Molecular Modeling Exercises and Experiments

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Using Molecular Dynamics Simulation To Reinforce Student Understanding of Intermolecular Forces

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The simple fact that most things exist as liquids and solids is a testament to the importance of intermolecular forces. These forces are important in many common and interesting observable phenomena from drug interactions *(1)* to the dyeing of fibers *(2)*.

The nature of intermolecular forces has been studied for many years, and their description continues to be the subject of quantitative modeling *(3)*. In his monograph "Cohesion. A Scientific History of Intermolecular Forces", John Rowlinson makes the point that much of what we understand about intermolecular forces can be explained by Newton's laws of classical mechanics *(4)*. Students are often surprised that, in a science where so much of the discussion is about quantum mechanics, the use of classical mechanics can be used to explain some important chemical phenomena. In fact, the interaction of atoms, ions, and molecules can often be explained using these simple laws. The application of these laws to calculate and project the motion of chemical species is called molecular dynamics simulation (MDS).

Historically, the first example of using a computer to solve the classical equations of motion for several hundred molecules represented as hard spheres was published in 1957 *(5)*. Seven years later, the motions of 864 argon atoms were studied to simulate their motions in the liquid state at 94.4 K *(6)*. In 1971, researchers at the Argonne National Laboratory simulated a sample of bulk water using 216 rigid molecules at a density of 1 g cm^{-3} and 34.3 °C *(7)*. It was not until 1977 that the first dynamic simulation was applied to a biological system. The dynamics of a folded globular protein was described using the equations of motion for the constituent atoms *(8)*. Fourteen years later, MDS was used to explore a heptanucleotide portion of a bacteriophage. From that study stereochemical parameters such as hydrogen bond lengths and angles, helix twist, and roll angles were determined *(9)*. More recently, as modeling techniques have improved, the use of MDS has played an important role in studying the properties of single-wall carbon nanotubes *(10)* and the interaction of metallic clusters *(11)*. As the technique grows in popularity, it seems reasonable that students be exposed to this approach of predicting molecular behavior.

In 1997, Alan and Gwendolyn Shusterman published in this *Journal* a seminal article on what was then "a powerful new method for teaching students about electronic structure and its relevance to chemical phenomena" *(12)*. They used computer-generated, three-dimensional, pictorial models of molecules showing the distribution of electron density that allowed students to visualize concepts from polarity to bond order. At the time that work was published, few images of electrostatic potential maps of molecules could be found in general chemistry. Now, a decade later, it is unlikely that any general chemistry textbook can be found that does not include illustrations of molecules showing these electrostatic potential maps.

Until recently, the use of computer-generated models has been limited mostly to static images showing polarity, orbitals, or electron density. The calculation of the behavior of species comprising a bulk material was too costly. However, increased computing power has made the use of MDSs possible.

Over the past year, MDS has entered the educational arena in lower-level chemistry courses. At the 233rd National American Chemical Society meeting, two presentations were made in which the technique was used in the classroom. The first presentation discussed how MDS can be used to help increase students' abilities to visualize the particulate nature of matter and dispel common misconceptions regarding intermolecular forces, covalent bonding and structure, phase changes, and acid strength *(13)*. The second presentation described MDS use in a first-semester organic chemistry laboratory to model several essential oils obtained by steam distillation *(14)*. The various calculated properties of the molecule were then used to help students design projects that were subsequently performed and presented at the end of the semester.

At The University of Tulsa, several MDSs have been introduced into the curriculum of the molecular modeling course, a required, majors-only course with one semester of organic chemistry as a prerequisite. While the primary course content involves using molecular mechanics and quantum calculations to determine structures, energies, orbitals, and electronic structures of chemical species, MDSs have been introduced as a way of discussing intermolecular forces. At The University of Central Missouri, MDSs have been used to introduce and reinforce concepts such as phases of matter, intermolecular forces, and acid strength. In both institutions, many of the students indicated that the simulations helped them visualize what had always been a rather abstract concept.

This article presents some of the experiments that have been used successfully. Sufficient details are provided so that any student or instructor with the appropriate software can perform these simulations. They have been found to be very valuable in helping students visualize the nature of intermolecular interactions and the ramifications of those interactions.

Molecular Dynamics Simulation

Molecular dynamics simulations (MDS) used in this article were performed using Odyssey for Windows (version 2.1.0) available from Wavefunction, Inc. *(15)*. These activities could be modified to work with other molecular dynamics software, some of which have been described in this *Journal (16–18)*. Odyssey was chosen for its ease of use and availability of preprogrammed activities for student exploration.

