On the role of hydrogen bond strength and charge transfer in an on-water Diels-Alder reaction: Semiempirical and free energy calculations

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Accelerated chemistry at the oil-water interface has been receiving increasing attention. However, the mechanisms behind the enhanced reactivity on-water are not yet clear. In the spirit of the second-generation Car-Parrinello method, we use a modified Langevin-type scheme to accelerate density-functional based tight-binding molecular dynamics in order to investigate the free energy of two Diels-Alder reactions on-water: the cycloaddition of cyclopentadiene with ethyl cinnamate and that with ethyl thionocinnamate. The only difference between the two studied molecules is that the carbonyl oxygen of the cinnamate is a thiocarbonyl sulfur in the thionocinnamate, hence the first is a strong and the second a weak hydrogen bond acceptor. We find that the mechanism for the reaction differs at the transition states, and we uncover the role of hydrogen bonds in the reaction along with the reaction path. The hydrogen bonds, and therefore the water interface, stabilize the configurations of the reactants for the formation of new bonds to occur. Our results suggest that the acceleration of Diels-Alder reactions does not arise from an increased number of hydrogen bonds at the transition state, but that charge transfer plays a significant role. However, the presence of water and hydrogen bonds is determinant for the catalysis of these reactions.

I. INTRODUCTION:

Water is of paramount importance to life and its role in biological processes has long been recognized. However, its use in chemistry is less established, as many substances of interest are not soluble in water, which has restricted the use of water for chemical reactions. The discovery of the acceleration of Diels-Alder reactions of small non-polar groups dissolved in water in 1980¹, and the more recent catalysis on-water², has changed this panorama. Lately, more examples of the acceleration of chemical processes at the interface with water have been described³⁻⁷.

The mechanism by which reactions are accelerated at aqueous interfaces is still not clear due to two main reasons⁸. Firstly, a theory of solvation at interfaces is more complex than bulk solvation and is an active topic of research. Secondly, the wide variety of phenomena occurring at aqueous interfaces may imply that there is a variety of mechanisms, making the interpretation of experimental results a complex task. Computational models are highly desirable to understand experimental results and elucidate the underlying mechanisms driving the reactions at aqueous interfaces. Jung and Marcus proposed a mechanism for on-water catalysis based on the availability of free OH bonds at the interface, interacting through hydrogen bonds with the molecular species⁹. This is in contrast to the homogeneous in-water case, where hydrogen bonds require higher energy to be broken and are

therefore less available¹. Yet, in-water reactions can be accelerated due to the Breslow hydrophobic effect^{10,11}. Other mechanisms for the acceleration of on-water reactions have also been proposed. Recently, an experimental study found an additional increase in the reaction rate of diethyl azodicarboxylate and quadricyclane cycloaddition when performed on micro-droplets, which they coined "on-droplet" chemistry¹². It has been suggested that this is due to the surface-to-volume ratio and supports the acid catalysis mechanism of Beattie and co-workers¹³, where reaction with water at the interface results in both the protonated substrate and free OH⁻, which is stabilized by its strong adsorption at the interface. Interestingly, a recent review presents contradictory and unexplained mechanisms. Instead, a revised on-water model is proposed¹⁴, where the interfacial water molecules would undergo partial polarization because of a loss of balance between donation and acceptance of hydrogen bonding through the Grotthuss mechanism at the interface.

The wide variety of proposed mechanisms for the acceleration of reactions at the interface with water, highlights the importance of using computational methods to shed light on the catalysis mechanism at water interfaces. The studied systems have been, however, limited by the high computational cost of quantum mechanical electronic structure calculations. The use of improved methodologies allows us to treat the required degrees of freedom efficiently and at the same time accurately, which allows us to analyze the reactions at realistic heterogeneous interfaces. This is of great importance in order to uncover the interplay of hydrogen bonds and reaction accelerations on-water. Previous on-water reaction studies have shown some insights. A lowering of the free energy barrier

