal{H} = K_N + V_N$ with $K_N$ the kinetic energy, $\beta = k_B T$, and $k_B$ the Boltzmann constant. Then macroscopic values of a properties can be evaluated by the ensemble average of microscopic value of that
property $B(q^N, p^N)$ as

$$\langle B \rangle = \iint B(q^N, p^N) f(q^N, p^N) \, dq^N \, dp^N.$$  \hspace{1cm} (1.8)

Here ensemble average means the average over configurations with thermodynamic characteristics such as temperature $T$, volume $V$, and number of atoms $N$ set. Eq. (1.8) is valid for the canonical (NVT) ensemble. For other systems, such as isothermal-isobaric ensemble (fixed $N$, $P$ and $T$), alternative formulae are appropriate.

Sometimes, classical MD simulations sample configurations ineffectively. Configurations can get trapped in potential energy minima making sampling over the entire potential energy surface difficult. To overcome this problem we used special sampling techniques, particularly parallel tempering, and window or stratified sampling discussed next.

1.3.1 Parallel tempering

Sugita and Okamoto~\cite{31} developed a molecular dynamics version of the parallel tempering method, which exploits Monte Carlo concepts to improve the sampling for rough landscape problems. This technique is particularly appropriate for systems with molecules having several local minima potential energy configurations.~\cite{32,33} The parallel tempering method involves propagating simulations at several temperatures simultaneously, \textit{i.e.}, in parallel. High temperature simulations can cross energy barriers with facility and explore configurational space effectively. After a specified number of MD steps, MC configurational swaps are attempted between replicas at different temperatures.

In selecting temperatures for the replicas, the sampled potential energies of adjacent replicas must not be too different (FIG. 1.6). Swaps are attempted and then
accepted according to a detailed balance requirement, and the criterion for acceptance is based on Metropolis procedure; specifically

\[ p = \min\left[1, \exp^{(E_i - E_j)(\beta_i - \beta_j)}\right] \]  

with \( p \) is the probability of acceptance of a swap between replicas \( i \) and \( j \) at temperature \( T_i \) and \( T_j \). \( \beta = 1/k_B T \) is the thermodynamic beta based on Boltzmann’s constant \( (k_B) \) and temperature \( (T) \). An established relation suggests temperatures for replicas, and number of replicas necessary for a particular system, to make the parallel tempering method effective.

**Figure 1.5:** Representation of phase space. At low temperature molecule can stuck into energy minimum configuration (shaded region) but at high temperature, it can overcome energy barriers and can explore entire conformational space (shaded region and white space). Swaps between high temperature and low temperature replica allows system to escape from energy minimum configuration at low temperature.

### 1.3.2 Window sampling

Window (or *stratified*) sampling focuses sampling in narrowly defined configurational regions of a system, then the results for different strata are pieced together
in a final reconstruction step. This reconstruction utilizes the general concepts of importance sampling and is employed frequently for calculations of free energy and potential of mean force (pmf). This method can be applied to any reaction coordinate but we selected distance as a reaction coordinate. We used it to effectively sample in the regions of low probability polymer conformations to generate potentials of mean force between head groups of polymers. In a simple view, the potential function $V(r)$ is written in terms of stratifying potentials $V'(r)$ as,

$$V'(r_i) = V(r) + W(r_i)$$  \hspace{1cm} (1.10)

The harmonic weighting function $W(r_i) = k_w(r_i - r_0)^2$ is commonly applied on each window where, $r_0$ is the initial distance and $r_i$ is distance of a particular window $i$ and $k_w$ is force constant acting on the atoms or molecules under consideration.

Multiple windows are simulated independently with harmonic stratifying potentials forcing simulation to sample particular ranges with good frequency and the potential of mean force is reconstructed using Weighted Histogram Analysis Method.
Figure 1.7: Replicas at different temperatures and Monte Carlo tested exchanges after a set number of simulation steps. Swaps are attempted only between adjacent replicas and configurations are exchanged after successful swaps. This configurational swapping allows low temperature replica to explore configurations widely.

1.4 Outline

Ultimate aim of this study would be to develop a defensible molecular level theory for oil spill dispersants. Such a theory requires molecular-scale understanding of conformations and phase behavior of dispersants. This is an initial step towards that molecular theory and uses molecular simulation techniques to understand PEO polymer solutions. This study should be useful in designing experiments to understand molecular-scale features in PEO solutions and phase behavior of these solutions.

There are two major parts in this thesis; first, simulations of PEO polymer
solutions to understand molecular-level structures; in the second part we will try to understand and improve classic Flory-Huggins theory for these systems including the concentration dependence of the Flory-Huggins interaction parameter. These two parts can help in transforming lab-scale results for oil spill dispersants to real life ocean-scale applications.

Hydrophobic interactions are important to aqueous self-assemblies, surfactants and biomolecules. Hydrophobic interactions are a fundamental issue for our scientific and technical interests here. Though calling-out “hydrophobic interactions” is commonplace in textbooks and monographs treating water and aqueous solutions, rigorous experimental definition of hydrophobic interactions has been elusive. Experimental determination of this primitive hydrophobic bond has been hindered by low solubility of these moieties in water. In Chapter 2, we will look into hydrophobic interactions with a goal of establishing a definition of a hydrophobic bond that is accessible to molecular-scale physical measurements. Our idea is to study hydrophobic groups carried into aqueous solutions by hydrophilic PEO oligomers. Contact of hydrophobic capping groups, e.g., methyl groups, might then provide a direct opportunity to study hydrophobic bonds. This should provide a helpful direct comparison with primitive hydrophobic bond between two methane molecules. This chapter will discuss designing experiments for such measurements.

In Chapter 3, we take a broader look at the microstructures of capped PEO oligomers that we study in water and a non-polar (n-hexane) solvent. As noted earlier, this polymer is part of oil spill dispersants and therefore, one should study their behavior in both aqueous and non-polar environments. Our results identification of three major conformational regions exhibited by PEO polymers in solution: loop-closure, globule and extended regions based on the probability distribution of end-to-end distance between polymer caps. Selection of end-to-end distance over traditional radius
of gyration calculations is discussed. The loop-closure region, with caps contacting each other, is later studied in more detail in Chapter 3 as it corresponds to a primitive hydrophobic bond feature. The distribution of polymer heavy-atom density relative to center of mass of polymer solute is also discussed to extract further insight into intra-chain structure.

Chapter 4 is about direct numerical test of the controversial Pratt-Chandler theory of hydrophobic interactions. Atomic-sized hard spheres were inserted in pure water configurations obtained for our simulations and second virial coefficient of all successful insertion is calculated. It was found that, these hydrophobic interactions between inserted hard-spheres were more attractive than predicted by Pratt-Chandler theory. Osmotic second virial coefficients obtained were negative ($B_2 < 0$) and more attractive with increasing temperature.

We noted above the need for structural data and thorough understanding of phase behavior for effective thermo-physical modeling of oil spill dispersants. Chapter 5 will discuss the classic Flory-Huggins model of phase behavior of polymer solutions. This chapter addresses the long-standing problem of the concentration dependence of the Flory-Huggins interaction parameter $\chi$ in PEO(aq) systems. This is done by calculating the excess chemical potential of the small molecule (water) solvent using quasi-chemical theory (QCT). Selection of $\lambda$ parameter for QCT and binding energy distribution and various approximations were discussed in detail.

In the final chapter, preliminary neutron scattering results are discussed. These experiments were designed to address molecular simulation studies. The Nano Ordered MAterials Diffractometer (NOMAD) at Oak Ridge National Laboratory was used to collect high resolution structural details of deuterated PEO polymers in heavy water. The instrument and experimental setup are discussed, in addition to the preliminary results. Initial results are encouraging; more involved, but feasible experi-
ments are proposed in this chapter.
Chapter 2

Direct observation of hydrophobic bond

2.1 Introduction

Hydrophobic interactions are central to super-molecular self-assembly in aqueous solutions, including the folding of soluble globular proteins. A surprising development of recent years is that for entropy-dominated hydrophobic solubilities we now have statistical mechanical theories that are fully defensible on a molecular scale, exploiting all available molecular-scale data. In contrast, our understanding of the statistical solvent-induced forces between neighboring small hydrocarbon molecules in water — hydrophobic interactions — has not experienced the correspondingly conclusive progress despite intense computational effort.

The principal impediment to progress in understanding hydrophobic interactions is the lack of an accessible direct observation of a primitive hydrophobic bond, such as the CH$_4$···CH$_4$ potential of mean force. Because simple hydrophobic species, such as CH$_4$, are only sparingly soluble in water, direct observations of primitive hydrophobic interactions are difficult to achieve; instead the influence of hydrophobic interactions is inferred in more complex systems — protein folding being the fore-
most example. Where limited thermodynamic evaluation of hydrophobic interactions has been experimentally achieved for soluble, but more complex hydrophobic species with higher aqueous solubilities, those experiments set-off a substantial modeling effort that has not untangled this complicated issue.

Hydrophobic interactions are important in PEO solutions. Principle impediment of experimental access to these molecular scale features can be tacked by using PEO polymers. Design of neutron scattering experiments will also be discussed.

2.2 Methods

The previous chapter gave an overview of the methods used. Here we focus on Fig. 2.1 which was obtained by parallel tempering over times of 20 ns/replica with 32 temperatures spanning 256-550 K, using AMBER 10 with the same molecule numbers and cubical volume $V = 32.254 \text{ nm}^3$ for each replica. Basics of parallel tempering method were discussed in detail in Section 1.3.1. Monte Carlo swaps of configurations had an overall success rate of 23%. The SPC/E model treated the 1000 water molecules, and an extended atom model with the Generalized Amber Force Field (GAFF) was used for the single chain molecule. The solid line in FIG. 2.1 is a stratified recalculation of the loop-closure feature, adopting a harmonic potential for the radial displacement coordinate covering the range of 0.3-1.0 nm uniformly with 15 windows, then reconstituting $P(r)$ on that range with a weighted histogram method. This second set of calculations lasted 20 ns/window. The undetermined multiplicative constant in the stratified calculation of $P(r)$ is adjusted to match the direct observation from the parallel tempering in the region of the first minimum (Fig. 2.1).
2.3 Results and discussion

Here we show (FIG. 2.1) that the probability density $P(r)$ of end-to-end separations of a $\text{CH}_3(\text{CH}_2-\text{O-CH}_2)_m\text{CH}_3$ ($m = 21$) oligomer in water exhibits a distinct hydrophobic bond between the two end C-atoms. Cumulative distribution $\int_0^r P(x)4\pi x^2 dx$ (dashed line) is also plotted. The left vertical axis is non-dimensionalized with the observed $\langle r^2 \rangle^{1/2} = 1.56$ nm. These atom-pair correlations are intrinsically measurable by X-ray and neutron diffraction.[57]

Two distinct sets of calculations were combined to obtain the present results: firstly, parallel tempering[33] to establish the overall structure of $P(r)$ and, secondly, windowing[56] to achieve satisfactory spatial resolution in the interesting loop-closure regime, $r < 0.7$ nm. Direct observation of the contact feature would rest on a few percent of the parallel-tempering data set, i.e., about 2% of the molecules are in
loop-closure configurations. The overall parallel-tempering results permit evaluation of the undetermined scale factor (zero of the potential of the average forces) for the windowing results.

