

Ab Initio and Density Functional Theory Modeling of the Chiroptical Response of Glycine and Alanine in Solution Using Explicit Solvation and Molecular Dynamics

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Abstract: We investigate ways in which simple point charge (SPC) water models can be used in place of more expensive quantum mechanical water molecules to efficiently model the solvent effect on a solute molecule's chiroptical responses. The effect that SPC waters have on the computed circular dichroism of a solvated glycine molecule are comparable to, albeit somewhat weaker than, that of quantum mechanical waters at the coupled cluster CC2 level of theory. The effects of SPC waters in fact correlate better with QM-CC2 waters than quantum mechanical waters computed with density functional theory (DFT) methods, since they do not promote spurious charge transfer excitations that are a known deficiency with most popular density functionals. Furthermore, the near zero order scaling of point charge waters allows multiple layers of explicit solvation to be modeled with negligible computational cost, which is not practical with CC2 or DFT levels. As a practical example, we model the molar rotations of glycine and alanine, and track their convergence.

Introduction

Molecular modeling of molecules in solution poses a continuing challenge. The amino acids which comprise our proteins are of great interest, and modeling them in solution phase is drawing increasing interest. Glycine, being the smallest of this class of molecules, is a natural target for ab initio computations. Many recent papers have been published on the solvation of this molecule, several of which we cite here.^{1–12} Alanine, the second smallest amino acid and the smallest which is chiral, has also gathered significant attention.^{8,13–15}

A recent focus of our research has been modeling the chiroptical response properties of amino acids in solution.^{16–19} These interactions of chiral molecules with polarized light include specific rotation/molar rotation at fixed wavelengths, optical rotatory dispersion, and circular dichroism.^{20,21} We as well as others^{8,22–24} have employed continuum solvation models²⁵ in our earlier studies of these properties. Such methods, among the most popular being the Polarizable Continuum Models (PCMs) and the COnductor like Screen-

ing MOdel (COSMO), do well to model bulk solvent effects. However they fare more poorly for short, explicit solvent-solute interactions such as hydrogen bonding, which is important for aqueous solutions of highly polar molecules such as glycine. For these, a more detailed solvent model is called for, such as one incorporating several solvent molecules explicitly. The exploration of such explicit solvation on chiroptical properties has only recently begun.^{26–28} Here we continue this exploration with a look at how differing explicit solvation models affect the chiroptical response properties of the glycine and alanine molecules and at the performance of simplified models that, unlike the continuum models, treat the solvent molecules as discrete entities. Replacing a continuum such as COSMO or PCM by discrete solvent molecules comes at the added cost of averaging over many solvent-solute configurations. For this purpose, we employ molecular dynamics calculations.

This work begins with a look at how water molecules congregate around a glycine molecule that they are solvating and how those solvent effects decrease as a function of solute-solvent distance with various model systems. It next probes more deeply into how the solvent molecules are

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perturbing the molar rotation and circular dichroism response of the glycine molecule, paying particular attention to how the solvent affects the lowest energy electronic excitation of the solute. It then explores the differences and similarities of using quantum mechanical water molecules and those comprised simply of point charges for solvation modeling, discussing the benefits and shortcomings of both methods. Finally the average molar rotations resulting from thousands of TDDFT calculations of glycine and alanine will be compared with experiment.

Computational Methods

Many of the computational methods used in this work are detailed in two previous publications, where TDDFT based computations of optical rotations of amino acids were exhaustively benchmarked.^{17,19} All quantum mechanical data were computed with the Turbomole²⁹ quantum chemical software, version 5.7.1. The calculations were performed with the Becke three parameter B3LYP and BHLYP hybrid functionals³⁰ as well as the CC2 coupled cluster method³¹ as implemented in the Turbomole code. Dunning's aug-cc-pVDZ basis set³² was used. For some calculations the COnductor-like Screening MOdel (COSMO)³³ of solvation was applied to the ground state. Molar rotations were calculated at the wavelength of the sodium D line (589.3 nm). All molar rotations are reported in units of $\text{deg}\cdot\text{cm}^2/(\text{dmol})$. The center of mass of the glycine molecule has been used for the coordinate origin for all response calculations. While results attributed to the length representation of the electronic dipole operator are formally origin dependent, this dependence is minimized in variational methods when large basis sets such as aug-cc-pVDZ are used; see our earlier work and the references cited therein.¹⁷ Origin dependence does not vanish upon basis set saturation for the CC2 method.^{34,35} However, the small difference in the results using the origin dependent length operator and the independent velocity operator did not effect our conclusions.

Geometries used in the quantum mechanical calculations were generated with the GROMACS³⁶ molecular dynamics program, version 3.3.3, in a fashion similar to Mukhopadhyay et al.²⁶ Molecular dynamics of a glycine molecule were run in a cubic periodic solvent box measuring $25 \times 25 \times 25$ nm containing 509 Simple Point Charge (SPC) water molecules, resulting in a system with an average density of 1.0 g/cc. To avoid possible artifacts from the cubic shape of the periodic box, no water molecules greater than 12.5 nm from the center of the solute were included in the subsequent quantum mechanical calculations. The all-atom OPLS-AA³⁷ force field was used for the simulations, which were carried out at 300 K with a time step of 1 fs. Snapshots of the simulations for subsequent computations of Circular Dichroism (CD) and optical rotation were taken every 10 ps, which was a sufficient duration for energetic and chiroptical response calculations of adjacent configurations to be uncorrelated.

Results and Discussion

Glycine Solvation As a Function of Distance. Explicit solvation at the quantum mechanical level entails significant

computational costs. With this in mind, any development of such a solvation model should first consider how many explicit solvent molecules are needed in a system in order to affect full solvation on the solute. Fortunately, with respect to the solvation of the amino acid glycine, we can benefit from the experience gained in previous studies. Several articles have been published on the topic, much of which is summarized in the recent work of Aikens and Gordon.² They concluded, *inter alia*, that "Eight water molecules do not appear to fully solvate the glycine molecule.". As we are interested in the effects that water molecules have on the chiroptical response properties of amino acids such as glycine, we must further investigate just how many of these molecules are needed to "fully solvate" glycine, so that we may have some idea of how many water molecules should be included in system that aims to model the full effects of explicit water molecules on this solute.

Before delving into the energetics of solvation, let us first consider the structure that the water molecules form around the glycine solute. To look at how solvent molecules orient themselves about the solute a radial distribution plot was created from 4096 snapshots of a glycine in water dynamics simulation. The results are depicted in Figure 1.

From the plot it is apparent that the density of the solvent reaches a maximum around 3.7 Å from the solute center and then dwindles to a minimum at 5.0 Å. Integration of the area between the solute and the minimum at 5.0 Å reveals approximately 16 water molecules are contained in this innermost solvation shell. Integration through the next minimum in solvent density at 7.0 Å adds another 30 water molecules in a second solvation sphere, giving a total of 46 waters needed to fill two solvation spheres. Beyond this the water appears to have little structure with respect to the solute and maintains a density close to that of pure water. If we set a cutoff for a third solvation shell at 9.0 Å, it would mean including approximately 100 water molecules in the first three shells. A typical snapshot of a molecular dynamics simulation of glycine including one, two, and three solvent shells of water is illustrated in Figure 2.

