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Acknowledgements

We would like to take the time and the effort to thank my CHE 476 (Computational Chemistry) classmates for useful discussions in order to accomplish this publication. We would also like to thank the Department of Chemistry for this wonderful opportunity and resources that we were able to use to conduct this type of valuable research.

Diol-Mediated versus Water-Mediated Proton Transfer Reactions

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ABSTRACT The triple-proton-transfer reactions of 8H-1,8-naphthyridin-2-one (8H-naph) have been investigated by employing different *ab initio* quantum mechanical methods. The proton transfer reactions studied were facilitated through complexation of 8H-naph with a 1,3-propanediol molecule or two adjacent water molecules. Identical proton transfer reactions were studied using a model system of 8H-naph to investigate the validity of computational approaches that use model systems to study more complex systems. The solvent effects on the structures were investigated for comparison to the initial gas phase calculations. The potential energy, reaction force, and work profiles were studied along the intrinsic reaction coordinate to monitor the developing proton transfer reactions.

INTRODUCTION

Within the realm of biological and photochemical practices, the transferring of a proton from one atom to another is one of the most important and fundamental concepts of study (1,2). The reactions taking place within these biological and photochemical processes generate the transfer of a proton over long hydrogen bond distances.

In recent studies, systems of van der Waals complexes between heteroaromatic molecules and polar molecules have become of great interest due to their vast applicability in the biological realm. Several applications include one; aromatic rings with a hydroxyl group can serve as prototypes in biomolecules, meaning that different H-bond conditions within biomolecules can be studied, two; different hydrogen bonding conditions can be studied

simply by choosing relatively weak solvents to relatively strong solvents and three; aromatic chromophores allow the convenient usage of laser-spectroscopic methods (2).

Aromatic rings are unique in that many of them have visible-frequency absorption features, while most molecules will not interact strongly with visible – frequency light.

The importance of these small polar molecules is derived from the large distance that exists between the donor and acceptor atoms in the proton transfer. With the assistance of the polar molecule, the proton transfer is able to proceed as the polar molecule serves as a “proton highway” to connect the donor and acceptor atoms. In the present paper, the intermolecular proton transfer reactions of 8H-1,8-naphthyridin-2-one (8H-naph) and a simplified model system are investigated through facilitating diol or water molecules.

A similar study investigated the excited-state proton transfer mechanism of 7-

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hydroxyquinoline facilitated through two methanol molecules (2). The structure of 7-hydroxyquinoline and 8H-naph differ only by the replacement of a ring carbon atom with a nitrogen atom in 8H-naph. The study presented here examines the triple proton transfer for 8H-naph and a model system of 8H-naph to compare the results and see if a similar mechanism would be achieved in both approaches.

If true, this could lead to the further validation of using simplified models to study more complex systems.

METHODS

Computational Methods

Geometry optimizations, frequency calculations, and single-point energy calculations were performed with the HF and MP2 levels of theory along with the HF/6-31+G(d) basis set used in the Gaussian 09 package of programs (3). The effects of a water solvent were investigated using the self-consistent reaction field (SCRF) method. The profiles of energy, force, and work were studied along the intrinsic reaction coordinate (IRC) for the diol and water molecule reaction pathways. The structure for the 8H-naph and model molecules are shown in Figure 1.

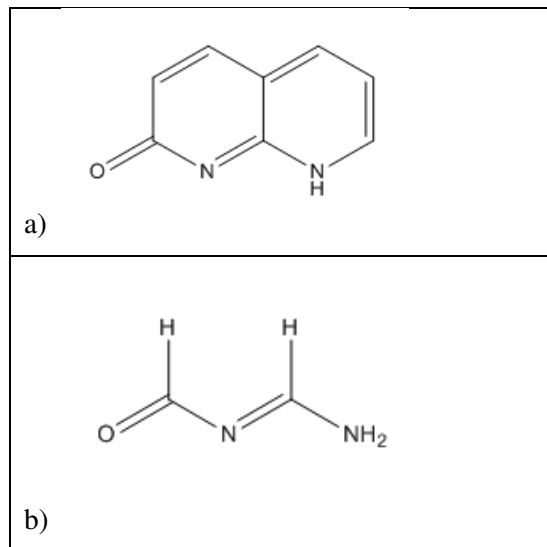


Figure 1: Structures for 8H-naph and model system.