The shape of $P(r)$ in the loop-closure region is similar to the predicted pair distributions for model inert gases in water. On the basis of the stratified evaluation of $P(r)$, the most probable $-\text{CH}_3\cdots\text{CH}_3-$ hydrophobic bond length is about 0.4 nm. The slight shoulder on the large-$r$ side of the principal maximum of $P(r)$ is a remnant of a RISM cusp and reflects the ethyl end-capping.

A direct comparison with results for $\text{CH}_4\cdots\text{CH}_4$ obtained with the same models and stratification methods (FIG. 2.2) shows good agreement in the placement of the principal peak, and the large-$r$ shoulder of the principal peak is more obvious. Contact pairing configurations are more prominent than solvent-separated ones in both of these cases, supporting a standard view of this hydrophobic interaction.

**Figure 2.2:** Comparison of the probability density of FIG. 2.1 (solid curve) with results from the $\text{CH}_4\cdots\text{CH}_4$ potential of mean force obtained with the same models and stratification methods (dashed curve) as FIG. 2.1.
A separate evaluation (not shown) of the solubility of CH\(_4\)(aq) with these models compares well with experiment. This substantiates the view that this model solute naturally represents hydrophobic methane. These probability densities differ in outer shells due to detailed differences between the solvent and the chain molecule medium.

It is natural also to compare these pdfs with what would be obtained if the solvent were absent (FIG. 2.6). The comparison shows that water swells this soluble chain molecule (FIG. 2.1), as is the case also with aqueous dilution of a PEO melt. This supports the view that the chain molecule globule might have a secondary effect on the hydrophobic interaction which is of first interest here.

Note that the boundary between the low-extension \( r < \langle r^2 \rangle^{1/2} \) region and a high-extension region is definite (FIG. 2.1). On the basis of the similarity with the results for FIG. 2.2 the end-cap pair appears to be shielded within a uniform fluid environment in the low-extension region. Furthermore, end-caps are more concentrated in the smaller-volume polymer globule of FIG. 2.6 than in the larger-volume polymer globule of FIG. 2.1. The non-dimensionalized probability densities incorporate that distinction without which the maximum probabilities would differ by nearly a factor of three. This point is consistent with the observation from FIG. 2.2 that if the probability densities there match roughly at large-\( r \), then the maximum values also approximately match.

The high-extension \( r > \langle r^2 \rangle^{1/2} \) tail of the probability density (FIG. 2.1) is reasonably described by a linear-response behavior

\[
- \frac{d}{dr} \ln P(r) \approx a + br .
\] (2.1)

A Gaussian model for \( P(r) \) at high-extension would not be centered on the origin, however, and in that sense a traditional Gaussian model would be unsatisfactory in the high-extension region.
A natural view of the present case is that the chain molecule carries this hydrophobic pair into solution and permits them to find one another with reasonable frequency. The underlying assumption is that the hydrophobic interaction is sufficiently local that the effects of the supporting chain molecule are secondary. This is a reasonable assumption that can be experimentally tested by variation of the chain length and capping groups. Increasing hydrophobicity of caps could be achieved by replacing methyl groups with iso-propyl, iso-butyl and CF$_3$ caps. We performed similar molecular simulations with these capping groups and calculated $P(r)$ same as FIG. 2.1. The results are shown in FIG. 2.4 and 2.5. As expected, hydrophobic loop-closure region was seen in all the cases and in case of iso-propyl and iso-butyl caps probability of this hydrophobic bond region was higher than methyl capped variant of same polymer. Nonetheless, the present realization is consistent with the view that hydrophobic interactions are typically expressed in the context of other effects in micelles, membranes, and the structure of soluble proteins.

2.4 Conclusion

Simple characterizations of hydrophobic effects, i.e. whether they are attractive or repulsive, depend on the specific properties examined and the comparisons made. For example, well-developed theoretical analyses show that hydrophobic interactions can be repulsive for the osmotic second virial coefficient. Other comparisons illuminate different aspects of hydrophobic interactions. Sometimes hydrophobic interactions are judged by adopting another solvent that provides a natural comparison to the case of the water medium. Sometimes it is most direct to judge hydrophobic interactions by comparison with standardly hydrophilic solutes, polar, H-bonding, or ionic species in water. We propose that identification of an experimentally accessible case that also permits detailed molecular theory and computation should assist in
**Figure 2.3:** Cumulative probability density for iso-propyl and iso-butyl capped PEO polymer in 2000 SPC/E water molecules. Probability of hydrophobic bond region is higher in these cases compared to CH$_3$ capped polymers.
Figure 2.4: Probability density for iso-butyl and iso-propyl capped 21-mer PEO polymer in 2000 SPC/E water molecules.
Figure 2.5: End-to-end distance distribution between CF₃ capped 21-mer PEO polymer. The distribution shows all three microstructures anticipated in the aqueous PEO chains.

resolving such alternatives.

Though this hydrophobic interaction is intrinsically measurable, analysis of X-ray and neutron diffraction experiments on such systems will require specific and thorough support from molecular simulations, as is the current practice. Isotopic substitution and labeling will be essential. Consideration of fluorinated caps such as –CF₃ should make this hydrophobic interaction more prominent yet.

The chain molecules considered here have broad technological interest because of their biocompatibilities. They are also intrinsic to the dispersant materials used in response to oil spills. Small angle neutron scattering and fluorescence and light-scattering studies have shown that the aqueous solution interactions of (–OCH₂CH₂⁻)ₙ polymers are sensitive to the end-capping of the chains. The importance
Figure 2.6: As in FIG. 2.1 but without water present. The left vertical axis is non-dimensionalized with the observed $\langle r^2 \rangle^{3/2} = 1.06$ nm.

of end-effects is also supported by the sensitivity of solution phase diagrams to the $(-\text{OCH}_2\text{CH}_2^-)_n$ lengths. These observations suggest hydrophobic bonding of the $-\text{CH}_3$ caps, and that manipulation of capping groups might help in understanding hydrophobic interactions on a molecular scale by exhibiting a localized hydrophobic bond.
Chapter 3

Microstructures of capped ethylene oxide oligomers in water and \textit{n}-hexane

3.1 Introduction

Arguably the most important water-soluble synthetic polymers, PEO chain molecules are also soluble in common organic solvents and are intrinsic to the dispersant materials used in response to oil spills. This chapter establishes molecular-scale microstructures of PEO oligomers in aqueous solutions, information preparatory to molecular-scale theories of the structure and function of these species in solution.

The molecular versatility of PEO/PEG polymers in solution makes them a challenge for molecularly specific statistical thermodynamic theory. For example, their conformations respond sensitively to the solution environment. Common-sized PEO molecules are helical in \textit{n}-propanoic, isobutyric, and isopentanoic acid solutions coexisting with liquid water. But that pronounced helicity emphasizes by contrast the point that these chains exhibit generic coil structures in aqueous
solutions. Though the helices are not evident in bulk liquid water, and indeed also not in acetic acid nor in isobutanol nor in \( n \)-butanol, helix formation does seem to require at least a trace of water.\(^{[70]}\)

The solvent plays an intrinsic role in the solution thermodynamics also. The conformational sensitivity noted above is associated with a polymer size fractionation between those coexisting solutions.\(^{[69],[70]}\) Experimental evaluation of a Flory-Huggins interaction parameter for PEO/PEG in either water or methanol shows compositional dependence that is substantially different in these two cases.\(^{[71],[72]}\) This will be discussed in more detail in chapter 5.

In many applications,\(^{[73]}\) and specifically for dispersants used on oil spills,\(^{[7]}\) the PEO/PEG chains are decorated with junction, head, or capping groups. The work below anticipates those molecular designs, but treats explicitly only the simplest capping group, (methyl) -\( \text{CH}_3 \). Correlations associated with capping groups serve to focus structural analyses and the following work focuses on the radial distributions of capping groups. Alternatively, spatial extensions of chain molecules in solution are often characterized by a mean square-radius of gyration \( \langle R_g^2 \rangle \), and that information is addressed below for the cases treated. A conclusion we draw from the recent exhaustive treatment of longer alkanes in water\(^{[74],[75]}\) is that distributions of \( R_g^2 \) are less informative of molecular structure than spatial correlations between chemical groups such as capping groups. The results below should provide further clarification of that issue. We note that single-molecule pulling experiments\(^{[76–81]}\) are becoming a new source of microstructural information, though not yet at the molecular resolution of interest in the present work. Those important experiments do not track the radius of gyration specifically, but instead manipulate lengths between tethered chemical groups.

Numerous traditional statistical thermodynamics theories of aqueous PEO/PEG
solutions have been suggested; some representatives were noted in our initial report,\textsuperscript{17} and we do not attempt a review here. An alternative non-traditional procedure for theory development accepts that simulations are necessary for evaluation of molecular theories of liquids, that simulations will always be carried-out in any case, and so the simulation work might as well contribute to formulation of physical theories. Of course, analyses for those purposes must express the natural physical concepts underpinning molecular theories, and those analyses must be sufficiently general. We have argued elsewhere\textsuperscript{82} that the recent developed molecular quasi-chemical theory achieves those requirements. Molecular quasi-chemical theory has lead over that past decade to resolution of the most basic puzzles of hydrophobic effects.\textsuperscript{44,45} We intend here to establish, for the interesting and important aqueous solutions considered, the groundwork required for fully defensible molecular theory.

As noted already, direct high-resolution molecular simulations are necessary for the theory development that is sought. Because these systems are important practically, many simulation calculations are already available. Again, we do not attempt a review here, but merely note a recent contribution\textsuperscript{83} that gives access to the substantial available literature.

The results below were obtained by combination of standard molecular simulation procedures appropriate for the configurational sampling requirements of CH$_3$(CH$_2$-O-CH$_2$)$_m$CH$_3$ chain molecules in water and n-hexane solvents.\textsuperscript{17} Further specific details are provided in the section\textsuperscript{3.4} We note here that the combined results support comparisons over a range of molecule extensions, between different chain molecule lengths, between different-sized simulation systems, and between water and n-hexane solvents.

A curiosity of this simulation work is that with the typical time-scales and length-scales it is easy to observe (Fig.\textsuperscript{3.1}) molecular-scale break-up of a fluid column
to produce droplets, and then reformation of a fluid column.

3.2 Results and Discussion

From small to large end-to-end lengths, the observed probability density (FIG. 3.2) displays three distinct regions: loop-closure, globule, and high-extension (elastic). The loop-closure feature is closely similar to a primitive hydrophobic bond, which has been extensively studied by simulation but not yet susceptible to experimental measurement due to solubility limitations. In contrast (FIG. 3.3), distributions of $R_g^2$ are less distinctive of these microstructural features.

For liquid water the loop-closure feature is largely independent of oligomer size (FIG. 3.4). This feature in liquid water is different from what is observed in $n$-hexane and for non-solvated chains (FIG. 3.5). These points support the identification of the loop-closure feature as an experimentally realizable hydrophobic bond.

The globule region is clear for the hydrated chains, but not for the case of $n$-hexane solvent (FIG. 3.6). Thus in the organic solvent the chains are collapsed relative to the more swollen hydrated oligomers. This also supports the interpretation of intrachain interactions from the perspective of simple aqueous solution examples.