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FIG. 1. Diels-Alder reaction with cinnamates (**1**) and cyclopentadiene (**2**) at the interface with water. When the carbonyl oxygen in ethyl cinnamate (**1a**, or hydrogen-bond-"on") is replaced by a thiocarbonyl sulfur, a thionocinnamate (**1b**, or hydrogen-bond-"off") is obtained. The product **3** shows the newly formed bonds (dashed lines) between **1** and **2**. The average bond distance of these two newly formed bonds will be used as a reaction coordinate for our free energy calculations.

has been reported for a solvated retro-Diels-Alder reaction using 50 water molecules (in-water) in comparison to the vapor phase reaction. The authors used Car-Parrinello molecular dynamics simulations and concluded that the water solvent is pivotal for this effect, especially for compounds containing an electron-donating substituent¹⁵. The role of microsolvation on reaction rates has also been highlighted. Pestana et al. used ab-initio simulations to investigate a retro-Diels-Alder reaction in bulk water under different confinements and found that the acceleration was similar between the different confinements¹¹. Therefore, the determining factor for the catalysis is the microsolvation, which implies that no additional catalysis would be expected for on-water via a local hydrogen-bond mechanism. Karhan et al. compared the homogeneous with heterogeneous Diels-Alder reaction between dimethyl azodicarboxylate (DMAD) and quadricyclane (Q)¹⁶, and found that the number of hydrogen bonds for the transition state and reactants was similar and only slightly increased as expected from Jung and Marcus⁹. Recently, Salem and Kühne revisited the DMAD with Q reaction using an energy decomposition analysis of the reactants, the transition state and the product in the presence of three water molecules, and discovered that charge transfer plays an important role¹⁷. Yang and co-workers also recently highlighted the role of charge transfer using an ab-initio quality neural network to model a cycloaddition reaction on-water¹⁸.

In this study, we investigate the importance of hydrogen bond strength for accelerating an on-water Diels-Alder reaction, inspired by an experimental study on the Diels-Alder reaction with ethyl crotonthioate as dienophile¹⁹. We studied two systems, shown in Fig. 1, of two slightly different reactants that can both form bonds with cyclopentadiene. The first reactant is ethyl cinnamate, which contains a carbonyl oxygen, which we will refer to as the H-bond-"on" system from now on. The second reactant is ethyl thionocinnamate¹⁹, hence a thiocarbonyl sulfur replaces the carbonyl oxygen. As sulfur has a weaker hydrogen-bond interaction with water¹⁹, we will call this the H-bond-"off" system.

II. COMPUTATIONAL DETAILS

The modeling of a realistic heterogeneous interface is an important aspect in order to investigate the effect of the water interface on the acceleration of reactions. To achieve this, we have used the second-order density functional tight-binding (DFTB2) approach²⁰, as implemented in the CP2K suite of programs²¹. This method allows us to approximately treat the quantum nature of the electrons by determining the charge density self-consistently. The efficiency of DFTB2 lies in between density functional theory and classical molecular dynamics. Even though systems in the order of thousands of atoms are now feasible with DFTB2^{22,23}, the evaluation of the free energy of the chemical reactions at the interface requires several simulations, sampling at different points along a reaction coordinate. To make this possible, we employ a grand-canonical linear-scaling technique together with the second-generation Car-Parrinello method^{24,25}, where the numerical precision is reduced²⁶, and a modified Langevin scheme is used to compensate for this²⁷, thereby improving the efficiency²⁸, while keeping the accuracy of the self-consistent charge densities²². This allowed us to efficiently perform more than 70 simulations for the two systems of interest and to obtain the free energy profile of the on-water reactions. Each system consisted of 22 cyclopentadiene molecules, 4 cinnamates, and 278 water molecules. The reactant molecules were chosen close to the interface with water, and they remained there during the simulation time. We used the original mio-1-1 parameters for the organic molecules²⁰, as well as modified force-matched parameters for liquid water²⁹.

Free energy calculations were done using an umbrella sampling potential $k(\xi - \xi_0)^2$ along with the reaction coordinate ξ ³⁰. This reaction coordinate was chosen as the average distance of the two bonds that are formed in the Diels-Alder reaction (Fig. 1). The free energy was evaluated along this coordinate between 4.5 Å (the reactants) and 1.5 Å (the product) at every 0.1 Å with a force constant of $k = 470 \text{ kcal/mol/Å}^2$. Four additional umbrella windows were simulated close to the identified transition states with a tighter force constant of $k = 1880 \text{ kcal/mol/Å}^2$ and at every 0.05 Å, simulating two additional umbrella windows at each side of the transition state. The weighted histogram analysis method (WHAM) was employed to recover the eventual unbiased free energy profiles^{31,32}.