RESULTS AND DISCUSSION

8H-naph and Model Monomer

The proton transfer reaction mechanisms were studied for the two systems shown in Figure 2 through diol and water facilitated transfer. The model system was derived from 8H-naph by extracting just the relevant atoms from the aromatic structure, which take place in the proton transfer.

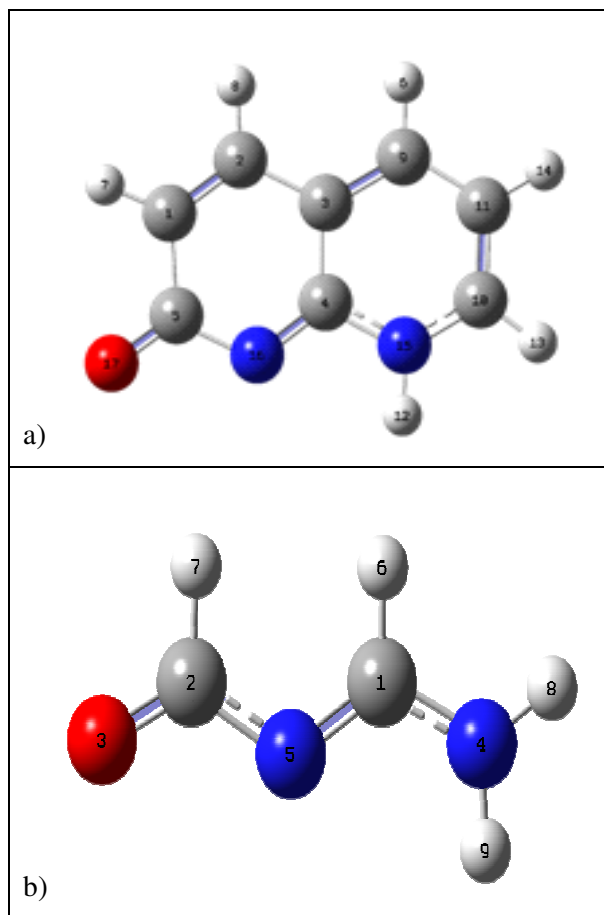


Figure 2: Analogous structures, as shown in Figure 1 for 8H-naph and model system. Color-coding for parts (a) and (b) are as follows; red represents an oxygen atom, gray represents a carbon atom, smaller - light gray represents a hydrogen atom, and blue represents a nitrogen atom. (a) 8H-naph structure with the proton transfer occurring between the N15 proton donor and the O17 proton acceptor. (b) Model system structure with the proton transfer reaction occurring from the donor N4 atom to the acceptor O3 atom.

The two forms shown in figure 1 will be referred to as the ‘keto’ forms in the remainder of the discussion. The final product forms, which are present following the proton transfer will be referred to as the “enol” forms as the oxygen will be protonated in these structures instead of the nitrogen atom.

Energy Comparisons

8H-naph Energy

The keto and enol structures for the 8H-naph diol and water complex structures were individually optimized using both the 6-31+G(d) and MP2 level of theory. Each structure was analyzed in a vacuum phase as well as a solvent phase to understand the solvent effects on the mechanism of proton transfer as seen in Tables 1 and 2.

Table 1: Relative Energies for Diol-Mediated Proton Transfer

	HF/6-31+G (d) with ZPE	HF/6-31+G (d) w/o ZPE	MP2/6-31+G(d) w/o ZPE	HF/6-31+G(d) w/o ZPE in Solvent	MP2/6-31+G(d) w/o ZPE in Solvent
Reaction energy (ΔE°) (kcal/mol)	8.14	8.15	9.43	-1.65	-3.42
Forward Barrier Energy (ΔE^F) (kcal/mol)	21.00	23.95	8.88		
Reverse Barrier Energy (ΔE^R) (kcal/mol)	29.14	32.10	18.32		

The reaction energy, forward barrier, and reverse barrier were only collected for the vacuum phase. The energy collected without the zero-point energy for both the HF and MP2 methods provide inconsistent theory in the vacuum phase. The MP2 energy should be lower

than the HF energy as HF over-compensates the electron-repulsion interactions(4). The data provided for both the HF and MP2 in solvent provide results consistent with the theory. The negative reaction energy in the solvent phase warrants further study. The energy collected under the HF level of theory results in a significant difference compared to the energy under aqueous conditions.