To have a uniform reference for the solvation energy, all energies for the interaction between the solvent and the solute were obtained from quantum mechanical calculations. In the molecular dynamics framework used here, such calculations are inherently more time-consuming than the dynamics calculations used to generate the configurations, so the number of water-glycine interactions as well as the number of sampling snapshots had to be limited. Here we considered at the individual interactions of each of the nearest 256 water molecules with the glycine solute. Since this entailed performing that number of costly *ab initio* calculations for every snapshot examined, only the first eight sampling geometries of the dynamics simulation were used for this example. In the interest of possibly saving computational resources in the future, each water molecule was modeled once in the full quantum mechanical (QM) set, with a full compliment of electrons and basis functions, and once as a set of negative (oxygen) and positive (hydrogen) point charges. The charges for this model were those from the 3 point

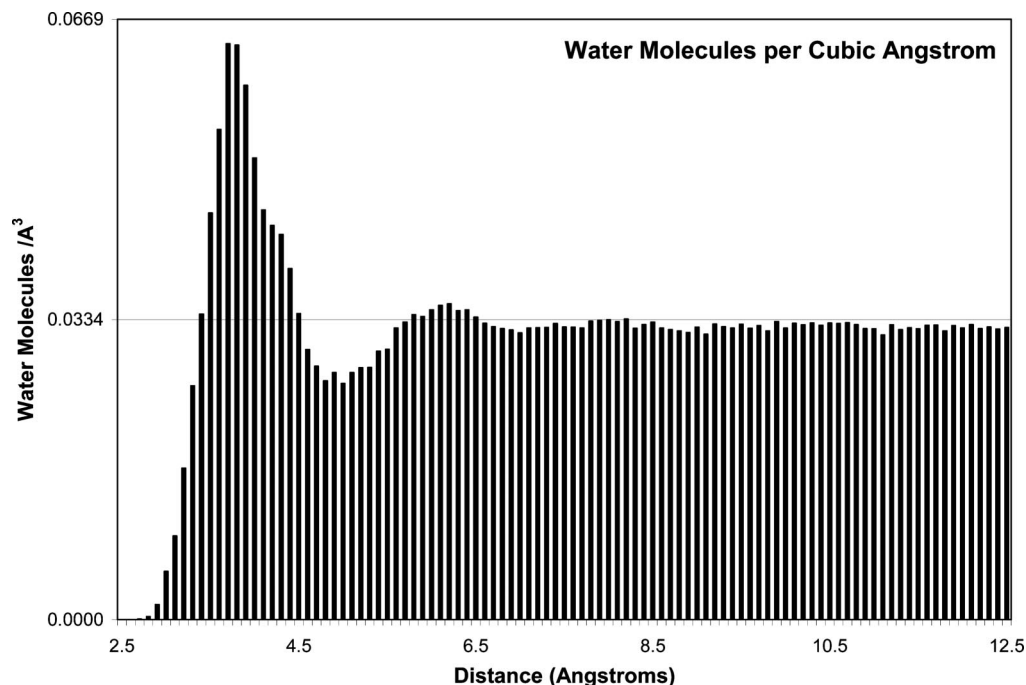


Figure 1. Molecular dynamics simulation of glycine in water: Probability of finding a water molecule (per cubic angstrom) as a function of distance from the solute. Solute position is defined as the center of solute mass; solvent position is defined as the location of its oxygen nucleus. Radial shells with a width of 0.1 Å were used to generate the plot. For reference, pure water with a density of 1.0 g/cm³ has 0.0334 water molecules per cubic angstrom.

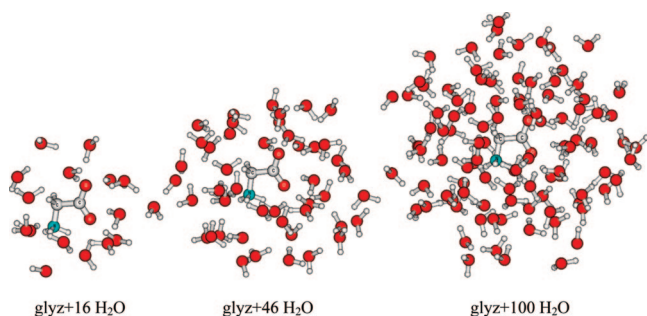


Figure 2. Representative configurations of a glycine molecule surrounded by 16, 46, and 100 water molecules which approximate one, two, and three shells of solvation, respectively.

TIP3P type waters.³⁸ For each calculation the interaction energy was calculated by subtracting the sum of the energy of the glycine molecule and the water molecule from that of the glycine-water system (no correction was made for basis set superposition). Note that this is only really partial solvation energy, since only a single molecule of solvent is being considered. The results are depicted in Figure 3.

The energetic results are consistent with what is expected from the radial distribution of the water molecules. The water molecules in the innermost solvation shell, those within five angstroms of the solute center, are those with the greatest effect on the energy. This effect is largely negative, which indicates the stabilization of the highly polar glycine zwitterion by the polar water molecule. Note that this stabilizing effect is seen when point charge water molecules are used as well as when full QM waters are modeled. This indicates that the dipole-

dipole interaction, which can be effectively modeled by the SPC waters, plays a prominent role in the solvation.

For water molecules farther from the solute, the solvation effect is lessened and becomes dominated by pure dipole-dipole interactions. The energetic effect of waters in the second solvation shell, those between approximately 5 and 7 Å, is far smaller, on average less than half the magnitude of those in the inner shell. Beyond that distance solvation effects dwindle further. At 9 Å from the solute center, about where the 100th water is located, the effect upon solvation has become small compared to the level of accuracy inherent in the ab initio calculations.

Glycine: Solvent Effects on Molar Rotation. The recent focus of our research has been the modeling of the chiroptical properties, including molar rotation, of amino acids in solution. Incorrect modeling of the Boltzmann populations of amino acid conformers, caused in part by an insufficient solvent system, has been considered as one possible source of error. This is especially true since these conformers can have both large positive and negative rotations, which should match experimental results only upon calculation of a correct weighted average of their responses. Another important part of this current model, which was absent in earlier works, is the direct effect that explicit solvent molecules have on optical rotation. It is important to study their effects separately, which makes the glycine and alanine zwitterions attractive candidates for study since each has only one local minimum structure.¹⁷ Glycine draws particular interest not only because of its low molecular weight but also since it is symmetrical, making it a good test case as a system which can exhibit a chiroptical response depending on its