MDSs are performed using basic Newtonian laws to describe the motion of molecules and ions. There are good resources published in this *Journal* that describe the principles of molecular dynamics *(19)* and provide students a hands-on introduction to molecular dynamics *(20).* Unlike a movie that might be found on a CD or downloaded from the Internet, molecular dynamics are used to predict molecular and ion motions based on the properties of the species. As a result, each student simulation is an independent experiment. The specific motions of the species will depend on how each experiment is set up. While the outcomes of the computational experiments from different students are similar, the exact pathway to the solution differs for each student. In other words, each calculation is a true experiment for which the outcome is not known.

In any given simulation, the students construct a simulation cell or use one that comes preprogrammed. The cell contains chemical species and will have a density that is set by the designer. From this starting point, the program examines the positions of the chemical species in the cell at $t = 0$. Based on these initial positions and the properties of the species (charge, polarity, size, etc.) the forces acting between the species are calculated using theoretical equations that have been shown to apply to such systems. From these calculated forces, the acceleration of each chemical species can be calculated. The result is a speed and direction. Using an appropriate time interval, a new position of each chemical species within the simulation cell can be determined and displayed. These new locations can be used as the starting point for the next cycle in which the same steps are repeated. The result is a dynamic simulation showing the movement and interactions of the various chemical species.

The power of this technique is that students can watch molecules interact, moving from one region of the cell to another. At first motions may seem almost random, but as the simulation continues, a specific direction is observed. These motions reinforce the concepts of intermolecular forces to which students are exposed in class. It is rewarding to hear students talk spontaneously about what they are seeing on the screen and try to make sense of the specific interactions that they are observing. At times, students seem to take an interest in a specific molecule, watching its behavior with respect to the others in the cell. This method captures the attention of the students as it is dynamic and stimulates them visually.

Preprogrammed Experiments

There are a series of preprogrammed experiments that are included with the Odyssey software. To use them, students click on the Experiments links on the initial page. Clicking on a particular experiment opens a page associated with this topic. Each experiment contains preprogrammed simulations, explanations, and questions that students may think about or instructors may assign. However, the preprogrammed instructional material is limited. To have the simulations achieve the instructional goals of the course, guided-inquiry worksheets were designed to guide students through the simulation and prompt them to focus on different aspects of the simulation. These guided inquiry worksheets incorporate some of the material in the preprogrammed Odyssey worksheets (due to student preference of having all the questions together), but significantly extend what is expected from the students in terms of analysis and making connections to macroscopic properties of matter.

Setting Up a Simulation Cell

Perhaps the most powerful aspect of Odyssey is that, in addition to preprogrammed experiments, students can create their own MDS experiments to perform. Specific instructions on how simulation cells were constructed for the work presented here can be found in the supplemental material. It is important that the species be built properly, and an understanding of electron dot structures and molecular geometry is essential before proper cells can be constructed.

In many simulations, the "density" of the system was set below that reasonable for a condensed phase. While the use of low densities may seem unrealistic, they need not be cause for concern. Empty space in a cell should be viewed as a nonpolar environment. Using lower densities is important for many simulations as they reduce experimental cost (time) without compromising results. Using higher densities often decreases the visual effectiveness of an experiment. To simulate bulk matter, the program uses "periodic boundary conditions". This means that the cell "wraps around" in all three dimensions. Removing the periodic boundary conditions increases the cost of the overall simulation because of the time it takes for the molecules of interest to move away from the walls of the cell. At low densities, there is enough open space in the cell for fewer unimportant collisions between molecules. As a result the simulation proceeds faster without changing the final outcome. Use of this technique allows several experiments to be performed within a single class period.

A variety of simulation experiments are described below. Most of these experiments require only a few minutes of simulation to see results. In a few cases, a simulation may need to run for as much as half an hour. Some of these simulations are suitable for in-class, lecture presentations. One advantage of actual simulations over movies, is that occasionally students will ask what would happen if a different substance from the one the instructor selected was used. The lecture instructor can, within a minute, make the change and repeat the simulation, answering the student's question immediately.