Table 2: Relative Energies for Water-Mediated Proton Transfer

	HF/6-31+G (d) with ZPE	HF/6-31+G (d) w/o ZPE	MP2/6-31+G(d) w/o ZPE	HF/6-31+G(d) w/o ZPE in Solvent	MP2/6-31+G(d) w/o ZPE in Solvent
Reaction energy (ΔE°) (kcal/mol)	7.72	9.85	2.24	-1.90	-3.87
Forward Barrier Energy (ΔE^F) (kcal/mol)	24.26	24.26	19.86		
Reverse Barrier Energy (ΔE^R) (kcal/mol)	31.98	34.11	22.10		

The reaction energy, forward barrier, and reverse barrier were once again only collected for the vacuum phase. The energy collected without the zero-point energy for both the HF and MP2 methods provide consistent theory in the vacuum phase, as the MP2 energy should be lower than the HF energy due to the inclusion of electron correlation. The negative reaction energy in the solvent phase indicates a need for further studies; in particular to discern the large difference observed between the vacuum and aqueous results in the HF level of theory.

Model Energy

Analogous energy calculations were made for the model-diol and model-water complex systems as seen in Table 3 and Table 4.

Table 3: Relative Reaction and Energy Barriers for Model-diol Complex System

	HF/6-31+G(d) with ZPE	HF/6-31+G(d) w/o ZPE	MP2/6-31+G(d) w/o ZPE	HF/6-31+G(d) w/o ZPE in Solvent	MP2/6-31+G(d) w/o ZPE in Solvent
Reaction energy (ΔE°) (kcal/mol)	12.46	11.63	9.45	16.23	12.84
Forward Barrier Energy (ΔE^F) (kcal/mol)	34.38	36.57	26.97	39.22	29.44
Reverse Barrier Energy (ΔE^R) (kcal/mol)	21.93	24.94	17.52	22.99	16.59

Looking at the difference between the HF and MP2 methods, whether vacuum or in solvent, the reaction energy and energy barriers are lower for all calculations done using the MP2 method. This is a result of the better account of electron correlation effects as HF overestimates the contribution by electron interactions (4). In the comparison of aqueous to vacuum systems, the ΔE° and ΔE^F are higher indicating that the model-diol complex is destabilized by the addition of a solvent since more energy is required for the reaction to proceed.

Table 4: Relative Reaction and Energy Barriers for Model-water Complex System

	HF/6-31+G(d) with ZPE	HF/6-31+G(d) w/o ZPE	MP2/6-31+G(d) w/o ZPE	HF/6-31+G(d) w/o ZPE in Solvent	MP2/6-31+G(d) w/o ZPE in Solvent
Reaction energy (ΔE°) (kcal/mol)	13.39	13.10	11.99	17.67	15.71
Forward Barrier Energy (ΔE^F) (kcal/mol)	38.08	40.38	32.31	27.69	22.09
Reverse Barrier Energy (ΔE^R) (kcal/mol)	24.69	27.28	20.32	10.02	6.38

The model-water complex system yields lower reaction energies and energy barriers from calculations between the HF and MP2 theory as expected due to correlation effects. Comparing the solvent phase calculations to the vacuum, there is a decrease in both ΔE^F and ΔE^R for the aqueous phase indicating that the transition state is lower in energy and therefore more stable in the presence of a water solvent.

8H-naph vs. Model Energies

Due to the nature of the proton transfer, the interaction between the cycles of transferring between both system yields the basis set superposition error (BSSE) where the atoms begin to overlap, which is shown in a calculation. Each structure, for both the water-mediated and diol-mediated structures, underwent a BSSE calculation to provide the energy associated with this intermolecular complexation. The complexation raw and corrected energies are shown in Tables 5 and 6.

Table 5: Raw and Corrected Complexation Energy with the Aromatic System

	Raw Complexation Energy (kcal/mol)	Corrected Complexation Energy (kcal/mol)
Diol_keto	-18.77	-16.87
Diol_enol	-15.8	-13.57
Water_keto	-25.14	-22.31
Water_enol	-21.74	-18.49

Table 6: Complexation Energy of Model-diol and Model-water Complexes

	Raw Complexation Energy (kcal/mol)	Corrected Complexation Energy (kcal/mol)
Diol_keto	-13.71	-12.29
Diol_enol	-17.10	-14.88
Water_keto	-21.45	-18.86
Water_enol	-23.42	-20.31

As a result of the overlapping basis sets from the individual molecules an error ranging from 11.26 – 17.58% is introduced. The observed lower raw complexation energy is a result of the overlapping basis sets and is not a result of the chemistry of the system. Tables 5 and 6 depict a general trend where the corrected complexation energies for the water complexed systems with both the 8H-naph and model system are increased. This is a result orienting three molecules in the complex rather than just the two-molecule complex formed with the diol complex systems.