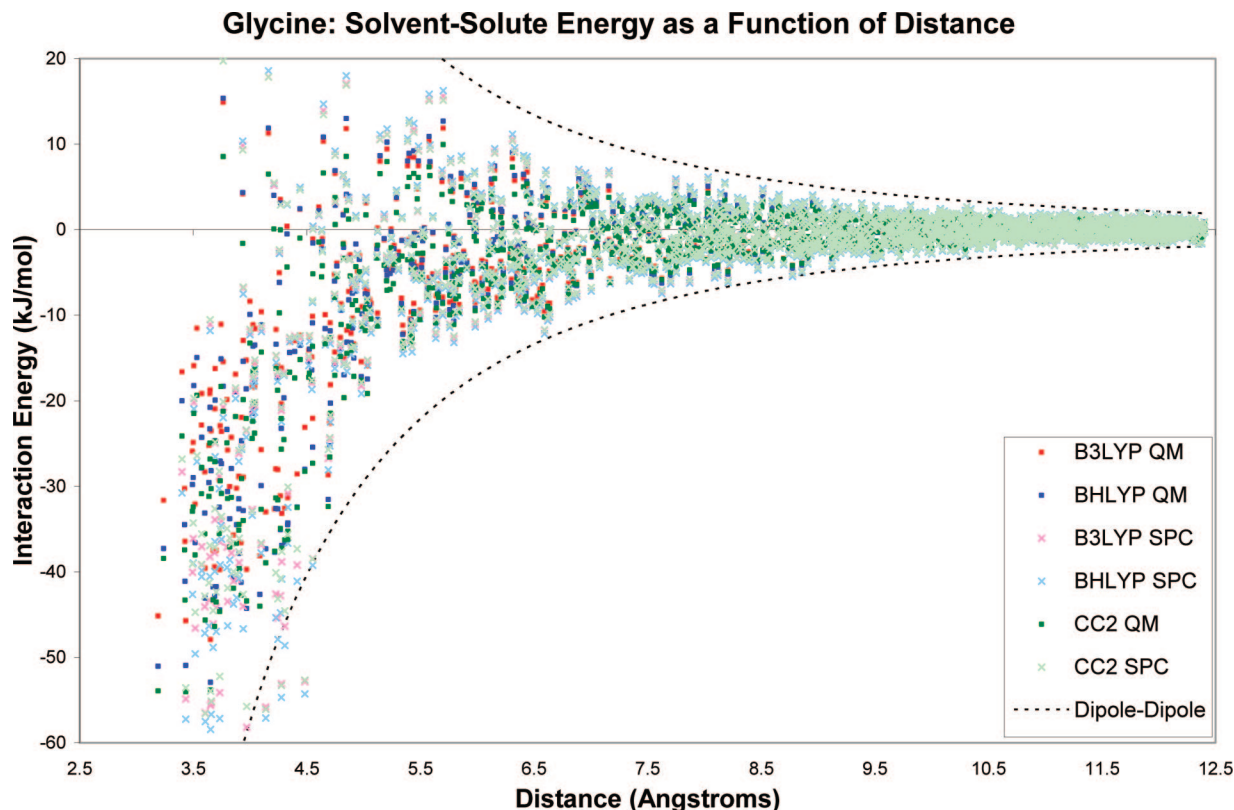


Figure 3. The energy of solvation caused by one water molecule upon glycine as a function of the distance between the oxygen atom of the water and the center of mass of the glycine. ($E_{\text{interaction}} = E_{\text{solute+solvent}} - E_{\text{solute}}$, with $E_{\text{solute}} = 0$ when SPC waters are used.) The closest 256 water molecules considered at in each of eight snapshots of a molecular dynamics simulation. Calculations at the B3LYP, B3LYP, and CC2 are shown in red, blue, and green, respectively. Full quantum water results are shown in dark colors, while those from SPC point charge waters are in lighter colors. The range of variation in energy expected from static dipole-dipole interactions is depicted by the dashed line, computed using dipole moments of 13 and 2.35 Debye for glycine (using an average value from Destro et al. and references cited therein)³⁹ and water (using the value for the TIP3P model),³⁸ respectively.

configuration, responses which we know must average to zero over time.

To investigate the aspects of explicit solvation a linear response calculation of molar rotation at 589.3 nm of a glycine-water system was performed on each of the MD snapshots considered in the previous section. Again both full QM and SPC waters were used, and the B3LYP and B3LYP hybrid functionals were considered. The CC2 method was not used here because of the lack of a CC2 implementation for optical rotation in the software used for this work.

While the glycine molecule is itself an achiral molecule, a snapshot of a solvated glycine can exhibit a chiroptical response for a combination of two reasons: First, the glycine molecule itself can be found in geometries where its plane of symmetry is broken. It has an equal probability of being captured in both dextrorotatory and levorotatory conformations. For the limited sample size of eight configurations, we were fortunate to find that the unsolvated glycine molecule had a positive molar rotation exactly four times and an equal number of negative molar rotations. The second reason that a solvated glycine molecule may exhibit a nonzero molar rotation is the asymmetrical orientation of a water molecule with respect to the glycine. This is the phenomenon of interest; in order

to isolate this solvent effect on molar rotation response calculations were carried out on glycine both with and without the presence of a water molecule and subtracting the two molar rotations. (If the water molecule could adopt a chiral configuration,⁴⁰ we would have to consider its molar rotation as well; however, an isolated water molecule has only three atoms which are inherently coplanar and thus can have no intrinsic chirality regardless of how its geometry is distorted by vibration.) The results of these calculations are shown in Figure 4.

As expected, a water molecule has a pronounced effect on the molar rotation of a glycine-water system, and the magnitude of that effect varies inversely with the distance between the solvent and solute molecules. The magnitude of this change in molar rotation remains rather consistent regardless of whether a point charge or quantum mechanical water causes the perturbation. A drastic change however can be seen when the amount of exact exchange in the hybrid DFT functionals is varied. The change in molar rotation caused by solvation is much greater in the B3LYP hybrid than in the B3LYP; the cause of this change will be discussed in the next section. The large magnitude of the solvent effect on the molar rotation illustrates the challenge of successfully averaging this quantity over the course of a