Visualizing the Effects of Intermolecular Forces

Relative Strength of Ion–Dipole and Ion–Induced Dipole Interactions

To demonstrate the relative strength of ion–dipole and ion–induced dipole interactions, students construct a simulation cell using 1 sodium ion, 30 chloromethane molecules (selected as a non-hydrogen bonding polar species), and 30 tetrachloromethane molecules. The density was set at 1.10 g cm^{-3}. In Odyssey, students have a choice of ways to look at molecules and ions. Figure 1A shows a snapshot of the simulation cell in which the sodium ion and the chloromethane molecules are shown as space filling models and the tetrachloromethane molecules are shown as ball-and-spoke structures. The result of this simulation highlights two phenomena: First the ion interacts more strongly with the polar chloromethane molecules and is surrounded by them, and second, the chloromethane molecules tend to associate with each other excluding the tetrachloromethane molecules. The preprogrammed Odyssey simulation on ion–dipole interactions focuses on the solvation of the ion rather than allowing for the comparison of the intermolecular forces. While the impact is more limited than the student constructed simulation, it still allows students to better visualize what happens to ionic compounds in water.

Relative Strength of Dipole–Dipole and Dipole–Induced Dipole Interactions

In a similar way, students construct a simulation cell using chloromethane and tetrachloromethane, but instead of using an ion, they insert a polar, molecular species such as SO_2. (All cell conditions are the same as above.) The results of the simulation are shown in Figure 1B. The negative, chlorine end of the chloromethane molecules are pointed at the sulfur atom as would be expected for the less electronegative sulfur atom in the polar molecule. The simulation shows clearly that polar molecules interact preferentially with each other while the nonpolar tetrachloromethane molecules are excluded.

Miscibility of Dimethylsulfoxide in Methane and Water

While the accessibility of powerful computers makes MDS possible, the calculations can still be slow for systems with large molecules or a large number of small molecules. To minimize the time to obtain results from a simulation, some shortcuts can be taken. In this simulation, students generate a simulation cell with 30 molecules of water, 30 molecules of methane, and 5 molecules of dimethylsulfoxide. Rather than using a density of that corresponding to an aqueous solution, a density of 0.1 g cm^{-3} is used. When water is used, the intermolecular forces are strong enough that the water "condenses" without the need for the cell boundary. Methane is used as a surrogate for any nonpolar solvent. Figure 2A shows the result of the simulation after 8×10^{-11} s of simulated time. The water molecules have all condensed and the dimethylsulfoxide clearly is associated with the water molecules.

Miscibility of Sulfur Hexafluoride in Methane and Water

When students generate a simulation cell with 30 molecules of water, 30 molecules of methane, and 5 molecules of sulfur hexafluoride under the same conditions above, the result is shown in Figure 2B. Students can contrast the results as this cell shows the water molecules still condense, but the sulfur hexafluoride molecules are found with the methane molecules.

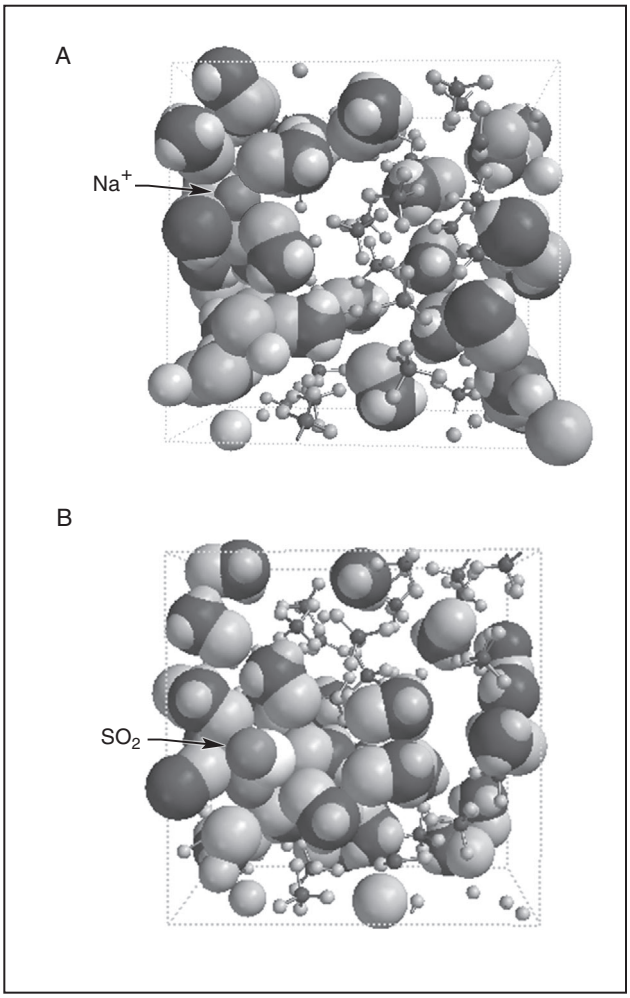

Figure 1. (A) Simulation cell showing a sodium cation (space filling) surrounded by the polar chloromethane molecules. (B) Simulation cell showing a sulfur dioxide molecule (space filling) surrounded by polar chloromethane molecules. For clarity, in both cells, the chloromethane molecules are space filling while the tetrachloromethane molecules are ball-and-spoke models.