The profiles of the density of chain C-atoms, measured relative to the chain centroid, are different (FIG. 3.7) for the two solvents. For $n$-hexane, the density profiles are similar for the different chain lengths when the distances are scaled by the observed $\langle R_g^2 \rangle^{1/2}$. This similarity does not obtain for the case of water. In water and for the smaller chains studied, the carbon material exhibits a distinctive enhanced concentration in the middle of the distribution, a feature that is not evident for the case of $n$-hexane. This interesting internal condensation is characterized by a length-scale smaller than $\langle R_g^2 \rangle^{1/2}$. Thus the overall density profiles show less similarity on the $\langle R_g^2 \rangle^{1/2}$ scale, and the internal condensation feature is not evident for the largest
Figure 3.1: Formation and then break-up of a fluid column by reconnection across periodic boundary conditions. For visual convenience, three images are shown laterally in each frame. In this case the droplet/column structure is composed of water with one $\text{CH}_3(\text{CH}_2-\text{O-CH}_2)_m\text{CH}_3$ ($m=11$) chain molecule (in VDW representation) that here resides near the interface. The majority material in the background is $n$-hexane.
33

$m=31$ chain.

### 3.3 Conclusions

The probability density for end-to-end distance (and the associated pmf) for CH$_3$(CH$_2$-O-CH$_2$)$_m$CH$_3$ is more revealing of chain microstructures than are the corresponding results for the radii of gyration. For water, the pmf identifies three distinct regions: loop-closure, globule, and high-extension regions. In water, the loop-closure feature is similar to a primitive hydrophobic bond and is insensitive to chain length. The globule region exposes a water-swollen chain, and is not evident in the $n$-hexane results. Chain C-atom density profiles from the chain centroid are different in the water and $n$-hexane cases. For $n$-hexane (but not water), the density profiles are similar for the different chain lengths when the distances are scaled by the observed $\langle R_g^2 \rangle^{1/2}$. For water (but not $n$-hexane) and the smaller chains considered, the carbon material exhibits a distinctive, enhanced concentration, or internal condensation, at the centroid core of the structure.

### 3.4 Methods

Two different simulation techniques were used for the molecular dynamics calculations. The first class of calculations used parallel tempering\textsuperscript{[87]} to achieve enhanced sampling of the mixing characteristics with water or $n$-hexane solvent, and of CH$_3$(CH$_2$-O-CH$_2$)$_m$CH$_3$ chain conformations. The chain molecules were represented by a generalized amber force field (GAFF),\textsuperscript{[88]} the SPC/E model for water,\textsuperscript{[89]} and optimized potentials for liquid simulations (OPLS-AA) were used to describe $n$-hexane in those simulations.\textsuperscript{[90]} GROMACS 4.5.3 molecular dynamic simulation package\textsuperscript{[29]} was used for all parallel tempering simulations spanning the 256-550 K temperature range with 32 replicas (for $m = 11$, and 21, cases) and 40 replicas (for $m = 31$). Long-
range electrostatic interactions were treated in standard periodic boundary conditions using the particle mesh Ewald method with a cutoff of 0.9 nm. The Nose-Hoover thermostat maintained the constant temperature and chemical bonds involving hydrogen atoms were constrained by the LINCS algorithm. Energy minimization and constant pressure density equilibration was performed at 300 K to set the constant volume conditions, and then production calculations for each replica set were extended to 10 ns. Parallel tempering swaps were attempted at a rate of 100/\text{ns}, and the temperature grid chosen resulted in a success rates of 15-25%.

The second class of simulations obtained higher spatial resolution in the loop closure region using the windowing stratification method. In these simulations a harmonic interaction between the capping atoms of the $\text{CH}_3(\text{CH}_2-O-\text{CH}_2)_m\text{CH}_3$ chain was exploited to concentrate the sampling of the end-to-end distance to each particular window. For a $\text{CH}_3(\text{CH}_2-O-\text{CH}_2)_m\text{CH}_3$ chain in water or $n$-hexane, we performed simulations with radial displacement coordinate covering the range from 3.0-10.0 Å uniformly with 15 windows. Trajectories were recorded for 10\text{ns}/\text{window} at the temperature of 297.1 K. $P(r)$ was then reconstructed over the whole range using the weighted histogram analysis method (WHAM).
Figure 3.2: (upper) Probability density $P(r)$ for end-to-end (CH$_3$\ldots CH$_3$) length for [CH$_3$(CH$_2$-O-CH$_2$)$_m$CH$_3$](aq) with $m = 21$. The normalization of this graph is chosen to suggest the analogy with conventional atom-atom radial distribution function in liquids. (lower) Potential of the average end-to-end forces showing distinct loop-closure, globule, and high-extension regions. The choice of normalization for the upper panel sets the origin of the y-axis of the lower panel, and the same convention is followed in both cases. Results here for $r < 1.0$ nm were are obtained utilizing the WHAM procedure. Those high resolution results were matched to overall observation of $P(r)$ from molecular simulations with parallel tempering.
Figure 3.3: For [CH$_3$(CH$_2$-O-CH$_2$)$_m$CH$_3$]$_{aq}$, distributions of the square radius of gyration displaced vertically for visual convenience, extracted utilizing GROMACS analysis tools. Scaling of the abscissa brings the results for different lengths into a similar range: $\langle R_g^2 \rangle^{1/2} = 0.61, 0.84, \text{ and } 1.22 \text{ nm for } m = 11, 21, \text{ and } 31, \text{ respectively}$. These values are larger than the ideal $(1/\sqrt{6})$ proportion of the observed $\langle r^2 \rangle^{1/2}$. The dashed curves are results for an ideal Gaussian chain, asymptotically correct for large extensions.\cite{85}

Figure 3.4: High resolution results for $r < 1 \text{ nm}$ for several chain lengths from windowing/WHAM calculations.
In the loop-closure region, the \([\text{CH}_3(\text{CH}_2-\text{O-CH}_2)_m\text{CH}_3] (m = 21)\) oligomer behaves differently in \(n\)-hexane and water, and the results for \(n\)-hexane are similar to those obtained with no solvent (ideal). The temperature variation here is small, \(T = 297\) K (water), 302 K (ideal), and 297 K (\(n\)-hexane).
Figure 3.6: (upper) For CH₃(CH₂-O-CH₂)ₘCH₃ (aq) chains, at constant density corresponding to 300 K and $p = 1$ atm: parallel tempering results for different chain lengths and system sizes overlap each other on normalized end-to-end distance. Globule and high-extension regions are separated at $r \approx \langle r^2 \rangle^{1/2}$ for these chain lengths and system sizes. (lower) Corresponding results for $n$-hexane at constant density ($T = 300$ K and $p = 1$ atm): Separation of a globule region and a high extension region is indistinct here. A Gaussian (parabola) model satisfactorily fits the data in this high extension regime.
Figure 3.7: Chain C-atom density profiles relative to center of mass of the CH$_3$(CH$_2$O-CH$_2$)$_m$CH$_3$ polymers. The dashed curves show the predictions for an ideal (Gaussian) model chain for the cases of the matching colored solid curves. The hydrated shorter chains exhibit peaked profile structures near the middle of distribution, but ideal model well approximates the density profile observed for the longest chain. The n-hexane solvated polymer shows more nearly droplet structures.
Figure 3.8: Contributions from individual chain C-atom density relative to center of mass of CH$_3$(CH$_2$-O-CH$_2$)$_{11}$CH$_3$ polymer in water. Central C-atoms (C12-C13 and C11-C14) contribute to the peak concentration region seen in FIG.3.7.
Chapter 4

Direct Numerical Test of the Statistical Mechanical Theory of Hydrophobic Interactions

4.1 Introduction

The osmotic second virial coefficient

\[ B_2 = \lim_{R \to \infty} \left\{ -2\pi \int_0^R [g_{AA}(r) - 1] r^2 dr \right\} \equiv \lim_{R \to \infty} B_2[R] \quad (4.1) \]

has so far been the only direct experimental check on the molecular theory of hydrophobic interactions between slightly soluble gases (A) in liquid water.\cite{48,51,91,92}

Here \( g_{AA}(r) \) is the usual radial distribution function of AA pairs at infinite dilution. Because of low solubilities for solutes of interest, the necessary experiments are challenging, and the initial comparisons between the only available molecular-scale theory\cite{93} and direct measurements of \( B_2 \) showed poor agreement.\cite{51,91,92,94} Explanations for the discrepancy have been suggested\cite{95,97} but the underlying disagreement has persisted.\cite{98}
One explanation for this discrepancy focuses on the differences between the actual interactions for accessible experimental cases and the hard-sphere solute-water interactions natural for the molecular theory. In this setting, direct high-resolution determination of hydrophobic interactions for the hard-sphere models treated by the theory would be a helpful step, but that has not been accomplished so far. The case of atomic-size hard-sphere solutes has not been treated specifically mostly because hard-sphere models are inconvenient in available molecular dynamics simulations.

These problems are of basic importance because hydrophobic interactions are universally acknowledged as fundamental contributions to the stability of folded or aggregated biomolecular structures in water. Hydrophobic interactions are also expected to become more favorable with increasing temperature for physiological temperatures. Hydrophobic interactions can then be described as favorable for aggregation and *endothermic* at moderate temperatures. This is a primary conceptual puzzle that theories of hydrophobic effects should clarify.

A summaries of the substantial efforts to clarify these issues are available. As an example, $B_2$‘s for the specific cases of Ar and CH$_4$ solutes have been estimated to be unusually small, due evidently to substantial cancellation between contributions from repulsive and attractive intermolecular forces. In the same context, $B_2$ for Kr(aq) has been estimated to be repulsive (positive). Of course, interactions that are attractive on balance lower the osmotic pressure and are characterized by negative values of $B_2$. A broad conclusion is that attractive and repulsive interactions can play conflicting roles with the consequence that merely realistic simulation of a case of interest, *e.g.*, CH$_4$, might not provide transparent physical conclusions. In addition, the integrated quantity $B_2$, particularly the $R \to \infty$ limit, is a subtle target for molecular simulation calculations.

In parallel with simulation efforts, the foundation of the molecular theory of
Figure 4.1: A configuration of $5 \times 10^3$ water molecules (red and silver) together with the inclusions (blue spheres) identified by $n_t = 2 \times 10^5$ trial placements of a hard sphere with distance of closest approach to an oxygen atom of 0.31 nm. This size corresponds approximately to an Ar solute for which the van der Waals length parameter $\sigma_A$ is about 0.34 nm, thus adopting $0.31 \text{ nm} - 0.17 \text{ nm} = 0.14 \text{ nm}$ as a van der Waals contact radius of the water oxygen atom. Hard sphere solutes of this size have about maximal AO contact density.
hydrophobic effects underwent a surprising renovation. The physical concern for the PC theory, the available theory for \( g_{AA}(r) \) for hard-sphere solutes, was its disregard of orientational correlations between a solute and neighboring water molecules. That orientational structure had long been regarded as the essence of the challenge of a statistical mechanical theory of hydrophobic effects. Of course, the orientational structure is implicit in the experimental equation of state which is utilized in the molecular theory.

The point of view that the water orientational structure is essential was strongly analyzed by separating the hydration entropy of hydrophobic solutes into translational and orientational contributions. It was found that the orientational contribution to the hydration entropy could be about one-third of the whole, and thus not at all negligible.