III. RESULTS

The use of the an approximate linear-scaling method along with the DFTB2 method was first tested to assess its accuracy in obtaining free energy profiles. For this, the converged full-DFTB2 reference free energy profile was obtained using explicit diagonalization in conjunction with a tight self-consistent field (SCF) threshold of 10^{-7} , and compared to a set of equally long second-generation Car-Parrinello simulations using the modified Langevin approach with a moderate SCF criterion of 10^{-6} , resulting in a 4-fold increased efficiency for the Langevin-DFTB2 scheme. In Fig. 2, the relative

FIG. 2. Relative free energy profiles as obtained by the full-DFTB2 (black curve) and the accelerated Langevin-DFTB2 methods (red curve), respectively. The umbrella sampling simulations were analyzed using the WHAM code³². The standard deviations were calculated using the bootstrap analysis and shown as a shaded areas behind each curve. These results show that the Langevin-DFTB2 method entails free energy profiles that are identical (within the statistical uncertainty) to those obtained by the full-DFTB2 method, though at reduced computational cost.

free energies, which are identical within the corresponding statistical uncertainty (error sampling was obtained using the bootstrap analysis implemented in the WHAM code³²), are compared to each other, thereby indicating that the Langevin-DFTB2 method provides accurate estimates of free energies. Therewith, we employed Langevin-DFTB2 to obtain 100 ps simulations for each of the 35 different umbrella windows along ξ for both the H-bond-“on” and the H-bond-“off” systems.

The resulting relative free energy profiles are shown in Fig. 3 for both the H-bond-“on” (red curve) and -“off” (yellow curve) systems. The different shape of the two free energy profiles indicates a different activation of the cycloaddition reaction even though the two systems differ only by the carbonyl C=O or thiocarbonyl C=S group, which do not directly participate in the formation of new chemical bonds. The energy barrier of formation is obtained as the difference in the relative free energies between the reactants (at the $\xi \approx 4.5$ Å) and the transition state. In the case of the H-bond-“on” system, the transition state is located at ~ 2.1 Å and the energy barrier is ~ 13 kcal/mol, while the transition state for the H-bond-“off” system is located around ~ 1.9 Å and the energy barrier is ~ 24 kcal/mol, respectively. Beside the larger free energy barrier for the Diels-Alder reaction occurring at the water interface of the H-bond-“off” system, another difference between the two reactions is the free energy of formation of the products, i.e. $\Delta A = A_{\text{product}} - A_{\text{reactant}}$. This is $\Delta A < 0$ (-14 kcal/mol) for the H-bond-“on” system and $\Delta A > 0$ ($+7$ kcal/mol) for the H-bond-“off” system, indicating an exothermic and endothermic reaction, respectively. Next, the umbrella sampling trajectories were analyzed to obtain

FIG. 3. Relative free energy profiles obtained from umbrella sampling simulations using the accelerated Langevin-DFTB2 scheme for the H-bond-“on” (red curve) and H-bond-“off” (yellow curve) systems, respectively. The shaded area shows the statistical errors as estimated using the bootstrap analysis within the WHAM code³².

atomistic insights of the differences in the free energy barriers and corresponding energies of formation.