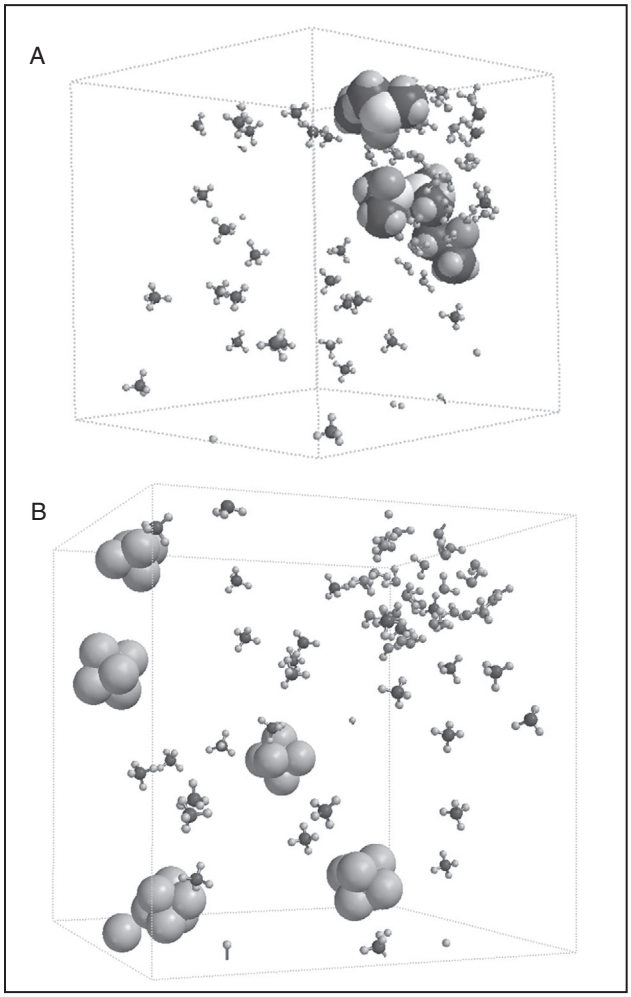

Figure 2. Simulation cell showing (A) the affinity of dimethylsulfoxide (space filling) molecules for water relative to the nonpolar methane, and (B) the preference of sulfur hexafluoride molecules (space filling) for the nonpolar phase. In both cases, the water molecules and the methane molecules are ball-and-spoke models.

Structure of Solid Benzene

The solid-state structure of solid benzene consists of a "fishbone" structure *(21)*. This structure can be simulated. Using the Organic building pallet (to change pallets, click the Molecule/Ion button and choose the desired pallet) students can select Benzene under Rings, and place a benzene molecule on the screen. In this simulation, the density is set at 0.2 g cm^{-3} and four benzene molecules are used. Once the simulation has started students can change the temperature of the simulation by right clicking on the background and selecting properties. Using the properties drag menu, temperature is selected from the heading Thermodynamics. The temperature is decreased to −250 °C. The benzene molecules begin to interact with each other as shown in Figure 3. Regardless of the initial structure, at low temperatures, the benzene molecules align themselves just as is observed experimentally.

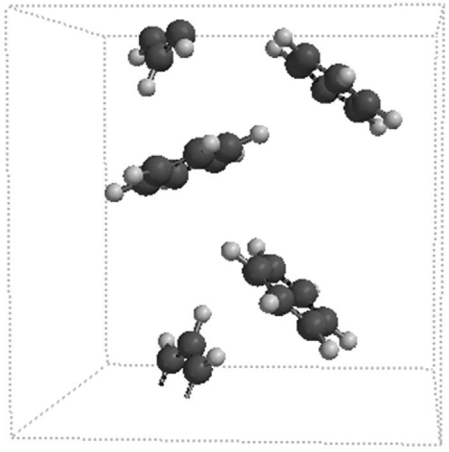

Figure 3. Simulation showing the simulated "fishbone" structure of benzene.