At about the same time it was noticed that the whole of the statistical mechanical theory could be formulated without explicit identification of orientational structure. That orientational structure becomes involved in the theory thus renovated by inclusion of \( n \)-body correlations with \( n \geq 3 \). In the information theory format, \( n \)-body correlations can be added incrementally. When that is done with the natural Poisson default model, it is found that free energy predictions worsen in going from \( n=2 \) to \( n=3 \). The \( n=2 \) theory is accidentally accurate in this sense. This unexpected accuracy cannot be explained by the argument that the \( n=2 \) theory is consistent with the successful description of packing effects in the Percus-Yevick theory for the hard-sphere fluid for the following reason: when the information theory is designed to be exact for the case of the hard-sphere solvent, by utilizing the default model numerically determined for that case, the free energy predictions worsen again. Of course, a sophisticated default model such as the default model numerically determined for the hard-sphere solvent does re-
flect \( n \)-body correlations for \( n \geq 3 \). Thus, an \( n=2 \) theory is simple,realizable, and can be accurate. But accuracy for specific physical issues are questions for specific verification.

A conclusion of this discussion is that for the assessment of attractive interactions associated with hydrophobic solutes, a reference system, e.g., the hard-sphere solute case, is not well established. The work below determines \( g_{AA}(r) \) numerically exactly for hard sphere solutes in a computer simulation model of water, and thus takes the zeroth-order step toward a detailed molecular theory of additional intermolecular interaction features.

### 4.2 Theory

We seek the cavity distribution function

\[
y_{AA}(r) = \exp[\beta u_{AA}(r)]g_{AA}(r)
\]

for atomic-size hard spheres on the basis of the potential distribution theorem (or test particle) approach.\(^{112,113}\)

\[
y_{AA}(1, 2) = \frac{\langle e^{-\beta \Delta U^{(2)}_{AA}} | 1, 2 \rangle_0}{\langle e^{-\beta \Delta U^{(1)}_A} \rangle_0 \langle e^{-\beta \Delta U^{(1)}_A} \rangle_0}.
\]

Here \( 1/k_B \beta = T \). Eq. (4.3) anticipates evaluation with trial placements of hard-spheres at specific points, such as the two points \( (1, 2) \). \( y_{AA}(1, 2) = y_{AA}(r) \) will depend only on the magnitude \( r \) of the displacement between positions 1 and 2. The notation \( \langle . . . \rangle_0 \) indicates the average over the configurations of water without the solutes present. \( \Delta U^{(1)}_A = U(N + 1) - U(N) - U(1) \) is the binding energy for insertion of an A atom, and for the hard sphere case considered here is either zero (no overlap with a water oxygen atom) or positive infinity. Thus \( e^{-\beta \Delta U^{(1)}_A} \) is an indicator function...
Figure 4.2: Cavity distribution functions for hard-sphere solutes in liquid water at pressure $p = 1$ atm, and four different temperatures. The spheres have van der Waals radii of 0.17 nm and distance-of-closest-approach to a water oxygen atom of 0.31 nm. The dots on the left vertical axis are values calculated independently on the basis of the zero-separation theorem.

for permissibility of an insertion at a point considered. We will treat the case that $\Delta U^{(2)}_{AA}$ for two trial placements is additive, $\Delta U^{(1)}_{A} + \Delta U^{(1)}_{A}$ for the AA atoms considered.

We rearrange this formula to make the numerical interpretation transparent. Note that the denominator factors of Eq. (4.3), being averages of indicator functions, are probabilities. Following the primitive understanding of conditional probabilities $p(A|B) = p(AB)/p(B)$, we use one of those denominator probabilities to introduce the expectation conditional on permissibility of that initial insertion. Taking the position of that first insertion to be the origin $\vec{0}$ we write

$$
\ln y_{AA}(r) = \frac{\left< e^{-\beta \Delta U^{(1)}_{A}} | \vec{r} \right>}{\left< e^{-\beta \Delta U^{(1)}_{A}} \right>_{0}}
$$

$$
4.4
$$
where $\vec{r}$ is the position of a trial placement relative to a permissible insertion. The average indicated in the numerator is conditional on the permissible placement at $\vec{0}$, though we do not set-up a further notation for that. Eq. (4.4) expresses the well-known zero-separation theorem \cite{14-16}.

$$y_{AA}(0) = \frac{1}{\langle e^{-\beta \Delta U^{(1)}_{\lambda}} \rangle_0},$$

(4.5)

since the numerator is one (1) under the condition of a permissible insertion at $\vec{0}$.

To estimate the ratio Eq. (4.4), we exploit many ($n_t$) trial placements into the system volume $V$, for each of $n_c$ configurations (Fig. 4.1). Those trial points will have the density $n_t/V$ and be statistically uniform. Out of the $n_t$ trial points, a smaller number $n_s(c)$ are permissible placements, and we estimate the denominator of Eq. (4.4) with

$$\sum_c n_s(c) / (n_c n_t) = \bar{n}_s / n_t.$$

We expect $(n_t - 1) \Delta V/V$ of those trial placements to land in a volume $\Delta V$ which is a thin shell of radius $r > 0$ surrounding a permissible insertion. Let’s denote by $\Delta n_s(r; c)$ the number of permissible placements obtained in the shell for configuration $c$. We estimate the numerator of Eq. (4.4) as

$$\sum_c \Delta n_s(r; c) / (n_t - 1) \Delta V/V = \Delta n_s(r) / (n_t - 1) \Delta V/V.$$

(4.6)

Combining these results, we have the estimate

$$\left( \frac{n_s}{V} \right) y_{AA}(r) \Delta V = \Delta \bar{n}_s(r),$$

(4.7)

when $n_t \to \infty$. This is the same formula as if the permissible insertions were actual particles though that is not the case here.

The formula Eq. (4.7) is operationally consistent with the zero-separation
Figure 4.3: Radial distribution functions for hard-sphere solutes in liquid water at $p = 1$ atm, and four different temperatures. The spheres have van der Waals radius of 0.17 nm and distance-of-closest-approach to a water oxygen atom of 0.31 nm. The prediction of the information theory model \cite{106,107} at $T = 300$ K is shown by the star and the gray dashed curve. This is numerically equal to the Pratt-Chandler theory, \cite{93} and so labeled $PC_{IT}$.

theorem Eq. (4.5) according to the following argument. Consider a small volume element surrounding the position $\vec{r} = \vec{0}$ that is known to be a permissible placement. We expect that all trial placements in this region should be permissible so $\Delta \pi_s(\vec{0}) \approx n_t \Delta V/V$ on the right-side of Eq. (4.7). Therefore, $y_{AA}(0) \approx n_t / \pi_s$ which is the operational content of Eq. (4.5).

4.3 Results and Discussion

Using standard methods (detailed below), this approach was implemented for the case that the hard-sphere distance-of-closest-approach to an oxygen atom was 0.31 nm, corresponding approximately to the case of an Ar solute. Larger solutes
would make the present calculations prohibitively difficult. The results for \( \ln y_{AA}(r) \) (Fig. 4.2) operationally satisfy the zero-separation theorem, show strong hydrophobic attraction at short-distances, and solvent-separated hydrophobic attraction qualitatively consistent with the PC theory. It is interesting that the \( \ln y_{AA}(r) \) for the various temperatures cross for \( r \approx 0.3 \) nm. At larger distances, hydrophobic interactions are more stabilizing at higher temperatures judged from the distributions. The radial distribution function \( g_{AA}(r) = y_{AA}(r) \) for \( r \geq 2 \times 0.17 \) nm = 0.34 nm (and zero otherwise, Fig. 4.3), scrutinizes these properties more closely. The contact values, \( g_{AA}(r = 0.34 \) nm), determined here are more than twice larger than the predictions of the PC theory. The contact values are higher for higher temperatures, indicating stronger hydrophobic contact attractions at higher temperatures, and agreeing with the results of Mancera, et al., and some of the preceding work discussed there.\[100\] The contact values of the PC theory also increase with increasing \( T \) but those increases are small,\[93\] and the PC contact values are sufficiently different from the numerical values found here that the small increases are not interesting.

It is commonplace for simulation calculations\[117,125\] to determine the temperature dependences of the AA potentials of mean force \( w_{AA}(r) \equiv -k_B T \ln g_{AA}(r) \) (see Fig. 4.6 and associated discussion below). That recent work is broadly supportive of the conclusions here, and is discussed further below. But \( w_{AA}(r) \) results address our present problems only indirectly because they test the statistical mechanical theory indirectly, and have not obtained \( B_2 \) for the purposes of isolating aspects of interactions of different physical type. Based on experience, the measurable osmotic second virial coefficients are more subtle, and despite interesting suggestions,\[17\] \( w_{AA}(r) \)'s have not been determined from experiment for molecular-scale hydrophobic solutes.

The \( B_2 \) integrals (Fig. 4.4) provide the solution thermodynamic assessment of these distribution functions. The \( B_2 \) values are negative for \( T = 300 \) K and
Figure 4.4: Running integral \( B_2[R] \) (Eq. (4.1)) for assessment of the \( R \to \infty \) value. The dotted curve for \( R \leq 0.34 \) nm is the positive contribution from the hard-core of \( g_{AA}(r) \) that is common to all here. The suggested \( R \to \infty \) values are decidedly negative (attractive) and become more attractive at higher temperatures. The biggest negative contribution is associated with contact hydrophobic attractions. Solvent-separated hydrophobic attractions near \( R \approx 0.7 \) nm are distinct but smaller. The predictions of the PC theory for \( B_2 \) in these circumstances are repulsive (positive).

become more negative at higher temperatures. The biggest negative contribution is associated with contact hydrophobic attractions. Solvent-separated hydrophobic attractions near \( R \approx 0.7 \) nm are distinct but smaller than contact hydrophobic interactions.

The significance of the solvent-separated hydrophobic interactions has been much discussed following the ground-breaking work of Pangali, et al.\textsuperscript{126,127} Those simulations treated Lennard-Jones (LJ) model solutes similar to Kr or Xe solutes. Simulation results (with LJ attractions) were compared with PC theory (not treating LJ attractions though modified for continuous repulsive interactions). Additionally,
those simulations determined $w_{AA}(r)$ only to within an additive constant, so comparisons proceeded after matching the two results at their minimum values, a convenient choice that has been often followed. This comparison can give the impression that the non-matched solvent-separated hydrophobic interactions are unusually variable or significant. If, for the purposes of comparison, the $w_{AA}(r)$ were matched at solvent-separated radii, then the Pangali, et al. results show stronger contact hydrophobic attractions than does the PC theory, qualitatively in agreement with the present work. Recent molecular dynamics simulations for Xe(aq) or CH$_4$(aq) pairs agree qualitatively with the present results and thus support this conclusion.

The molecular theory for the differences between the present results and those following from more realistic interactions has not had satisfactory resolution. But it is straightforward to compare our cavity distribution results that incorporate more realistic interactions. The first step in such a comparison is to separate the assumed Lennard-Jones (LJ) interactions into repulsive force (WCA)

$$u^{(0)}_{AA}(r) = \begin{cases} u_{LJ} + \varepsilon & \text{if } r \leq r_m, \\ 0 & \text{if } r > r_m, \end{cases}$$

(4.8)

and attractive force $(u_{AA}(r) - u^{(0)}_{AA}(r))$ parts. In the non-controversial initial approximation, LJ attractive interactions are neglected and WCA repulsive interactions are included according to

$$g_{AA}(r) \approx g^{(0)}_{AA}(r) = e^{-\beta u^{(0)}_{AA} y_{AA}(r)}.$$  

(4.9)

The results of this approximation are shown in FIG. 4.5. Direct numerical results for LJ-Ar in water simulation results are shown in FIG. 4.6. Inclusion of LJ attractive
interactions make hydrophobic interactions more repulsive. This may seem counter-intuitive, but is by now the expected behavior. The reason for this expected behavior is that solute-water attractive interactions compete with solute-solute attractive interactions, and when included fully with proper balance solute-water attractive interactions can dominate. Still, having this comparison specifically documented is an important step in getting this important phenomenon fully incorporated into molecular theory, and thus permanently understood. This argument contrasts with the observation above the determination of pmfs for non-polar molecules in water has been commonplace.