Comparing ΔE^F for the 8H-naph and model system for the diol-mediated reactions, the barrier is higher for the model system. This results from the smaller relative energy difference between the reactant and transition

state as 8H-naph is stabilized by delocalized electron density due to its aromaticity. The same behavior is observed for the water complexed systems. For both the 8H-naph and model systems complexed with water, the resultant reverse energy barriers were relatively similar.

Reaction Force

Following the optimization of the keto and enol forms, the transition state connecting each pair of structures was found. To achieve a more in depth view of the reaction pathway, the evolution of the energy and reaction force were investigated through an IRC calculation. The reaction force allows for the allocation of the energy barrier to individual processes such as the preparation and relaxation energy (5).

8H-naph Force

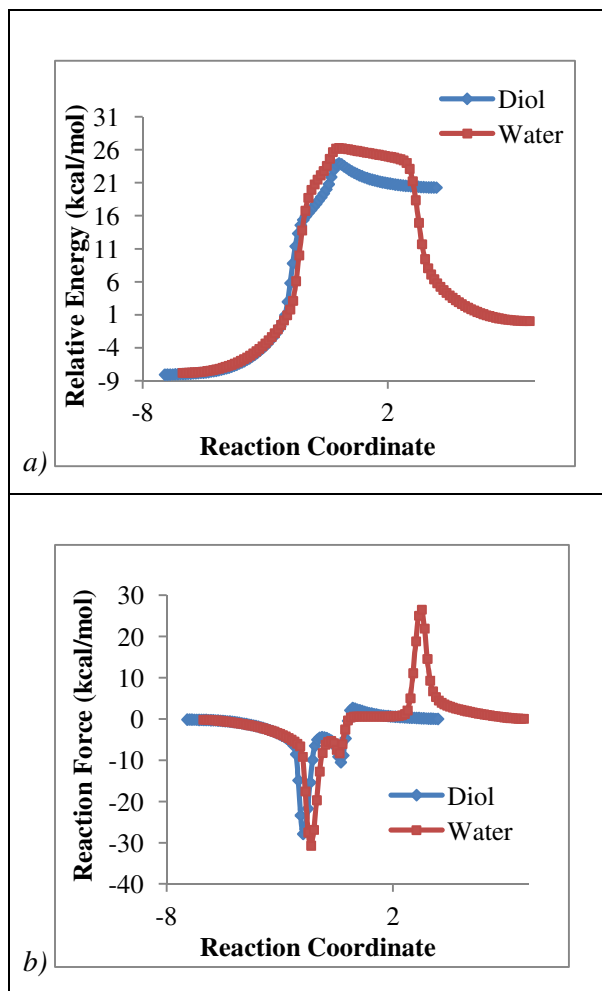


Figure 3: Force and relative energy data for the water IRC as well as the Diol IRC. (a) This graph shows the relative energy with respects to the reaction coordinate for both the diol and water mediated systems. (b) The graph provides both the diol and water reaction force pathways.

The IRC calculation in figure 2a for the diol system indicates the calculation became stuck in a well in the potential energy surface since the pathway stops abruptly. By optimizing the final structure given by the IRC, it was found that the structure goes without barrier to the enol structure as expected. According to the diol reaction force that was generated, figure 2b, 13.91 kcal/mol was devoted to initiate the protein transfer. With respect to the water reaction force that was generated, figure 2b, it requires 17.76 kcal/mol to achieve the first minimum required to initiate the proton transfer.

From the provided information, there is evidence that suggests that for the water mediated proton transfer, the energy, work, and force all increase when compared to the diol-mediated proton transfer. As the diol IRC pathway was not fully complete for this portion of the project, it is difficult to draw any conclusions from any behavior after the transition state.