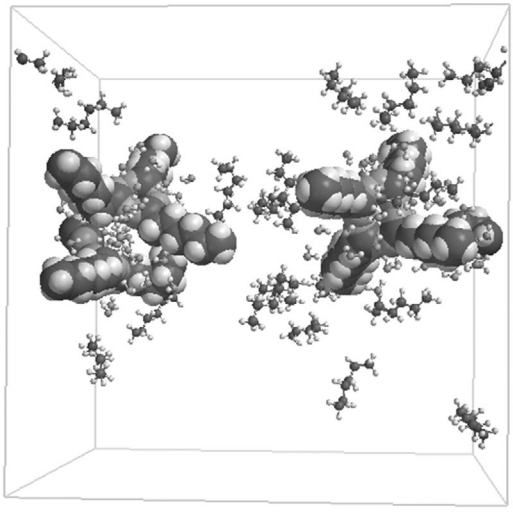

Figure 4. Simulation showing the formation of micelles. The model surfactant (heptanoate ion) is shown as space filling while the water molecules and hexane molecules are shown as ball-and-spoke models.

Formation of Micelles

The formation of micelles is a fundamental part of understanding surfactants and can be simulated readily. In this simulation 10 surfactant molecules (heptanoate ion) with the formula $C_6H_{13}COO^-$ are added to 80 water molecules and 20 hexane molecules at a density of 0.1 g cm^{-3}. A snapshot of the simulation cell after 7×10^{-11} s of simulation is shown in Figure 4. The cell is a little unusual as most of the cell represents the nonpolar part of the system, and the water "droplets" are represented by the two "clumps" of molecules. Nevertheless, in the simulation cell, there are two groups of surfactant molecules with their heads clearly associated with the water droplets and their nonpolar tails sticking into the nonpolar region of the system. If the number of water and surfactant molecules were increased, larger micelles would be produced, but this would be at the expense of the modeler's time. There is one other limitation to setting up the simulation cell this way. As one reviewer pointed out, micelles in an aqueous solution often are presented with the nonpolar tails interacting with a small sample of nonpolar material and the polar heads "facing out" into the water. The cell described in this simulation (low cell density) represents a "nonpolar environment." (Empty space is nonpolar.) A cell could be constructed with a high density and many water molecules to simulate an aqueous solution; however, the problems associated with using higher densities would limit the effectiveness of the simulation. These problems were described in detail earlier.

Environmental Applications

Recently a article was published in this *Journal* on teaching students to use their knowledge of intermolecular forces to predict the environmental distribution of pesticides *(22)*. The authors discussed the octanol–water partition coefficient and how atrazine and hydroxyatrazine, the degradation products, would have different environmental distributions. It seemed reasonable that simulations might be used to show the preference of atrazine for 1-octanol and hydroxyatrazine for water. The simulations were set up using 30 molecules of water, 30 molecules of 1-octanol, and 1 herbicide molecule at a density of 0.5 g cm^{-3}. In part, because of the higher cell density, maximum clarity of this simulation is obtained after about an hour, but even after 10–15 minutes, hydroxyatrazine shows association with water. The results can be seen in the two snapshots shown in Figure 5. The atrazine is found with the 1-octanol molecules (Figure 5A) while the hydroxyatrazine is associated with the water molecules (Figure 5B). Students may forget the calculation of the partition coefficient, but the image of the partitioning of the two substances will likely be remembered.

Application to Thin-Layer Chromatography

A laboratory exercise in which molecular modeling was used in conjunction with thin-layer chromatography was published several years ago in this *Journal (23)*. Students used thin-layer chromatography to measure the relative R_f values of a variety of compounds and compared those values to dipole moments that had been calculated from quantum calculations. For the solvent, students used hexane or hexane-dichloromethane mixtures. Since this separation technique depends on differences in intermolecular forces, it is reasonable to expect that the process could be simulated. A simulation cell was set up in which a "molecule" of silica (shown as the space filling Si_6O_{12} unit in Figure 6), 20 molecules of hexane, and 1 molecule of either

2-decanone or decane were added. To facilitate the simulation, a density of 0.50 g cm^{-3} was used. Snapshots from the simulations are shown in Figure 6. In Figure 6A, the decane molecule is located on the right side of the cell, away from the silica particle, while in Figure 6B the 2-decanone is located in such a way as the keto-oxygen is "nuzzled" against the silica particle. From knowing that the stationary phase of thin-layer chromatography is made up of the silica particles, students can visually see that the decanone will have more interactions with the silica resulting in a lower R_f value. To demonstrate that addition of a polar substance to the mobile phase should increase the R_f of 2-decanone, students can add dichloromethane molecules to the cell. Figure 6C shows the results of adding 20 dichloromethane molecules to the cell. The subsequent simulation confirms the expectation that the 2-decanone dissociates from the silica particle and becomes associated with the mobile phase. These results provide a visual means for students to understand the idea that different molecules will spend a different portion of their time in different phases, and that the composition of the mobile phase can affect the mobility of the solute.