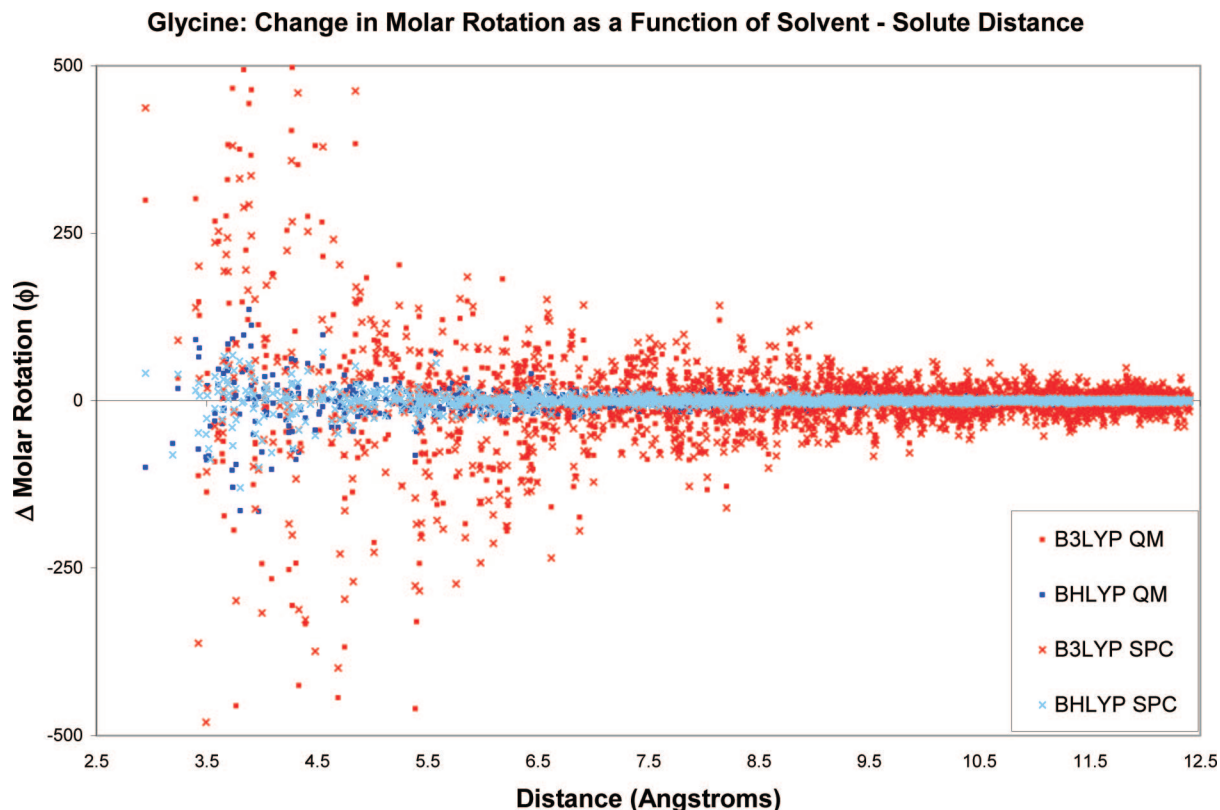


Figure 4. The change in molar rotation (ϕ) caused by a single water molecule as a function of its distance from the glycine center ($\Delta\phi = \phi_{\text{solute+solvent}} - \phi_{\text{solute}}$). Calculations were performed with the aug-cc-pVDZ basis at the B3LYP (red) and BHLYP (blue) levels of theory using QM (dark colored) and SPC (light colored) water molecules.

molecular dynamics simulation in order to minimize the statistical error.

Effects on the Circular Dichroism of the Lowest Excitation. The direct linear response method for calculating molar rotation used in the previous section performs the task very efficiently. However, it tells us little about *why* a molar rotation is what it is. Here we are interested in what electronic transitions are responsible for the molar rotation. This can be done by computing molar rotation via the sum over states method. In a prior study on aliphatic amino acids such as glycine, we confirmed that the lowest lying electronic excitation, the n to π^* transition of the carboxylate moiety has a large influence on the molar rotation observed at 589.3 nm.¹⁶ While to accurately model molar rotation by the SOS method nearly all possible excitations do need to be included, the excitation closest in energy to 589.3 nm is particularly important regarding the contribution from the carboxylate chromophore. As we are interested now in the effect an explicit solvent molecule has on this molar rotation, it is therefore beneficial to consider the effect this solvation has on the critical first electronic CD.

Using the same configurations as in the previous section, calculations of the rotatory strength and wavelength of the first excitation were performed at the B3LYP, BHLYP, and CC2 levels of theory using QM and SPC water molecules. In each case the change of the CD response caused by the solvent molecule was computed by subtracting from the CD of each water-glycine system the CD caused by an unsolvated glycine molecule in the same

geometry. The lowest electronic excitation of water is far higher in energy than that of the glycine, and so the first CD transition that is observed in the model is always centered on the solute. The solvent serves merely to perturb that transition within the solute. The results of these calculations are plotted in Figure 5.

Just as with the energy and molar rotation, the effect of a water molecule on the first CD excitation decreases with distance, as expected. The change in rotatory strength caused by the water has an equal probability of being positive or negative, as one would expect for a chiral molecule being perturbed by an achiral solvent. The change in the wavelength of that transition however tends to be negative at all levels of theory. That is, a nearby water molecule tends to induce a blue shift of the first transition.

This blue shift is far more pronounced at the B3LYP and CC2 levels of theory than with the BHLYP functional. In the gas phase model, this excitation takes place at 430, 393, and 287 nm, respectively. These are all far too low in energy compared to solution phase measurements of aliphatic amino acid CD, which indicate that this dichroism has a maximum in the range of 200 to 215 nm.^{41,42} Solvation increases this excitation energy and thus lowers its wavelength at all levels of theory, more so for B3LYP and CC2 than BHLYP. The contribution of a CD excitation to the molar rotation depends inversely on the difference between the wavelength at which the molar rotation is computed or measured (in this case that of the sodium D line, 589.3 nm) and the wavelength at which

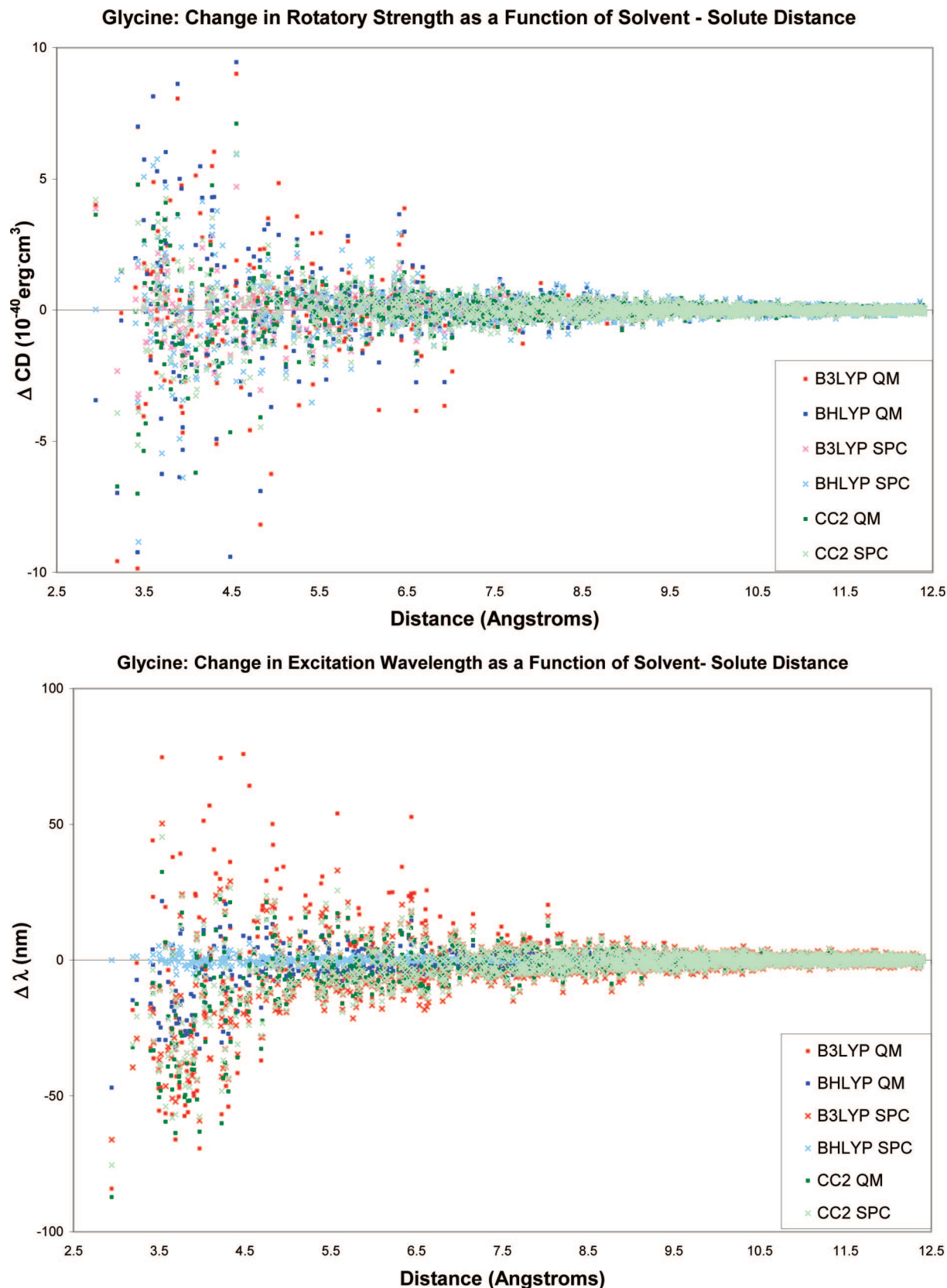


Figure 5. The change in circular dichroism of the first electronic transition as a function of water distance from the solute center. Change in rotatory strength (top) and wavelength (bottom) are plotted.