Inclusion of longer-ranged attractive interactions, i.e., London dispersion interactions, can change these $B_2$ values and trends depending on the balance of solute-
Figure 4.6: Radial distribution function between Ar atoms reconstructed from strati-
fying window calculations of the potential of mean force data (see Fig. 4.7). Notice that
hydrophobic interactions are weaker when atomic attractive forces are fully included.

solute and solute-water interactions. Here the inverse temperature dependence
happens to be preserved (Fig. 4.7). The local molecular field (LMF) theory is one promising suggestion for how to proceed with inclusion of longer-ranged inter-
actions, has commonalities with earlier intuitive proposals, and deserves further
development.

The temperature dependence observed here is sometimes referred to as an
inverse temperature dependence. This behavior might be counter-intuitive for the
following reason: hydrophobic association is typically rationalized as clumping of
inert solution inclusions due to specific structuring of their hydration shells. That
the specific structuring might be more significant at lower temperatures, so perhaps
the hydrophobic association should be stronger at lower temperatures, perhaps more
Figure 4.7: Potential of mean force calculated from window sampling method using weighted histogram analysis method (see Fig. 4.6).

important yet in super-cooled water. The fact that the $\ln y_{AA}(r)$ for the various temperatures cross in the core region (Fig. 2) already suggests that this rationalization is not simple. Whether the rationalized aggregation behavior is obtained depends on the degree that the spherical inclusions can overlap one another, and is not a trivial reflection of solubility behavior.

Hydration-shell structuring surely is an important factor in hydrophobic interactions. What this argument does not address is the distinctive equation of state of liquid water. Some well recognized peculiarities occur at higher-than-physiological temperatures; for example the compressibility minimum occurs at 46 C, under these low pressure conditions. The eventual statistical mechanical explanation of the similarly counter-intuitive entropy convergence hydrophobic phenomenon (at $T \approx 130$ C) depended firstly on proper involvement of the actual equation of state of
Indeed the calculations here also exploit that specific equation of state.

\[ r_B(A) = \langle n_A n_B \rangle \]
\[ r_B(A) = \langle n_A (n_A - 1)/2 \rangle \]
\[ r_B(A) = \langle n_A \rangle \]
\[ T = 300K \]

**Figure 4.8:** Occupancy data used in the information theory modeling shown in Fig. 4.3.

### 4.4 Conclusions

Hydrophobic interactions between atomic-sized hard spheres on water are more attractive than predicted by the available molecular theory, the Pratt-Chandler theory, as judged by osmotic second virial coefficients \( B_2 \) obtained here. The \( B_2 \) values for atomic-size hard spheres in water are attractive (\( B_2 < 0 \)), and more attractive with increasing temperature (\( \Delta B_2 / \Delta T < 0 \)) in the temperature range \( 300 \, \text{K} \leq T \leq 360 \, \text{K} \). Thus molecular-scale hydrophobic interactions are attractive and **endothermic** at moderate temperatures. These results constitute the zeroth-order step toward detailed molecular theory of additional intermolecular interaction fea-
tures, specifically attractive solute-water interactions.

4.5 Methods

The GROMACS\cite{134} package with the SPC/E\cite{53} model, was used to simulate liquid water. The Parinello-Rahman barostat used to establish the pressure at 1 atm and the Nose-Hoover thermostat maintained the temperature. Bonds involving hydrogen atoms were constrained by the LINCS algorithm. Conventional periodic boundary conditions and particle mesh Ewald, with a real-space cut-off at 1 nm, was used to treat long-range interactions. Simulation cells containing $5 \times 10^3$ randomly placed water molecules were created utilizing PACKMOL\cite{135} to match the experimental density approximately.

After $1 \times 10^4$ steps of energy minimization and 2 ns of density equilibration, trajectories of 20 ns (sampled 1/ps) were obtained at each temperature. Each simulation frame was analyzed for cavities based on $n_t = 2 \times 10^5$ trial placements with a distance of closest approach to an oxygen atom of 0.31 nm. Successful placements can be considered as hard spheres of radius 0.17 nm corresponding approximately to an Ar atom. The cavity analysis required an order-of-magnitude more computational effort than the generation of the molecular dynamics trajectories.

Considering the integrand of Eq. (4.1), $g_{AA}(r) \sim 1$ in the thermodynamic limit. For fixed particle numbers in a finite system, that subtracted value is less than 1 and the correction is $O(V^{-1})$, vanishing in the thermodynamic limit. In the present work, we do not have fixed numbers of A particles.

The information theory (IT) model\cite{106,107} (Fig. 4.3) was based upon the occupancy information indicated in Fig. 4.8, slightly different from the initial such calculations.\cite{44,106,107} The reason for this change was the view that this approach would be preferable where the dissociation limit ($r \to \infty$) was of particular interest.
The numerical results here are, in fact, not significantly different, but we record the details for completeness.

Referring to Fig. 4.8, for each \( r \) we exploit the information \( \langle n_A \rangle, \langle n_A (n_A - 1)/2 \rangle \), and \( \langle n_A n_B \rangle \). This data induces the probability model

\[
p(n_A, n_B) \propto \exp \left\{ -F(n_A, n_B; \zeta_1, \zeta_2, \zeta_3) \right\}/n_A!n_B!
\]

with

\[
F(n_A, n_B; \zeta_1, \zeta_2, \zeta_3) = \zeta_1 [n_A + n_B] + \zeta_2 \left[ n_A (n_A - 1)/2 + n_B (n_B - 1)/2 \right] + \zeta_3 n_A n_B ,
\]

the \( n_A \) and \( n_B \) being non-negative integers, and the \( \zeta_j \) Lagrange multipliers. Those Lagrange multipliers are obtained by optimizing

\[
\ln \sum_{n_A, n_B \geq 0} \exp \left\{ -F(n_A, n_B; \zeta_1, \zeta_2, \zeta_3) \right\}/n_A!n_B! + \langle F \rangle,
\]

as usual. With the optimized \( \zeta_j \), the hydration free energy of the AA diatom is obtained in terms of the normalizing denominator

\[
\beta \mu^{\text{ex}} = -\ln p(0, 0) = \ln \sum_{n_A, n_B \geq 0} \exp \left\{ -F(n_A, n_B; \zeta_1, \zeta_2, \zeta_3) \right\}/n_A!n_B! (4.12)
\]

Considering the distinction of this IT model from the initial applications, notice that

\[
n (n - 1)/2 = n_A (n_A - 1)/2 + n_B (n_B - 1)/2 + n_A n_B ,
\]

where \( n = n_A + n_B \). Therefore, optimizations that yielded \( \zeta_2 = \zeta_3 \) would be precisely equal to the initial IT model. That was never seen in these applications. We do
expect and observe that \( \zeta_3 \to 0 \) when \( r \to \infty \). Still the implied gross free energies are similar, and the variation of the free energies with \( r \) are not significantly different. The zero separation theorem is reasonably satisfied; the observed discrepancy in \( \ln y_{AA}(0) \) by about 0.1 on a magnitude of 18. The \( r \to \infty \) level of the gross free energies was computed directly, however, rather than relying on the zero separation theorem.
Chapter 5

Concentration dependence of the Flory-Huggins interaction parameter in aqueous solutions of capped PEO oligomers

5.1 Abstract

This paper studies the concentration dependence of the Flory-Huggins (FH) interaction parameter $\chi_{wp}(\varphi)$ with particular relevance to the free energy of mixing of the oligomer $\text{CH}_3(\text{CH}_2-\text{O-CH}_2)_m\text{CH}_3$ ($m=11$) liquid in water. We follow previous thermodynamic analysis of the FH model by focusing on the prediction for the chemical potential of a small molecule solvent, here water. Molecular quasi-chemical theory, with outer-shell interactions treated by a gaussian statistical approximation, then provides a serviceable technique to obtain the chemical potential of the solvent water. We test this theoretical analysis by treating simulation data for aqueous solutions of capped PEO oligomers. Consistent with experiment, we find that $\chi_{wp}(\varphi)$ is strongly dependent of the water volume fraction $\varphi$. Our analysis and results identify
an unexpected phase separation for CH$_3$(CH$_2$-O-CH$_2$)$_m$CH$_3$ ($m=11$) with coexisting oligomer volume fractions $(1-\varphi) \approx (0.21, 0.91)$ at $T = 300$ K and $p = 1$ atm. Direct observation of the coexistence of these two phases then supports the correctness of the analysis for the systems studied.

Our analyses and results also provide the osmotic pressure of these solutions. This point has not be noticed in previous thermodynamic analyses. The implied osmotic second virial coefficient ($B_2$) for these chains is positive and large, reflecting dominating repulsive interactions between the chains in the water, typically a good solvent for PEO oligomers. This result should be of foundational importance for definition of coarse-grained molecular models which eliminate the solvent in favor of pair interactions between chain molecules.

5.2 Introduction

A classic element of polymer solution physics, the Flory-Huggins model,[137,138]

$$\frac{\beta \Delta G_{\text{mix}}}{n_w + Mn_p} = \varphi \ln \varphi + \frac{(1-\varphi)}{M} \ln (1-\varphi) + \varphi (1-\varphi) \chi_{wp},$$ (5.1)

describes the free energy of mixing, here of $n_p$ moles of polymer liquid with $n_w$ moles of the water solvent; $\beta = 1/kT$, $\varphi$ is the solvent volume fraction, $M = \bar{v}_p/\bar{v}_w$ (the ratio of the molar volumes of the pure liquids) is the operational polymerization index, and $\chi_{wp}$ is the Flory-Huggins interaction coefficient. This work studies the concentration dependence of $\chi_{wp}$, an important issue for mixing of highly dissimilar liquids such as water and chain molecule liquids that have a non-trivial aqueous solubility. The Flory-Huggins model is routinely adopted for discussion of aqueous solutions of chain molecules of sub-polymeric length.[139][141]

Though the traditional statistical mechanical calculation that arrives at Eq. (5.1) is not compelling[99] — particularly for aqueous materials, the Flory-Huggins
model captures two dominating points. Firstly, it identifies the volume fraction $\varphi$ as the preferred concentration variable, associated with the physical assumption that the excess volume of mixing vanishes. This step partially avoids difficult statistical mechanical packing problems. Secondly, the form Eq. (5.1) captures the important reduction of the chain molecule ideal entropy by the factor $1/M$. The physical identification of $M = \bar{v}_p/\bar{v}_w$ as the polymerization index is rough but thermodynamically consistent as noted below. With these points recognized, the interaction contribution of Eq. (5.1) can be regarded as an interpolation between the end points $\varphi = 0$ and $\varphi = 1$ of the composition range.

The simplest expectation for the interaction parameter is

$$\chi_{wp} \propto -\beta \left( a_{ww} - \frac{2a_{wp}}{M} + \frac{a_{pp}}{M^2} \right)$$

(5.2)

where the parameters $a_{\eta\nu}$ gauge the strength of dispersion interactions in van der Waals models of simple liquids. That this description scarcely applies to aqueous solutions underscores the lack of physical clarity in considering $\chi_{wp}$ for aqueous solutions.