Model Force

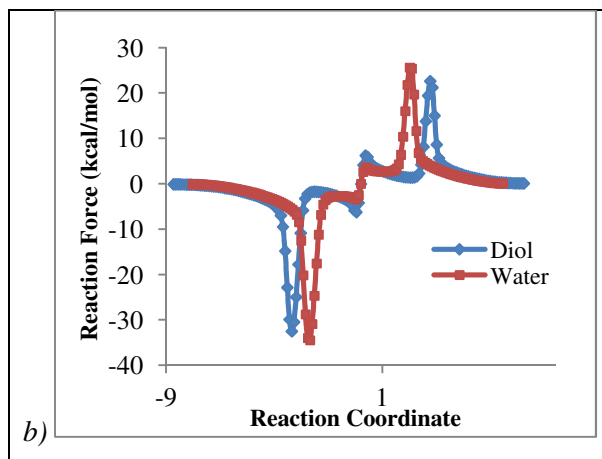
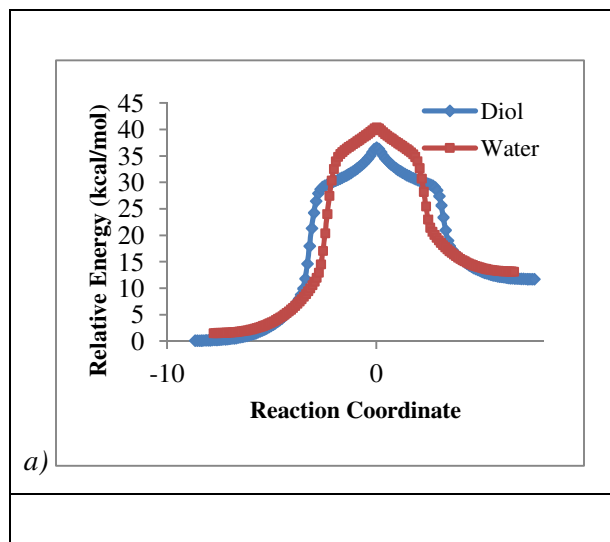


Figure 4: Relative energy and reaction force for model complex systems. (a) This plot reveals the relative energy pathway that the model diol and water complexed systems follow along the IRC. (b) The plot demonstrates the reaction force for both complexed systems.

The relative energy along the IRC for both systems clearly reveals that while the initial and final structures are close in energy, the transition state of the model-water system is 3.80 kcal/mol higher in energy. In figure 3a there is a characteristic shoulder, which appears in both curves. The structure at both of these points corresponds to the moment where the proton first begins to transfer from the nitrogen atom in the keto structure. This shoulder also corresponds to the first minimum point observed in the reaction force plot in figure 3b for both systems. To arrive at its minimum, the model-diol system requires 17.95 kcal/mol and the model-water system requires 22.46 kcal/mol. These energies correspond to about half or more than half of the forward barrier energies for the respective systems and are devoted to the preparation of the complex prior to the proton transfer. The remaining energy of the barrier height is devoted towards the actual transfer of the protons.

8H-naph vs. Model Forces

From the IRC of both the 8H-naph and model system, it is clear that once the first proton begins to transfer, the remaining protons follow in a non-concerted mechanism. To account for the large formation energy required for all

systems, the differences in the structures of the keto and enol forms were examined. As the keto transforms into the enol, the donor nitrogen atom in the keto structure has sp^3 -hybridized orbitals whereas after the transition occurs, the nitrogen atom in the enol structure has sp^2 -hybridized orbitals. As for the acceptor oxygen atom in the keto form, once the structure underwent the transfer, the oxygen atom transitioned from sp^2 -hybridized orbitals to sp^3 -hybridized orbitals. The 8H-naph and model system both exhibit similar behavior such that the formation energy for the diol systems is lower than the preparation energy required for the water systems. This is due to the lower energy barrier required in both cases for the diol complexed systems as seen by the IRC.

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We would like to take the time and the effort to thank my CHE 476 (Computational Chemistry) classmates for useful discussions in order to accomplish this publication. We would also like to thank the Department of Chemistry for this wonderful opportunity and resources that we were able to use to conduct this type of valuable research.

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CONCLUSION

While the overall trends between the 8H-naph and model system were the same, the differences in the specific behaviors are too great to validate the use of the model system instead of the full 8H-naph structure. To further the research of this study, the aqueous 8H-naph systems need to be further characterized to determine why negative energies were observed. To help understand the energy barrier differences between the vacuum and solvent states, the dipole moments and Mulliken charges should be examined.