the excitation occurs, per the Kramers–Kronig relationship. This leads to the explanation of why solvation has a more pronounced effect on the molar rotation of the

glycine molecule with the B3LYP hybrid functional than with the BHLYP. Solvation shifts the first electronic excitation wavelength farther from the sodium D line to

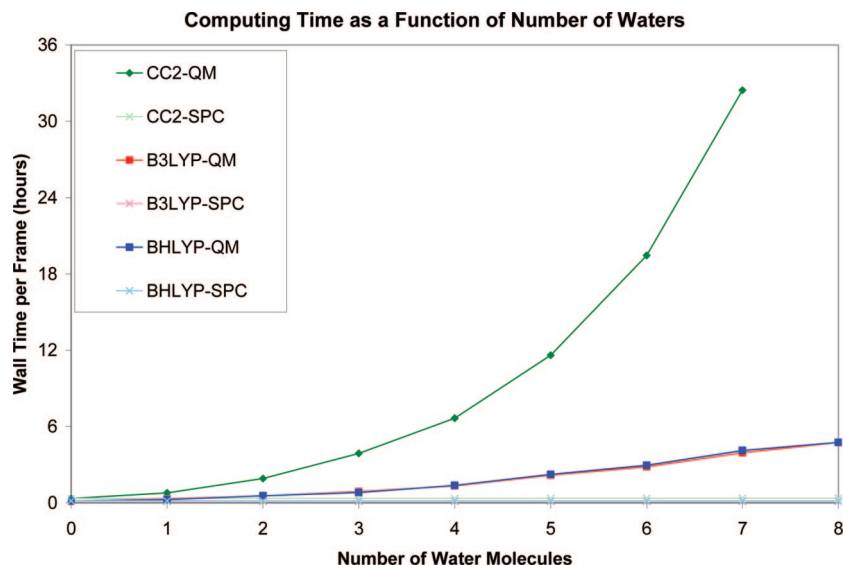


Figure 6. Time required to complete a CD calculation on a single snapshot of a glycine-water system as a function of the number of water molecules. Numbers reported are average values from 128 snapshot simulations. One core of an AMD 2.2 GHz 64-bit dual core Opteron processor was used for each calculation.

a greater extent with the B3LYP functional than with the BHLYP, where it was already much farther away to begin with. Note that the overall excitation energy changes upon full solvation (see Figure 8 below) are roughly comparable for CC2 and B3LYP (slightly larger for B3LYP) and significantly smaller for BHLYP.

The Correlation between Differing Levels of Theory.

When developing a model chemistry with efficiency in mind, it is helpful to compare the result computed at various methods with those calculated at the most robust level of theory available on a relatively simple system. Here the system of glycine and one water molecule has served as a microcosm of a glycine molecule solvated by multiple water molecules. We have at our disposal to perform multiple calculations on this system at a correlated wave function based level of theory (CC2/aug-cc-pVDZ). However as more waters are added, performing the coupled cluster calculation on an increasingly large system will become impractical and eventually impossible, due to the scaling of this method with respect to system size. This is illustrated quite clearly in Figure 6 where CD calculations (first electronic excitation only) on a system with a glycine and 7 water molecules take over one day *per configuration*, and hundreds of such configurations are required to achieve an averaged result that is a reasonable representation of the dynamic system. With larger systems that include more solvent molecules, modeling with more efficiently scaling methods such as density functional theory or the “zero order scaling” point charge waters becomes a necessity. Employing these point charge waters such calculations take approximately 22 and 8 *minutes* per configuration at the CC2 and DFT methods, respectively, regardless of how many waters are included. As such, it makes sense to take a close look at how closely more efficient model chemistries compare with the coupled cluster model.

In order to do this, we plotted the correlation of the change in the lowest CD excitation (both rotatory strength and wavelength) caused by various types of water molecules versus those changes caused by a QM CC2 water. The QM

CC2/aug-cc-pVDZ level of theory is used here as a point of reference since it is the highest level of theory which we determined as practical for the purpose of the present study. The correlation of the change in wavelength is depicted graphically in the top of Figure 7. The correlation of change in rotatory strength is shown in the bottom graph. Each data point corresponds to a distinct snapshot of a glycine in water molecular dynamics simulation; 128 snapshots were considered. For each geometry the glycine molecule was modeled at the QM level, and which ever single water molecule that happened to be closest to the glycine center at that point in time was included as well, either at the QM level or as a set of point charges.

The perturbations to the first excitation of glycine caused by water molecules modeled with all of the less costly methods correlate positively with that caused by a quantum water included at the coupled cluster level. For all of the methods except QM B3LYP, the slope of the correlation in wavelength is less than one, which indicates that the change in excitation wavelength, nearly always a blue shift, caused by the water is smaller in magnitude for the other methods than for full QM CC2. The SPC-CC2 method shows arguably the best correlation with QM-CC2, with a regression line slope of 0.87 and an R^2 value over 0.95; the SPC-B3LYP also correlates well, with a slope of 0.87 and an R^2 of nearly 0.87. The BHLYP methods, both full QM and SPC, tended to have their CD less affected by water than the other methods, principally since the first excitation with this DFT hybrid is already significantly blue-shifted compared to those calculated with the other methods. Note the correlation that is examined closely in Figure 7 is only that of the water molecule that is closest to the amino acid center in each configuration; for water molecules that are farther away, as was already shown in Figure 5, the correlation between methods appears to improve significantly.