The simple temperature dependence of Eq. (5.2) is a reasonable starting point, but aqueous solutions exhibit specific different temperature dependences, \textit{e.g.}, hydrophobic effects. Though temperature and pressure dependences deserve general resolution, composition dependences are more troublesome. The initial expectation Eq. (5.2) does not depend on concentration. But experiments on the PEG/water system show substantial dependence on concentration. Beyond that difficulty, those experimental exhibit a temperature trend opposite to the naive expectation Eq. (5.2), \textit{i.e.}, the experimental results show stronger interactions at higher $T$ as would be expected from the classic folklore of hydrophobic effects. In contrast, when the solvent is methanol the observed concentration dependence is less strong,
though non-trivial and trending with concentration in the opposite direction from the aqueous solution results. The temperature dependences for the methanol case is qualitatively consistent with the simple expectation of Eq. (5.2). In further contrast, with ethanol as solvent the observed concentration dependence is distinctly modest.

5.3 Theory

These puzzles may be addressed by analyzing the chemical potential of the water. Extracting the solvent chemical potential from Eq. (5.1) finds

$$\beta \Delta \mu_{w}^{(ex)} = \left( 1 - \frac{1}{M} \right) (1 - \varphi) + \frac{\partial (\varphi \chi_{wp})}{\partial \varphi} (1 - \varphi)^2$$

(5.3)

with $\Delta \mu_{w}^{(ex)}$ the interaction (or excess) contribution to the chemical potential of the water, referenced to the pure liquid case, i.e.,

$$\Delta \mu_{w}^{(ex)} = \mu_{w}^{(ex)} (\varphi, p, T) - \mu_{w}^{(ex)} (\varphi = 1, p, T).$$

(5.4)

In view of Eq. (5.3) we utilize the notation $\bar{\chi} (\varphi) = \partial (\varphi \chi_{wp}) / \partial \varphi$ as the empirical Flory-Huggins parameter. In these terms, Eq. (5.1) can be re-expressed as

$$\frac{\beta \Delta G_{\text{mix}}}{n_w + M n_p} = \varphi \ln \varphi + \frac{(1 - \varphi)}{M} \ln (1 - \varphi) + (1 - \varphi) \int_{0}^{\varphi} \bar{\chi} (\varphi') d\varphi'.$$

(5.5)

Further perspective on $\bar{\chi}$ (and thus on $\chi_{wp}$) is obtained from the osmotic pressure $\pi$,\[99\]

$$- \beta \pi \bar{v}_w = \ln \rho_w \bar{v}_w + \beta \Delta \mu_{w}^{(ex)}.$$  

(5.6)

Here $\rho_w$ is the density of the water in the solution, and this makes the standard approximation that the solvent is incompressible.\[120\] If the excess volume of mixing
vanishes, as assumed by the FH model, then \( \rho_w \bar{v}_w = \varphi \), and

\[- \beta \pi \bar{v}_w = \ln \varphi + \beta \Delta \mu^{(\text{ex})}_w, \tag{5.7}\]

Utilizing Eq. (5.3) and expanding through \((1 - \varphi)^2\) obtains

\[\beta \pi V/n_p \sim 1 + \left( \frac{n_p}{V} \right) \bar{v}_w M^2 \left( \frac{1}{2} - \bar{\chi} \right), \tag{5.8}\]

identifies the osmotic second virial coefficient \( B_2 = \bar{v}_w M^2 \left( \frac{1}{2} - \bar{\chi} \right) \), and then the factor \( M \) in Eq. (5.1). The subtracted \((1 - \varphi) \left(1 - \frac{1}{M}\right)\) of Eq. (5.3) describes excluded volume (packing) effects when the volume fraction is chosen as the concentration variable, and ideal mixing volumes are assumed. That term linear in \((1 - \varphi)\) is thus necessary for ideal behavior of the osmotic pressure at low solute concentration when the volume fraction variable is used. The intent of the original physical theory is that a concentration-independent \( \chi_{wp} \) should describe the effects of attractive interactions as in Eq. (5.2).

These theoretical considerations acquire practical significance from recent development of molecular quasi-chemical theory (Fig. 5.1) for the excess chemical potential of the water in aqueous solutions. The central result

\[\beta \mu^{(\text{ex})}_w (\varphi, p, T) = - \ln p^{(0)}(n_\lambda = 0) + \ln \langle e^{\beta \varepsilon} \mid n_\lambda = 0 \rangle + \ln p(n_\lambda = 0) \tag{5.9}\]

provides physical and systematically improvable approximations in terms of packing, outer-shell and chemical contributions, from left-to-right. The packing contribution is obtained from the observed probability \( p^{(0)}(n_\lambda = 0) \) for successful random insertion of a spherical cavity of radius \( \lambda \) into the simulation cell. Similarly, the chemical contribution is defined with the probability \( p(n_\lambda = 0) \) that a water molecule actually
present in the system has zero neighbors within the radius $\lambda$ of its O atom. The outer-shell contribution is a partition function, conditional on the inner-shell being empty, involving the binding energy $\varepsilon$. The condition simplifies the calculation to the extent that a Gaussian (normal) statistical estimate may be exploited. That result can then be expressed in terms of mean and variance of binding energies of molecules that have zero neighbors within radius $\lambda$,

$$\ln \langle e^{\beta \varepsilon} | n_{\lambda} = 0 \rangle \approx \beta \langle \varepsilon | n_{\lambda} = 0 \rangle + \beta^2 \langle \delta \varepsilon^2 | n_{\lambda} = 0 \rangle / 2 . \quad (5.10)$$

With this background, we evaluate

$$\frac{\partial (\varphi \chi_{wp})}{\partial \varphi} (1 - \varphi) = \beta \Delta \mu_{wp}^{(ex)} - \left(1 - \frac{1}{M}\right) (1 - \varphi) . \quad (5.11)$$

If we represent

$$\frac{\partial (\varphi \chi_{wp})}{\partial \varphi} = \sum_{n=0} c_n (1 - \varphi)^n , \quad (5.12)$$

then integrating, with $\varphi \chi_{wp} = 0$ at $\varphi = 0$, gives

$$\chi_{wp} = \sum_{n=0} \frac{c_n}{(n + 1)} \varphi \left[1 - (1 - \varphi)^{n+1}\right] . \quad (5.13)$$
\[
\frac{\Delta V_{\text{mix}}}{V} = 1 - (\rho_w \bar{v}_w + \rho_p \bar{v}_p)
\]

**Figure 5.2:** Relative excess volume of mixing; see TABLE 5.1

### 5.4 Results

We have thus analyzed \(\chi_{wp}\) for aqueous solutions for methyl-capped PEO oligomers\(^{17}\) \(\text{CH}_3(\text{CH}_2-\text{O-CH}_2)_{11}\text{CH}_3\) (TABLE 5.1). For these materials, the excess volumes of mixing (Fig. 5.2) are similar to experimental results for the similarly sized PEG 400\(^{14}\); negative, modest in magnitude though slightly larger than the comparable experimental case, and \(M = 27.6\). Radial distribution functions (Figs. 5.3 and 5.4) characterize the structures of these solutions.

Though the result Eq. (5.9) is correct for any physical \(\lambda\),\(^{14}\) we choose \(\lambda = 0.29\) nm as a balance between statistical and systematic accuracy. The Gaussian approximation will be more accurate for larger \(\lambda\). But the data set conforming to the condition \(n_\lambda = 0\) gets smaller and thus the statistical accuracy is degraded with
Figure 5.3: For $\varphi = 0.004$ (TABLE 5.1), the radial distribution function of heavy atoms (X) from water oxygen ($O_w$, solid red curve), and several partial contributions. Notice that the nearest two neighbors saturate the smallest-\(r\) peak of $g_{O_W X}$, and then that (dotted curve) those neighbors are almost all $O_p$. Thus, under these conditions about two (2) polymer O-atoms coordinate a water O-atom within a radius $\lambda = 0.29$ nm, and scarcely any other atoms.
Figure 5.4: (upper) Neighborship distribution of heavy atoms and (bottom) radial distribution function of heavy atoms \((X = O_w, C_p, O_p)\) from water oxygen for \(\varphi = 0.664\) (TABLE 5.1)
Figure 5.5: Binding energy distributions, in normal form, for water in PEO (aq) solutions.
increasing $\lambda$. The latter point becomes more serious at lower water concentrations because fewer water molecules are present. In the present context, only the difference Eq. (5.4) is required, so systematic errors should be balanced.

Indeed the distributions of binding energies observed (FIG. (5.5)) are satisfactorily normal. Composing $\bar{\chi}$ produces an interestingly structured result (Fig. 5.6). Extracting the individual quasi-chemical theory contributions to $\bar{\chi}$ (FIG. 5.7) shows that the distinctive variation with composition is due to the outer-shell (longed-range) contributions: a water molecule loses stabilizing outer-shell interaction partners at intermediate concentrations, and then restrengthens favorable outer-shell interactions on the solvent-poor side of the concentration range. The restrengthening of those longer-ranged interactions is tied to the fluctuation contribution of the Gaussian formula (Eq. (5.10)), the statistical variance of the sampled binding energies decreases with decreasing water content. This diminution of binding energy fluctuations lowers the solvation free energy with decreasing water content (lower dashed curve). These countervailing trends are not synchronous, so the additive result (red dashed curve) in non-monotonic. The fluctuation contribution goes beyond the typical mean-field (or van der Waals) description of Eq. (5.2).

With some trial and error, simulation of coexisting phases (FIG. 5.11) were initiated with chain-molecule volume fraction (left) $1 - \varphi = 0.34$ and (right) $1 - \varphi = 0.99$. After energy minimization, 1 ns of density equilibration was performed at NPT conditions and then 10 ns of production run was used for analysis. Water molecules were represented by SPC/E model and force field parameters for PEO chains were taken from OPLS/AA.

The discrepancy between the predicted coexistence points and the compositions exhibited in Fig. 5.11 might be due to inaccuracy of the theory including the assumption of ideal volumes of mixing, or due to insufficiencies of the simulation.
Figure 5.6: Notice that most of the range is between $-1$ and $1$. These results thus focus on $k_B T$-scale free energetics. The fitted curve is $(1 - \varphi)^2 (c_0 + (1 - \varphi) (c_1 + (1 - \varphi) (c_2 + (1 - \varphi) (c_3 + (1 - \varphi) (c_4 + (1 - \varphi) c_5))))))$ with \( \{c_n\} = \{-16.06, 47.47, 2.90, -202.70, 329.44, -162.84\} \). The dot-dashed curve shows the behavior that would be obtained if $\bar{\chi}(\varphi)$ were assumed to be independent of concentration with the limiting low concentration value.
Figure 5.7: A water molecule loses stabilizing outer-shell interactions at intermediate concentrations, and then restrengthens favorable outer-shell interactions on the solvent-poor side of the concentration range. The dashed-blue curve combines the packing and chemical contributions. The increase of that curve at high polymer concentrations is due to increased flexibility of water inner-shell coordination structures reflected in the chemical contribution.
Figure 5.8: 'Δ' indicates the difference from the pure solvent value, i.e., $\Delta \langle \beta \epsilon \rangle (\varphi) = \langle \epsilon \rangle (\varphi) - \langle \epsilon \rangle (\varphi = 1)$. With decreasing water content, the number of the effective outer-shell interaction partners decreases, in the mean (upper black curve). On the other hand, the statistical variance of the sampled binding energies decreases with decreasing water content. This diminution of binding energy fluctuations lowers the solvation free energy with decreasing water content (lower dashed curve). These countervailing trends are not synchronous, so the additive result (red dashed curve) is non-monotonic.
Figure 5.9: Note that this curve is concave-down.
Figure 5.10: Mixing free energy and double tangent construction. Note that the plot of the osmotic pressure (FIG. 5.16) identifying the same coexistence points directly demonstrates the equality of the osmotic pressure, and thus the solvent chemical potential Eq. (5.7), at these points.
Figure 5.11: Snapshot of coexisting phases with chain-molecule volume fraction (left) $1 - \varphi = 0.34$ and (right) $1 - \varphi = 0.99$. These separate phases have coexisted stably for about 20 ns of simulation time so far.