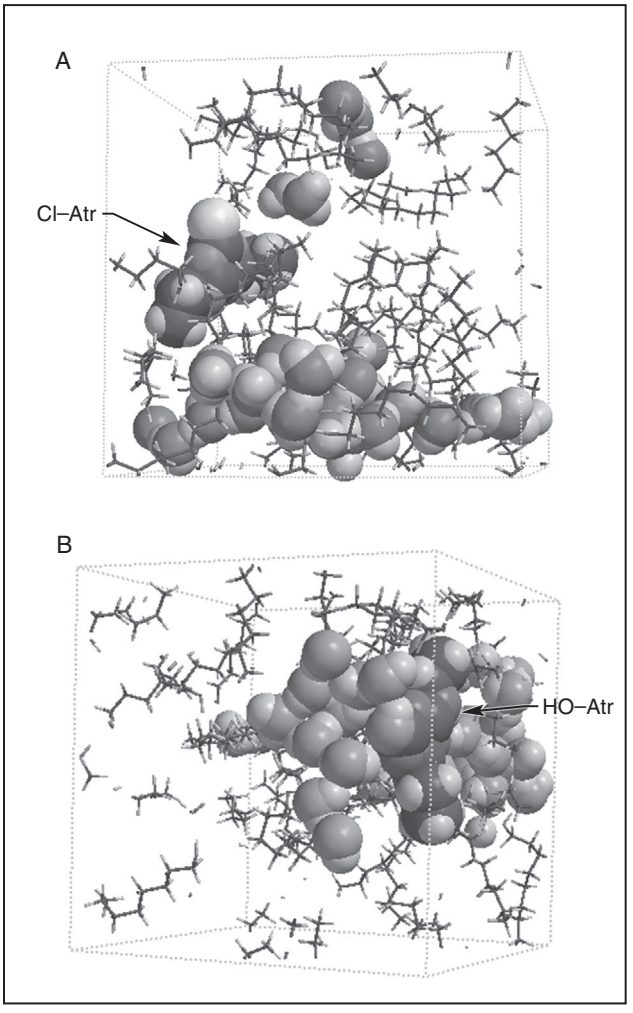

Figure 5. Simulation cells showing 30 molecules of water (space filling), 30 molecules of 1-octanol (tubes) and (A) 1 molecule of atrazine (Cl–Atr; space filling) or (B) 1 molecule of hydroxyatrazine (HO–Atr; space filling).