As noted the QM-B3LYP method seems to have the poorest correlation with the QM-CC2 method. It is the only method that shows a change in excitation wavelength that

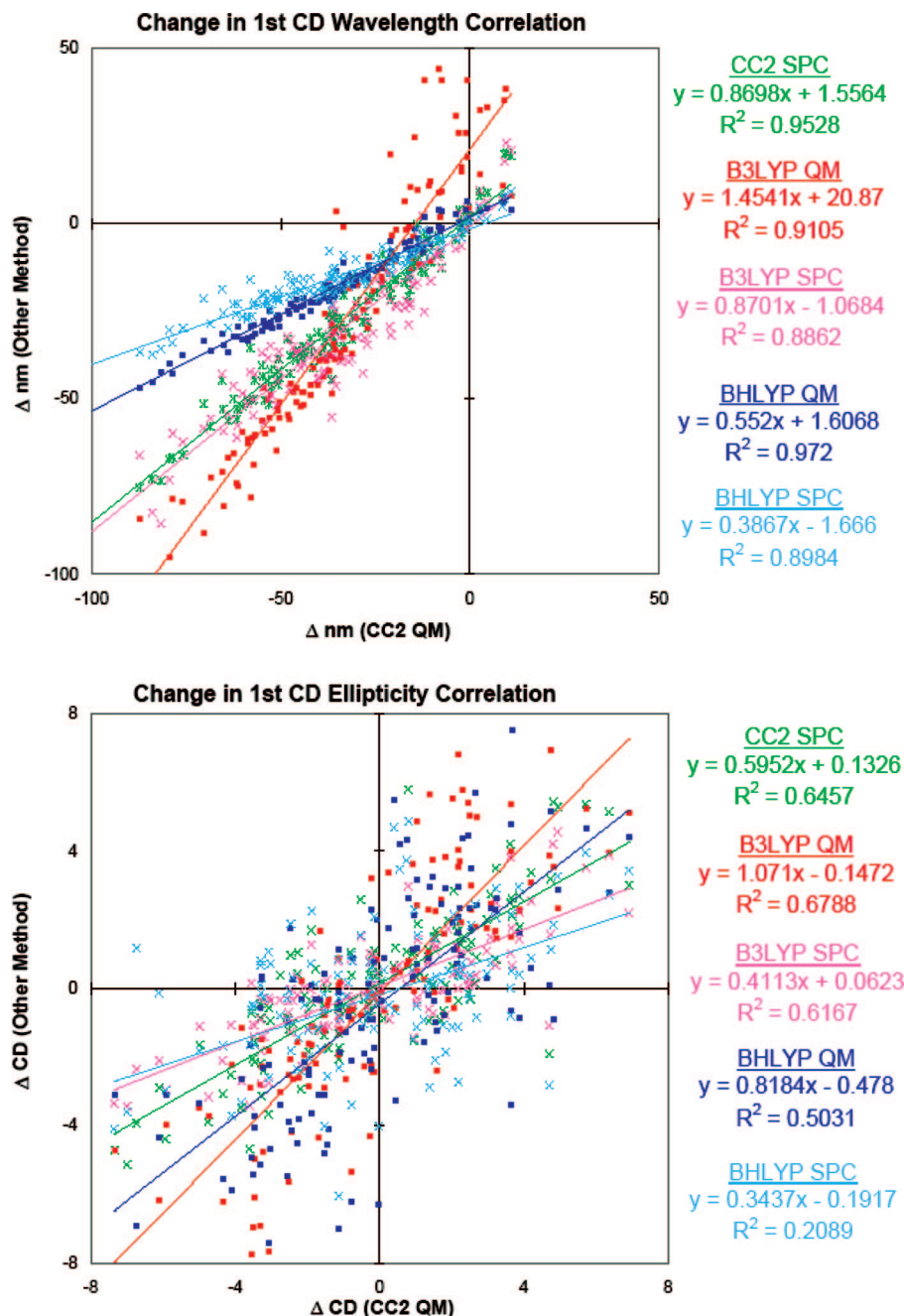


Figure 7. Correlation of wavelength (top) and ellipticity (bottom) of the first excitation caused by the closest water molecule to the glycine solute at various levels of theory with full CC2/aug-cc-pVDZ. 128 configurations were considered.

tends to be greater in magnitude than for QM-CC2. Furthermore, it is the only method that gives a significant number of red shifts to the first excitation for water-glycine configurations where the QM-CC2 method yields blue shifts. Adding a water molecule to a glycine zwitterion should induce a blue shift in its first excitation, due to the stabilization of the glycine electronic state by the solvent. Density functional theory, however, is known to have an issue with producing charge transfer excitations which are often unphysically low in energy. This deficiency, along with its particular consequences in supermolecular solvation simulations such as this one, has been discussed in detail recently by Neugebauer and co-workers.⁴³ Various methods are under development to compensate for this shortcoming.^{44–46} This charge transfer problem can be ameliorated somewhat

by using hybrid DFT functionals with a greater portion of exact exchange,⁴⁷ such as BHLYP. But with B3LYP, the combination of a QM solute and a QM solvent sets up a scenario where such a charge transfer excitation can take place between solute and solvent or even between two solvent molecules. As indicated by the red data points in the top of Figure 5, it appears to occur frequently enough at this level of theory to be an issue. With point charge waters this is obviously not an issue, since they have no electrons or orbitals to participate in such a nonphysical electron exchange. Thus, with the B3LYP functional the more simplistic point charge waters appear to better model the solvent perturbation of the first electronic excitation of glycine than more costly QM waters do.

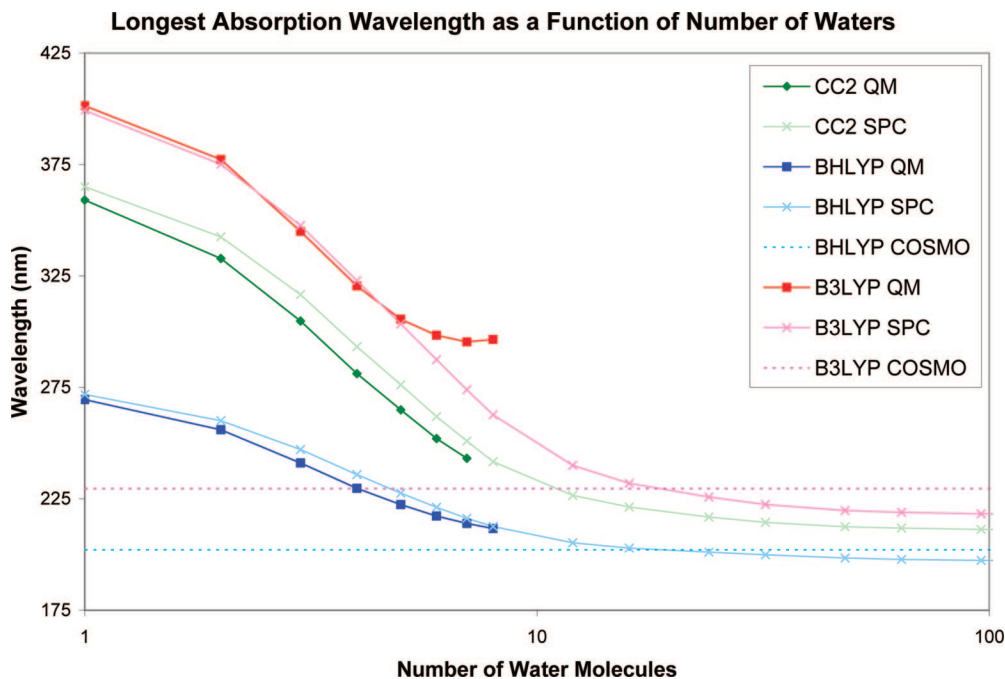


Figure 8. The effects of adding multiple water molecules on the 1st excitation wavelength of the glycine-water system. The results represent the weighted average of 128 configurations of the dynamics simulation of the longest absorption wavelength of various glycine-water systems.