5.5 Discussion

The observations here should be key to formulation of a physical theory of PEO (aq) phase transitions. We re-iterate that the interesting behavior (FIGS. 5.6 through 5.9) are dominated by interesting competition in evaluating the outer-shell contribution deriving from molecularly long-ranged interactions. Specifically, as the water-content decreases the mean binding energy decreases, but the dielectric constant decreases also (Fig. 5.15). Therefore, long-ranged electrostatic interactions become decisively stronger at very low values of the water-content.

Packing and chemical contributions shown (FIGS. 5.6) are not trivial and are the largest contributions at high water-content. Those short-ranged contributions result in a large, positive value for $B_2$. This point should be helpful for construction
Figure 5.12: Interfacial atomic density profiles for coexisting phases. The simulation treated 1030 SPC/E water molecules and 105 CH₃(CH₂-O-CH₂)ₘCH₃ (ₘ=11) oligomers at 300 K with \( p = 1 \) atm. Results are averaged over a production trajectory of 10 ns, sampled at 1/0.5 ps. The solid-black curve labeled “water” is \( \bar{\rho}_w(z) \equiv \varphi(z) \). The blue-dashed curve labeled “polymer” is \( \bar{\rho}_p \sum_\alpha \rho_{p\alpha}(z) / \sum_\alpha \), utilizing all atoms \( \alpha \) of these chain molecules. The latter combination would be expected to be \( 1 - \varphi(z) \) in view of the assumption of ideal volumes of mixing. Indeed the sum of those two curves (red solid curve) is satisfactorily close to 1.
Figure 5.13: Mean square displacement (MSD) of water in chain-molecule volume fraction $1 - \varphi = 0.34$ (red dashed line) and $1 - \varphi = 0.99$ (blue solid line). Results utilize simulation data of an additional 200 ps on coexisting phases. 40,000 configurations were saved and for the MSD calculations initial positions of water molecules were reset after every 5 ps. The results are averaged over number of water molecules. Calculations of red dashed line utilize 30 water molecules from the slab having highest water density profile in $z$-direction (FIG. 5.12). Similarly, for blue line, 13 water molecules were selected that are confined in polymer rich phase.
Figure 5.14: Velocity autocorrelation function (VACF) of water in chain-molecule volume fraction $1 - \varphi = 0.34$ (red dashed line) and $1 - \varphi = 0.99$ (blue solid line). Results utilize simulation data of an additional 200 ps on coexisting phases. 40,000 configurations were saved and VACF is calculated for every 1 ps. The results are averaged over number of water molecules and number of configurations. Calculations of red dashed line utilize 30 water molecules from the slab having highest water density profile in $z$-direction (FIG. 5.12). Similarly, for blue line, 13 water molecules were selected that are confined in polymer rich phase.
of coarse-grained models of the chains, *i.e.*, where the solvent is integrated-out as in a McMillan-Mayer approach. Coarse-grained pair chain interactions should be repulsive in this overall sense.

The results here demonstrate the ability to evaluate the osmotic pressures of PEG solutions. These systems are interesting in their own right, and important in a variety of practical settings including the broadly relevant osmotic stress studies. Therefore, further work should focus on molecular-scale calculation of these osmotic pressures generally.

The peculiarities observed here at very low water content are currently the most promising possibilities for explaining the puzzles observed in the experimental PEG phase diagrams at very low water context (*noted in Chapter 2*), *i.e.*, larger PEG chain molecules exhibit size-fractionation and helix-coil transitions under proper solutions conditions and the helix formation seems to require trace amounts of water. These issues deserve further study.
Figure 5.15: Static dielectric constants of PEO (aq) solutions as a function of polymer volume fraction using gromacs analysis code.
Figure 5.16: Reflecting the fact that water is a good solvent for these chain molecules, the osmotic second virial coefficient, $B_2$ (Eq. (5.8)) is positive and large.
Table 5.1: Parallel tempering simulations implemented within the GROMACS 4.5.3 molecular dynamic simulation package\textsuperscript{29} were used to improve mixing and the sampling of chain molecular conformations at the $T = 300$ K temperature of interest. The chain molecules were represented by a generalized amber force field (GAFF),\textsuperscript{88} and the SPC/E model for water.\textsuperscript{89} Long-range electrostatic interactions were treated in standard periodic boundary conditions using the particle mesh Ewald method with a cutoff of 0.9 nm. The Nosé-Hoover thermostat maintained the constant temperature and chemical bonds involving hydrogen atoms were constrained by the LINCS algorithm. Parallel tempering swaps were attempted at a rate of 100/ns, which resulted in a success rates of 15-30%. After energy minimization and density equilibration at 300.4 K and $p = 1$ atm, 40 replicas spanning 256-450 K, each at the same volume, were simulated for 10 ns. The pure liquid molar volumes were $\bar{\nu}_w = 0.0178$ dm$^3$/mole, $\bar{\nu}_p = 0.490$ dm$^3$/mole, so that $M = 27.6$. Configurations of the $T = 300.4$ K replica were sampled every 0.5 ps for subsequent analysis. The packing, outer-shell and chemical terms were calculated separately using the replica at 300.4 K. 30,000 uniformly spaced trial insertions were tried to estimate packing term. The generalized reaction field method\textsuperscript{1}, cutoff at 1 nm, was used to calculate the electrostatic contribution to the binding energies. Additionally, dielectric constants $\epsilon/\epsilon_0$ were evaluated to characterize better the solvent-poor characteristics of these solutions.
Chapter 6

Diffraction experiments

6.1 Introduction

Diffraction experiments can be an effective tool in extracting structural information on these polymers. Scattering experiments are well known for generating the phase behavior and the structural information in solutions, crystals, and many other types of materials. We can directly compare our molecular simulations understanding with experimental results. These neutron and light scattering experiments provided major insights into PEO chain structures. Hammouda, et al., investigated solutions of PEO for a range of molecular weights. They found that PEO chains form clusters in the aqueous environment but later Devanand countered, based on the light scattering data, that the PEO polymers do not necessarily aggregate in water. Devanand’s argument was later supported by one more light scattering study on several molecular weight PEO solutions. Second virial coefficient obtained in these two studies were positive, meaning that the interaction between polymers are repulsive and hinting toward non-clustering behavior. In another example, small angle neutron diffraction (SNAS) experiments on high molecular weight PEO solutions found helical and coil conformations of polymers in isobutyric acid. However, a trace amount of water was required for this transfor-
Neutron scattering experiments can be utilized in constructing phase diagrams and calculations of Flory-Huggins interaction parameter for PEO polymers. SANS experiments performed at National Institute of Science and Technology (NIST), using contrast matching techniques and fitting of data in classic Flory-Huggins model yielded interaction parameter and phase diagrams. Second derivative of FH model is related to structure factor and interaction parameter $\chi$. Testing our simulation results with these experiments will be challenging but careful sample preparations and extremely precise measurements combined with molecular simulations results can generate a dataset that could provide constructive base for development of fully defensible molecular level theory on these polymer solutions.

Single chain structure factor and water structure are well known from scattering experiments. So far, experiments studied radius of gyration $\langle R_g \rangle$ and we argued previously that the end-to-end distance calculation will provide better understanding of polymer conformation. End-to-end distance calculations require high resolution diffraction experiments at atomic length scales. Neutron diffraction experiments are known to provide atomistic level details of radial distribution functions. Our target of conducting these experiments is to gather all possible structure information, focussing mainly on end-to-end distance distribution and hydrophobic bond structure associated with it. Recent addition of Nanoscale Ordered Materials Diffractometer (NOMAD) instrument at Spallation Neutron Source (SNS), Oak Ridge National Laboratory is perfect for calculating radial distribution function in polymer solutions at intermediate length scale. High resolution of this instrument allows us to exploit small wavelength neutrons and understand structures at these length scale. In 2012, we wrote a proposal under "proof of principle" category to Oak Ridge National Laboratory and performed preliminary experiments in January 2013. The prelimi-
nary experiments were designed to check the feasibility of experiments proposed in our *J. Chem. Phys.* paper.\textsuperscript{17} The results are explained in section 6.3.

### 6.2 Instrument

NOMAD\textsuperscript{163,164} is neutron time-of-flight diffractometer designed to calculate radial distribution function of wide variety of samples *e.g.* liquids, solutions, glasses, polymers and crystals etc. High flux spallation neutron source at Oak Ridge national laboratory with wide variety of bandwidths and good detector coverage provides more pixels that directly corresponds to more accurate results. Pair distribution function from diffraction experiments involve determination of the scattered intensity as a function of momentum transfer $Q$ which is then related by a Fourier transform to the pair distribution function. NOMAD instrument can provide high-resolution pair distribution functions, small-contrast isotope substitution experiments and small sample sizes.

Fig. 6.1 shows outline of the instrument. Neutrons travel 19 m before reaching samples. They are guided by super mirrors and filtered by bandwidth choppers to achieve single wavelength neutrons. $T_0$ chopper blocks high energy neutrons that can create background noise and sample activation problems. Background noise is created due to large wavelength neutron that can reach the sample with new pulse of neutrons. The guide system increases flux of neutrons to 0.5 Å. Chopper speed can be varied to select different wavelength neutrons at different intensities.

#### 6.2.1 Sample and detectors

Sample and detection system is shown in FIG. 6.2 with neutrons entering the system in the direction of arrow. Sample is located 19 m away from the moderator and is surrounded by $^3$He linear position sensitive detectors. The data obtained from NOMAD instrument is directly proportional to the solid angle of diffracted neutron.
Figure 6.1: NOMAD instrument.

on to detectors. Extensive coverage of the detectors allow gathering of more data and NOMAD can carry out scattering experiments at faster speed. Detectors and sample holder is kept under vacuum during measurements. Samples are typically placed in the vanadium cell but in our preliminary experiments we used glass capillaries to hold the samples because glass capillaries require small amount of samples. Sample environment can be modified and there are provisions to use high pressure and high/low temperature sample environment.

6.3 Radial distribution function calculation

Radial distribution function is based on momentum transfer ($Q$). For NOMAD experiments, all scattering is assumed elastic and hence $Q$ is directly related to time of flight (TOF) of neutrons detected at pixel $i$, 

Figure 6.2: NOMAD sample chamber and detectors.

\[ Q_i = \frac{4\pi m_N}{h} \frac{l_i}{\text{TOF}} \sin \theta_i = 3176 \, \text{Å}^{-1} \mu s/\text{m} \frac{l_i}{\text{TOF}} \sin \theta_i, \]  

(6.1)

where, \( l_i \) is total flight path length, \( h \) Plank’s constant, \( \theta_i \) is scattering angle and \( m_N \) is neutron mass.