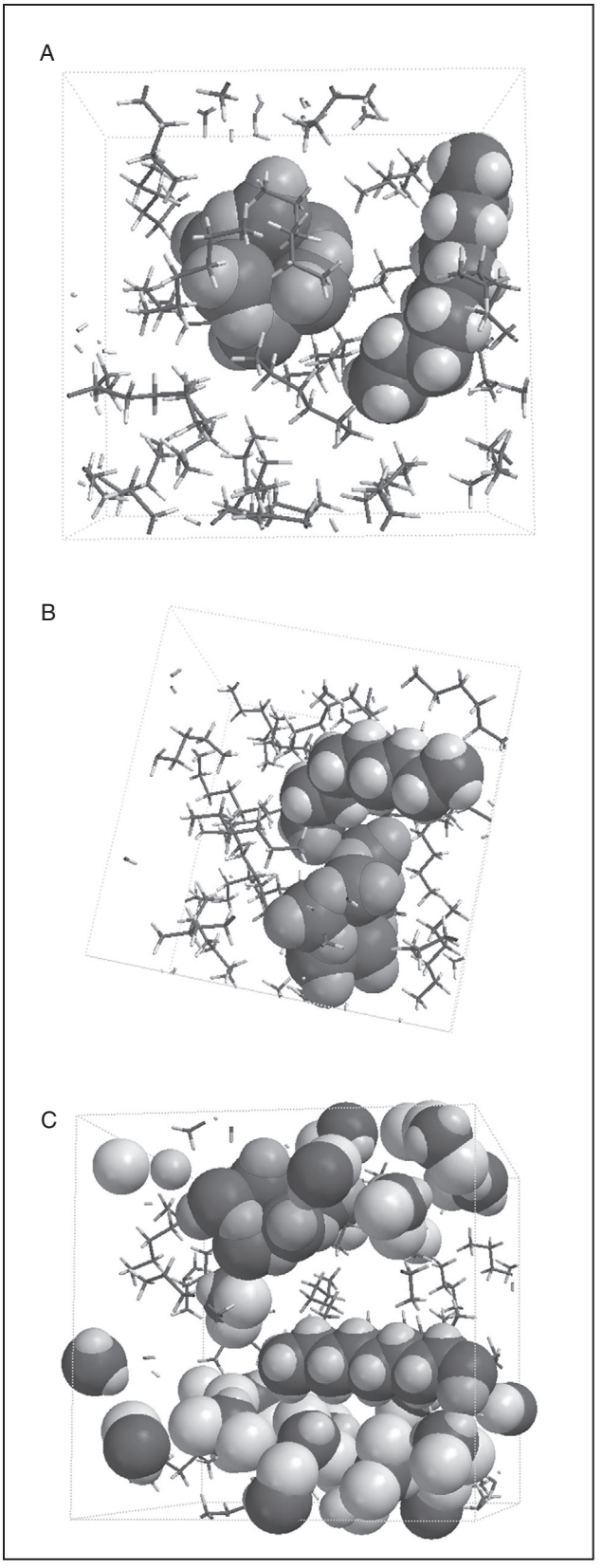

Figure 6. Simulation cell containing (A) 1 silica "molecule", 20 hexane molecules (tubes), and 1 molecule of decane, (B) 1 silica "molecule", 20 hexane molecules, and 1 molecule of 2-decanone, and (C) 1 silica "molecule", 20 hexane molecules, 20 molecules of dichloromethane and 1 molecule of 2-decanone.

Dispersion Forces and Number of Electrons

Students are taught that as the number of electrons in a molecule increases, there is an increase in the strength of the dispersion forces between the molecules. With some patience this effect can be simulated. When 25 molecules of tetrachloromethane and 25 molecules of methane are simulated as a gas at a pressure of 5.3 atm and 0 °C, the tetrachloromethane molecules begin to aggregate while the methane molecules show strictly gaseous behavior. The dynamic simulation is dramatic: the methane molecules can be seen bouncing around the cell while there is a single aggregate of tetrachloromethane molecules. A snapshot of the cell is shown in Figure 7.

Hydrogen Bonds and Relative Boiling Points

One of the more important intermolecular forces in chemistry is the hydrogen bond. Odyssey can show the presence of hydrogen bonds graphically as well as count them. In general chemistry instructors usually focus on the simplest forms of hydrogen bonds involving hydrogen atoms attached to an oxygen, nitrogen, or fluorine atom; however, there are dozens of different types of hydrogen bonds *(24)*.

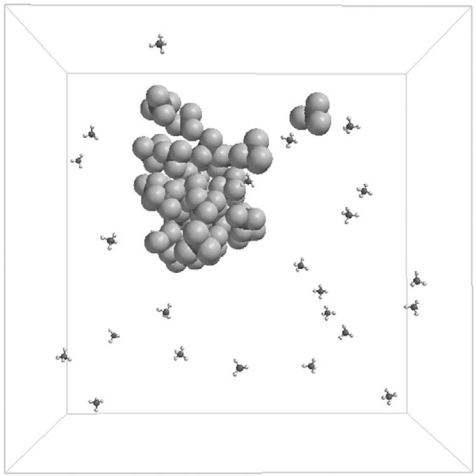

Figure 7. A simulated mixture of tetrachloromethane (space filling) and methane (ball-and-spoke) at 25 °C.

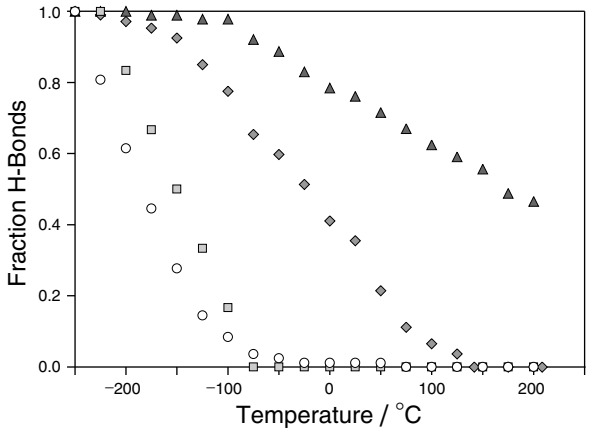

Figure 8. Plot showing the decrease in hydrogen bonding as a function of temperature for four hydrogen bonding species: (▲) H_2O, (○) HF, (□) H_2S, and (◆) NH_3. The fraction of H-bonds is relative to the H-bonds at –250 °C.