The magnitude of the apparent charge transfer problem is illustrated more dramatically in Figure 8. As one, two, three, and more waters are added to a water glycine system, we expect to see an initial decrease in the wavelength of the lowest electronic transition as the greater number of water molecules stabilize the highly polar glycine zwitterion and increase its HOMO–LUMO gap, with the effect leveling out as the number of water molecules increases. Point charge waters do not cause such unphysical results, and the longest wavelengths computed with these methods converge to slightly shorter wavelengths than those obtained with corresponding continuum based (COSMO) methods. The coupled cluster method does not suffer from the charge transfer problem, so the changes in wavelength at this method is quite similar for QM and SPC waters, regardless of how many are added. BHLYP appears to perform fine as well, though at around eight waters Figure 8 indicates that the charge transfer problem may be beginning to show itself with this QM method as well; using such a hybrid functional with a large portion of exact exchange has indeed compensated for part of the charge transfer excitation problem but has not eliminated it completely. We caution that while the trends shown in Figure 8 are quite consistent with a charge transfer problem, they do not prove that this is the cause or the only cause of the deviations seen in the TDDFT methods. It is also presently unclear if there is any spurious charge transfer present involving water orbitals or if the presence of the water exacerbates an intramolecular charge transfer within the solute.

As for the change in rotatory strength, as with the change in wavelength, there is a positive correlation among all of the solvation methods. At the QM-B3LYP level, the first rotatory strength tends to be larger in magnitude than at QM-CC2, whereas at the QM-BHLYP level it tends to be smaller.

This is in keeping with the excitation energies: the CC2 results tend to fall between those obtained with B3LYP and BHLYP. With point charge waters we consistently see perturbations that are too weak compared to QM-CC2. For example, using the SPC charge waters we see a perturbation to the rotatory strength of about 35–60% of that found with full QM CC2 water. This indicates the limits of the point charge water model; it simply cannot reproduce all of the interactions that take place between a water molecule and the solute such as those involving orbital overlap, polarization,⁴⁸ and quadrupole and higher order multipole interactions. They can however reproduce the dipole moment of the water molecule, and judging by the slope of the regression lines this seems to be the most important interaction.

Another issue of note is the R^2 values of the regression lines. This indication of correlation is rather poor, particularly between the intensities with the BHLYP hybrid and those at QM-CC2. We can see on the bottom graph of Figure 7 many instances where the sign of the CD does not agree between these methods. We have reason to believe that this may be caused by insufficient modeling of electron correlation. In an earlier work, we found that increasing the amount of exact exchange in a hybrid DFT functional eventually resulted in the wrong sign of the CD of the first excitation being modeled.¹⁷ For this modeling of one configuration CD of the alanine zwitterion, this sign change occurred at some point between the BHLYP and HF levels of theory, i.e. where between 50% and 100% exact exchange were used.

Mixed SPC/QM Solvation. Thus far, we have only considered the solvation of glycine by point charge or quantum mechanical water molecules but not both at the same time. However a model can be devised in which the water molecules closest to the solute are computed at the QM level, while those farther away are simultaneously

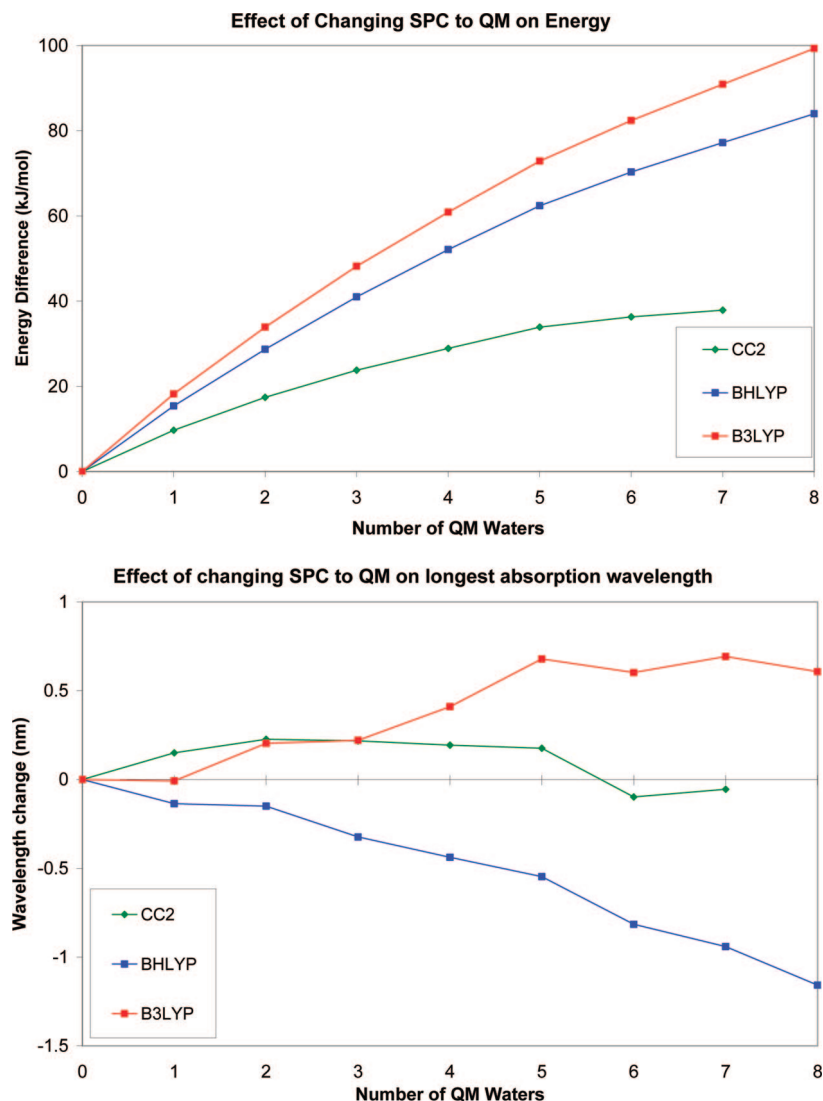


Figure 9. The difference in partial solvation energy and longest absorption wavelength of a glycine molecule solvated by 256 point charge water molecules and one solvated by n QM waters and $256-n$ point charge waters.

considered as sets of simple point charges. To evaluate the merits of such methods, we performed calculations of a system in which glycine is solvated by 256 point charge water molecules. These results were compared to computations in which glycine is solvated by n QM waters, where $n = 1$ to 8, and $256-n$ SPC water molecules. Waters were designated as QM based on their proximity to the solute center, with the closest being the first considered as QM, the next closest the second, and so on. The results are depicted in Figure 9 based on an average of 128 MD configurations each.

The discrepancies in close-distance solvation energies between point charge and quantum waters that was first noted in Figure 3 is even more apparent in the top of Figure 9. The water molecules considered in Figure 9 all reside in the first solvation shell, where they are apt to be in close contact with the solute, so we expect to see the most pronounced differences here. For the waters in closest contact with the glycine we see that the point charge waters result in a greater stabilization than do the QM waters, which is not unexpected since point charge

waters do not take into account some types of interactions, such as steric repulsion, which are more prominent at short distances. The point charge waters are far more similar to their corresponding QM waters with the CC2 method than with the DFT, though such differences are still significant. However we can see at all levels of theory the significance of using a QM water as opposed to a point charge water diminishes as the waters in question get progressively farther from the solute center.