Position and \( Q \) scale of each pixel is calibrated using standard samples and nominal \( Q_{i}^{\text{nom}} \) is based on nominal location in space with the single calibration constant \( C_i \) then effective momentum transfer is \( Q_{i}^{\text{eff}} = C_i Q_{i}^{\text{nom}} \). The measured neutron intensity from the sample is directly related to differential cross section. Incoherent scattering from Vanadium is subtracted and used to calculated proportionality constant required for calculation of differential cross section. Full conversion from measured intensities into a differential cross section is given by,
\[
\left( \frac{d\sigma}{d\Omega} \right)(Q) = \frac{1}{N_{\text{sample}} a(Q)} \left( \sum \frac{1}{A_{s,sc}} I_{sc} - \frac{A_{c,cs}}{A_{s,sc} A_{c,c}} I_c - MS \right) \tag{6.2}
\]

\(N_{\text{sample}}\) is number of atoms in sample, \(a(Q)\) is from sample holder (Vanadium scattering or in our case scattering from empty capillary). We assumed that all capillaries are identical. \(A_{s,sc}, A_{c,cs}, A_{c,c}\) are the attenuation of sample scattering in sample and container \((s, sc)\), attenuation of container in sample and container \((c, cs)\) and container in container \((c, c)\). I_{sc} and I_c are intensities detected at particular pixel from sample in container and container only. MS is the multiple scattering term from sample and container and summation is performed over all the pixels.

Radial distribution function is obtained by performing discrete Fourier-Bessel transform,

\[
g(r_j) - 1 = \frac{1}{2\pi^2 r \rho} \sum_{b} \sum_{i}^{N} Q \left[ \left( \frac{d\sigma}{d\Omega} \right) - \left( \frac{d\sigma}{d\Omega} \right)_{\text{self}} \right] \sin(Q_i r_j) \Delta Q \tag{6.3}
\]

If \(r_j = j\Delta r\) and \(\Delta r = \pi/Q_{\text{max}}\) then \(\sum_{i} \sin(Q_i r_j) \sin(Q_i r'_j) = 0\) and elements of \(g(r_j)\) are linearly independent. Uncertainties in measurement of wavelength of neutron detected (\(\delta\lambda\)) and scattering angle \(\delta\theta\) affect resolution of NOMAD but \(\delta\theta\) dominates majority of NOMAD detectors resolution.

**6.4 Preliminary experiment**

Molecular simulations results on aqueous single iso-propyl and iso-butyl polymer support the formation of hydrophobic bond (FIG. 2.4). In fact, these capping groups showed higher cumulative probability of forming hydrophobic bond compared to CH\(_3\) capped polymers (FIG. 6.5). Although, position of first peak was at higher \(r\) because of the sizes of these capping groups, all these polymers exhibit all three
structural features seen in CH$_3$ capped aqueous PEO solutions.

We purchased 2-Bromopropane (98 atom% Deuterium) and hydrogenated PEO (mol. wt. $\approx$ 600 gm/mol) from Sigma Aldrich Inc. Dr. Mathew Becker (University of Akron) and Dr. Michael Pauliatis (Ohio State University) used these raw materials to synthesize deuterated iso-propyl capped PEO polymers. 2, 3 and 4 wt% solutions of this highly pure deuterium capped polymer were prepared in D$_2$O solvent. Heavy water was used to minimize hydrogen content responsible for incoherent scattering of the samples. Samples were placed in 3 mm diameter glass capillaries and sealed with rubber cork (FIG. 6.4). After initial calibration, and identifying sample locations on sample holder, scattering data was collected for 4 hrs on each sample including for empty capillary and pure D$_2$O water.

Assumptions used for data reduction are, all capillaries are of same sizes, water structure does not change$^{165}$ in the presence of polymer and solution concentrations are accurate. These are important assumptions and they will also help us isolating data using simulation results and future experiments. Data from 4 wt After data reduction and subtracting scattering from pure water and empty capillary we got the radial distribution function for 4 wt% PEO solution from polymer to all other atoms including polymer itself (FIG. 6.3).

### 6.5 Results and discussion

These experiments were designed to gather structural information on PEO solutions with main focus on isolating hydrophobic bond region between end capping groups. These preliminary experiments encouraged us to explore these diffraction experiments on these polymers in different solvents. As stated previously in section 2.4, the hydrophobic capping groups in aqueous solutions of these polymers exhibit hydrophobic bond region at dilute concentrations. Low solubility of hydrophobic
Figure 6.3: Preliminary experimental results for radial distribution function between a polymer atoms (X) and any other atom (X’=polymer H,C,O and water O,D). This experiment utilized -CD$_2$(CD$_3$)$_2$ (isopropyl) capping groups on PEO oligomers (mw≈600).
moieties in water was impeding experimental proof of hydrophobic interactions and these polymers can be used to tackle that issue. Simulations results on radial distribution function of capping groups confirmed our hypothesis that PEO polymer carry these small hydrophobic groups in water allowing them to form hydrophobic bond with higher probability.\[17\] Isolation of hydrophobic interaction features from several other interactions present in the solutions will be challenging and these initial experiments were the first attempt to test the feasibility of such experiments. The results for radial distribution function between polymer atoms and all other atoms (including polymer itself) do show a significant peak in the interesting 4-6 Å region where other atom-pair distances are not contributing (FIG. 6.3). This feature demonstrates the primitive hydrophobic bond that we seek. More experiments targeting specific structure factors could help us solving this puzzle and experimentally calculate radial distribution function between end capping groups.
Figure 6.5: Cumulative probability density for iso-propyl and iso-butyl capped PEO polymer in 2000 SPC/E water molecules. Probability of hydrophobic bond region is higher in these cases compared to CH$_3$ capped polymers.
6.6 Future work

Differential cross section equation (Eq. 6.2) for system containing $N$ atoms can be written in expression of form,

$$\frac{d\sigma}{d\Omega} = \left\langle \sum_{i=1}^{N} \sum_{j=1}^{N} b_i b_j \exp[-i\mathbf{k} \cdot (\mathbf{r}_i - \mathbf{r}_j)] \right\rangle$$

(6.4)

where, $b_i$ and $b_j$ are scattering lengths for the nucleus of atom $i$ and $j$, and $\mathbf{r}_i$, $\mathbf{r}_j$ are position vectors. The brackets $\langle \ldots \rangle$ indicate thermal average, and the wave vector $\mathbf{k}$ provides the momentum transfer change of scattered neutrons. This differential cross section equation can be expressed as linear combination of structure factor $\hat{S}_{\upsilon \eta}(k)$ as,

$$\hat{S}_{\upsilon \eta}(k) = \rho_{\upsilon} \delta_{\upsilon \eta} + \rho_{\upsilon} \rho_{\eta} \left( \frac{4\pi}{k} \right) \int_{0}^{\infty} r \sin kr (g_{\upsilon \eta}(r) - 1) dr$$

(6.5)

where $\rho_{\upsilon}$ is the mole fraction of $\upsilon$ atoms, $g_{\upsilon \eta}(r)$ is the radial distribution function for $\upsilon \eta$ atom pairs and $k = |\mathbf{k}| = 2\pi/\lambda$. At this stage of data processing we gather information on one $\hat{S}_{\upsilon \eta}(k)$ and the remaining tasks are extracting individual $\hat{S}_{\upsilon \eta}(k)$ contributions of specific interest, and performing the inverse Fourier transform to obtain $g_{\upsilon \eta}(r)$ of interest.

The difficulty of extracting individual $\hat{S}_{\upsilon \eta}(k)$ contributions can be attacked by obtaining data on isotopically substituted materials for which the scattering lengths $b_j$ are different. This technique is called contrast matching. Contrast matching is a technique of isotope labeling of particular part in the system so that its scattering intensity matches with the solvent making it invisible in neutron scattering or diffraction experiments. This technique is widely used in SANS (Small Angle Neutron Scattering) to isolate and understand structural information of particular portion of the system. Difference between labelled and un-labelled system at same concentration
Figure 6.6: Zoomed into dilute PEO solution structure factor between polymer (C,O) and all heavy atoms in the system. This graph shows that intra and inter-polymer structures can be isolated based on equation.

Figure 6.7: Simulation strategy to isolate different parts of structure factor results.
can be used to cancel similar scattering terms and isolate particular $\hat{S}_{v\eta}(k)$. Hammouda et al. used this contrast matching technique on PEO polymer solutions of high molecular weights to study phase behavior. Striking difference between scattering lengths of hydrogen (scattering length) and deuterium (scattering length) can be used to our advantage to reduce $\hat{S}_{v\eta}(k)$ data. Future diffraction experiments should be designed using these strategies. It is also possible to match the scattering density of middle part (ethylene oxide) of our polymer to scattering density of solvent, making it invisible to scattering experiments. Our aim here is to calculate radial distribution function between end groups and diffraction experiments (high resolution instrument NOMAD) are feasible at these length scales. Fluorinated caps (CF₃) are simple hydrophobic groups and molecular simulations results on CF
capped polymers showed definite loop closure region comparable to CH₃ caps. One should investigate variations of end-capping, because the synthesis to introduce interesting end-caps is satisfactorily worked out.\textsuperscript{[54]}

Molecular simulations are essential ingredients of diffraction experiments on PEO polymers.\textsuperscript{[57,167]} Results of FIG. 2.1 and FIG. 2.4 show that these calculations are feasible and that adequate sampling is not a show-stopper. Molecular simulations on DMSO in water and diffraction experiments on the same are used effectively to isolate structure of water molecules.\textsuperscript{[168]} From MD simulation results (FIG. 6.8 and 6.7) we can isolate any structure factors. Intra and inter-chain structure factors for polymer chain (α) can be easily separated using Eq. 6.6

\[
\hat{S}(k) = 1 + \rho_\alpha 4\pi \int_0^\infty \frac{\sin(kr)}{kr} P(r) r^2 dr + n\rho_\alpha 4\pi \int_0^\infty \frac{\sin(kr)}{kr} (g(r) - 1) r^2 dr \tag{6.6}
\]

where second and third terms represent intra-chain and inter-chain structure factors respectively. \( n \) in this case is the number of polymer chains and \( \rho_\alpha \) is the density of polymer chains in the solution.

Although, the experiments proposed in this thesis will not be easy and require high precision sample preparations and measurements. The results will be highly sensitive to it. One can try to isolate as much structure factor information as possible from experiments and then use molecular simulation results to isolate rest of the information.
List of References


Biography

Mangesh Chaudhari was born on December 4, 1984 and is from Mumbai, India. Mangesh attended Institute of Chemical Technology (formally UICT) from September 2002 till May 2006 and completed degree of bachelor’s of technology (B.Tech.) in Oils, Oleochemicals and surfactants. Immediately after finishing his degree, he worked at Asian Paints India ltd, as a technology officer in R&D department. In August 2008, he came to United States to pursue his PhD degree in Chemical Engineering at Tulane University. During his time as a doctoral student, he worked with Prof. Lawrence R. Pratt. His research focus was on molecular simulations of polyethylene oxide polymer solutions. He published 2 peer reviewed journal articles and received Outstanding graduate student award of Department of Chemical and Biomolecular engineering at Tulane University in 2013.