In addition to the graphically visual display of the MDS, Odyssey also "looks" for hydrogen bonds and counts them. Students were instructed to simulate gaseous H_2O, HF, H_2S, and NH_3 to determine the number of hydrogen bonds as a function of temperature. They built four different gas simulation cells at 20 atm and −250 °C. Each cell had 50 molecules. After allowing the simulation to run for a short time the number of observed hydrogen bonds became constant. Students recorded the number and increased the temperature from −250 °C to +200 °C at 25 degree increments. For the typical student, the number of hydrogen bonds for H_2O, HF, H_2S, and NH_3 at 20 atm and −250 °C was 88, 83, 6, and 107, respectively. A typical student Excel plot of the data generated from Odyssey is shown in Figure 8. The data show hydrogen bonding decreased with increasing temperature for each species. The normal boiling point of H_2O, HF, H_2S, and NH_3 is 100 °C, 19 °C, −60 °C, and −33 °C, respectively.

It is important not to take the absolute value of the boiling point seriously; rather, the relative order is all that is important. The plot and experimental data agree that water and hydrogen sulfide should be at the extremes. The location of the ammonia curve is also in line with the relative boiling points. The only species that is surprising is the location of hydrogen fluoride. There may be two explanations for this observation. From a molecular dynamics point of view, HF is notoriously difficult to treat. Odyssey, and most other MDS programs, may not provide a faithful representation of the substance. For this reason, instructors may want to avoid using HF for simulations. Clearly, the intermolecular forces in HF are stronger than that predicted by the simulation. An alternative possibility is that liquid HF involves a large degree of covalency. This brings up an important point. Most MDSs are based on calculations in which covalent interactions do not change. For this reason, trying to simulate the dissociation of a strong acid in water will fail, because in that case, intramolecular bonds are being broken and formed. In the case of HF, the hydrogen bond is very different from that in ammonia, water, or hydrogen sulfide. The hydrogen bond in liquid HF involves a much larger degree of covalency than that found in any of the other three species. This covalency has been the subject of a great deal of study recently and is referred to as "negative charge assisted hydrogen bonding", (−)CAHB *(25)*. The observation that the boiling point of HF is so much higher than expected from the simulation, and that the (−)CAHB effect is ignored in the simulation, supports the conclusion of those who argue that there is strong covalent character in the HF hydrogen bonds.

The preprogrammed Odyssey activity on hydrogen bonding focuses on which molecules undergo hydrogen bonding and which do not using many of the molecules listed above, but students have no control of the contents of the simulation. The "experiments" do have controls that let students manipulate the appearance of the simulation. This particular experiment can be used to have students analyze trends in interactions and phases based on the degree of hydrogen bonding. A more significant aspect of hydrogen bonding that can be seen in the simulations but not in diagrams is the dynamic nature of hydrogen bonding. With static diagrams, students have a tendency to think of hydrogen bonds as fixed bonds rather than dynamic

intermolecular forces. The simulation allows students to see that hydrogen bonds are constantly forming and breaking as the molecules move. However, the instructional material that comes with Odyssey does not facilitate all of these observations and connections, so additional directions and questions are needed for students to develop the desired concepts.

Limitations of MDS

As demonstrated in this article, the use of MDS is a powerful tool that can be used to examine the intermolecular interactions in a number of systems. The successes of so many simulations leads to a tendency to try to answer questions that lie outside of the scope of the model or to expect the model to give quantitative results that agree exactly with experiment. Predicting relative boiling points of two substances might be possible, but trying to determine the exact boiling point of a substance by finding the temperature at which the molecules no longer associate with each other would be unwise. In addition, time limitations become a factor when the system to be examined becomes very large or complex. Even some systems that might appear to fall within the abilities of the method may fail to yield accurate results. For example, simulation experiments exploring ion pairing in aqueous solution failed to produce any results resembling what is known from conductivity experiments. Furthermore, as is always the case when computational methods are used, it is contingent upon the modeler to critically evaluate the results. While good simulations using sound modeling can produce valuable insight into the physical behavior of materials, applying methods indiscriminately can lead to nonsensical conclusions.

Conclusions

The use of MDS can greatly enhance the presentation of intermolecular forces for students. The technique can be used in the classroom as well as in laboratory settings. Simulations can be employed to augment existing experiments in general, physical, environmental, organic, and inorganic chemistry or can be used as stand-alone experiments in computational chemistry courses. The simplicity of how MDSs are generated is in stark contrast to the apparent complexity of quantum mechanics and is often much less intimidating to students. If it is an educational goal to provide students with a "feel" or "mental picture" of the physical phenomena associated with intermolecular forces, then MDSs can provide vivid visual representations that students can use to solve related problems or explain macroscopic behavior.

Acknowledgments

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