The effect of using QM as opposed to SPC water molecules for the innermost solvation is far less noticeable on the first excitation wavelength. As is shown in the bottom of Figure 9, switching from point charge to QM water molecules for even the innermost 8 water molecules of the 256 molecule solvation sphere results in a maximum change of around 1 nanometer in wavelength. At the CC2 level of theory, which should be the most reliable, this difference between QM and SPC waters is quite negligible, ~ 0.2 nm. This indicates that even for the closest held waters of the solvation sphere a simple point charge model

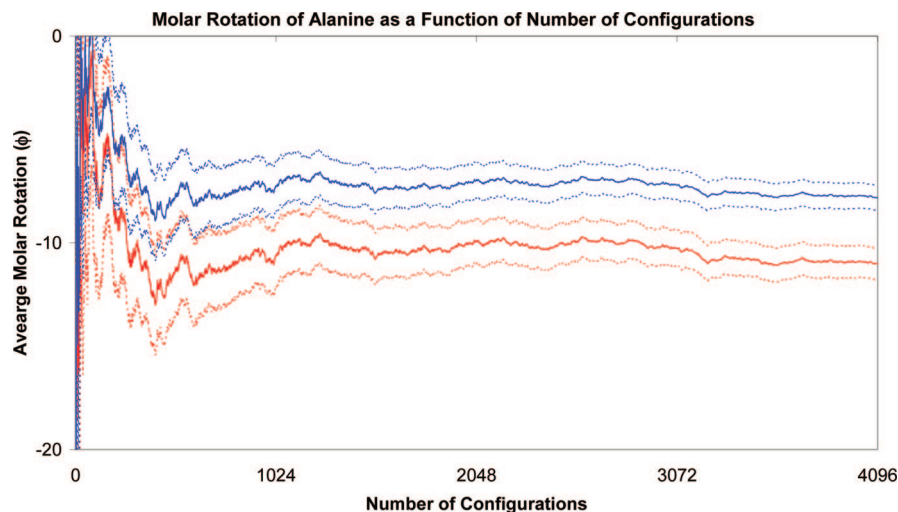


Figure 10. The convergence of the molar rotation of alanine as the number of averaged configurations increases. The BHLYP/SPC (blue) and B3LYP/SPC (red) methods were used. The running averages are represented by solid lines, while the error bars, at one standard deviation, are represented by dashed lines.

Table 1. Molar Rotation ($[\phi]$, $\text{deg}\cdot\text{cm}^2/\text{dmol}$) of Glycine and Alanine with Various Methods^a

molecule		expt	static COSMO		dynamic COSMO		dynamic SPC	
			B3LYP	BHLYP	B3LYP	BHLYP	B3LYP	BHLYP
glycine	ϕ	0	0.2	0.1	-0.9	-0.5	-1.0	-0.8
	\pm				1.4	0.9	1.1	0.8
alanine	ϕ	1.6	5.4	-1.5	-16.7	-10.9	-11.0	-7.8
	\pm				0.8	0.6	0.8	0.6

^a Experimental value for alanine is from ref 50. Calculations with static molecules were done by the same method used in our prior work.¹⁶ Error bars (\pm) represent one standard deviation of statistical error from the dynamics simulation.

is quite capable of modeling the solvent effects on this electronic excitation.

Glycine and Alanine: Comparing Molar Rotations with Experiment. This work so far has focused on the chiroptical response properties of glycine, a molecule that may serve as a means for calibrating our method but which is itself achiral. This serves the purpose of a “blank” for our molecular dynamics method of modeling molar rotation. The molar rotation of glycine must average to zero, and so whatever residual molar rotation that does not average out after computations on multiple snapshots of the glycine in water system will indicate some idea of how much statistical error is inherent in the method. It seems prudent here to also take this method and extend its application to a similar chiral amino acid, one whose chiroptical response properties ought not to average to zero over time and whose chirality, as exhibited in its molar rotation, can be modeled and compared to that of experiment. Alanine, the smallest *chiral* amino acid, serves as a natural target for such an investigation.

In this section 40960 ps molecular dynamics runs of glycine and alanine were performed under the same conditions as the glycine simulations in the foregoing sections. A total of 4096 equally spaced configurations were taken for subsequent molar rotation calculations. Both the B3LYP and BHLYP hybrid DFT methods were employed, using either our simple point charge waters or the COSMO continuum model that we used in prior works.^{16,17,19} For each selected configuration along the

molecular dynamics trajectories a molar rotation was computed, and that rotation was appended to a running average of molar rotations. Two examples, alanine in SPC waters with the BHLYP and B3LYP functionals, are shown in Figure 10. Convergence criteria are based upon the principles of signal averaging, under which the standard deviation of a data set should drop as $n^{1/2}$ per number of points averaged, n , if the points are uncorrelated.⁴⁹ We confirmed that for these systems this is the case when we allowed 10 ps to elapse between snapshots of the molecular dynamics run.

These results are compared with those obtained using static alanine molecules and the COSMO model as well as with those from experiment. These data and data from calculations on glycine are summarized in Table 1.

The data in Table 1 show that the molecular dynamics/point charge solvation method produces results comparable to earlier results with frozen solute molecules and a continuum solvent. All results are reasonably close to experiment and well within the margin of error typical of TDDFT based calculations.⁵¹ Error bars tended to be larger with the COSMO solvent model than with the discrete SPC waters and higher for the B3LYP hybrid than for the BHLYP. This is due to the relatively lower excitation energies obtained with COSMO and with B3LYP, which result in larger magnitudes of the computed molar rotations.

In addition to comparing our results to experiment, we should also mention the results of D’Abramo et al., who

performed dynamics based computations of alanine in water using TDDFT and a “perturbed matrix method” of solvation.¹⁴ Using this method they obtained a specific rotation of about $+60 \text{ deg} \cdot \text{cm}^3/(\text{g} \cdot \text{dm})$ for alanine, which corresponds to a molar rotation of $+53 \text{ deg} \cdot \text{cm}^2/\text{dmol}$. It would appear that our method is significantly closer to experiment. However, their rotatory dispersion calculations were performed with a truncated sum-overstates method. In contrast, the linear response method used here does not possess such truncation errors.⁵² As such, a direct comparison between results with our point charge solvation model and their perturbed matrix model is not currently possible, though the disagreement is likely due to the truncation error from the sum over states calculation of alanine.¹⁶

Conclusions

Simple point charge (SPC) water molecules have been shown to be a computationally efficient alternative to using quantum mechanical waters in modeling the solvent effect on a solute's chiroptical responses. The near zero order scaling of point charge waters allows hundreds of explicit water molecules to be considered at negligible computational cost. The effect that SPC waters have on the computed chiroptical properties of a solvated glycine molecule are comparable to those obtained with the much more expensive CC2 method. When density functional theory is employed, point charge waters may prove superior to explicit QM waters in simulating solvent effects on such response properties, since the point charge model does not exacerbate the problem of DFT with spurious charge transfer excitations. Calculations on the chiral amino acid alanine with the SPC/DFT method yield results that are in reasonably good agreement with experiment and marginally better than those with the same geometries and the COSMO/DFT method. Further benchmarking of the point charge/DFT protocol is presently underway.

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