A snapshot of the trajectories for each umbrella sampling simulation at the window corresponding to the transition states, at ~ 2.1 Å for the H-bond-“on” and ~ 1.9 Å for the H-bond-“off” system is shown in Fig. 4. A representative snapshot of the transition state of both systems revealed that the formation of the two C-C bonds occurs in an asynchronous way, i.e. the two C-C bonds are not simultaneously formed. For both systems, the first C-C bond is created and stabilized between cyclopentadiene and the cinnamate (see Fig. 1). However, the second C-C bond is formed in the H-bond-“on” system relatively easily, as it occurs in a single step. This is not the case for the H-bond-“off” system, where a transient bond is observed in Fig. 4b between the sulfur and a carbon atom of cyclopentadiene^{33,34}. This implies that the formation of the second C-C bond has to overcome an additional energy barrier in the H-bond-“off” system due to an interaction between the sulfur and cyclopentadiene. Thus, it is revealed that the carbonyl C=O species plays a stabilizing role during the approach of the reactants at the interface with water, and that the thiocarbonyl C=S species interferes with the formation of the second C-C bond which can be attributed to the stronger electronegativity of oxygen compared to sulfur and its ability to form stronger hydrogen bonds with water. However, further analyses are necessary to understand this mechanism in detail. Next, we have quantified the asynchronicity of the transition state as a way to characterize the mechanism of the Diels-Alder reaction by defining it as the difference in length between the newly formed bonds at the transition state, i.e. $\Delta C = C_{\text{bond}}^1 - C_{\text{bond}}^2$. The value of ΔC is small for the H-bond-“on” system and large for the H-bond-“off” system, respectively. Specifically, $\Delta C_{\text{on}} = 0.02 \pm 0.20$ Å and $\Delta C_{\text{off}} = 0.95 \pm 0.07$ Å, which indicates that the reaction hap-

FIG. 4. Snapshot of the transition states of the H-bond-"on" and H-bond-"off" systems, respectively. The formation of the second C-C bond is more stable for the H-bond-"on" system. The transition state of the H-bond-"off" system reveals the transient formation of a further S-C bond between the thionocinnamate and cyclopentadiene. This competition against the formation of the second C-C bond is responsible for the different relative free energy profile and higher energy barrier shown in Fig. 3.

pens synchronously in the strong H-bonded system and that it is asynchronous in the weak H-bonded system. This supports the notion that different reaction mechanisms are at work between these two systems, as indicated by the different shapes of the free energy profiles in Fig. 3.

The bond formation can be qualitatively traced using a charge population analysis at different steps during the reaction. Due to the ability of DFTB2 to self-consistently redistribute the electronic charges, the popular Mulliken population analysis is employed in this work³⁵. While there are other schemes, such as the density derived electrostatic and chemical net atomic charges^{36,37}, Mulliken charges provide a sufficiently accurate qualitative picture, when considering the approximations already made by the choice of the DFTB2 method. Applying a reweighting to the biased charges $P'(q)$, we recovered the corresponding unbiased charges via

$$P(q) \propto P'(q) \exp\left(\frac{k(\xi - \xi_0)^2}{k_B T}\right). \quad (1)$$

We then analyzed the charge population for six different groups shown in Fig. 5. First, the two carbon atoms directly involved in the cycloaddition reaction (Figs. 5a and 5b) show a different charge population evolution on the second carbon atom for the H-bond-"off" system, which is consistent with the earlier shown trajectories and asynchronicity of the transition states. Fig. 5c shows a large difference in the Mulliken charges between the carbonyl oxygen and thiocarbonyl sulfur atoms. The oxygen atom has a constant charge along the reaction path, whereas sulfur obeys a decrease of charge around the transition state. This is in line with the transient bond formation observed in the transition state trajectories between the sulfur and cyclopentadiene. Also, oxygen is more electronegative ($\sim -0.6e$) than sulfur ($\sim -0.4e$), which makes it a better hydrogen bond donor. The charge of the carbon atom bonded to this oxygen or sulfur atom is presented in Fig. 5d, and showing no change along the reaction path for either system. The same is true for Fig. 5e, which shows the oxygen atom in the C-O-C group of ethyl cinnamate or ethyl thionocinnamate that has a constant charge in both systems.

Finally, the total charge of cyclopentadiene, shown in Fig. 5f, increases from reactant to product and has a maximum that corresponds with the position of the transition state in the free energy profile of Fig. 3. The change in the total charge of cyclopentadiene is larger for the H-bond-"on" system. Next, we investigated the role of hydrogen bonds along the reaction profile.

An H-bond increase at the transition state has been suggested⁹ as a mechanism to explain the increase of reactivity on-water. The Mulliken charges of oxygen and sulfur showed the largest difference in the charge evolution along the reaction path (Fig. 5c) and in addition, the sulfur atom was found to behave differently and unexpectedly bond to cyclopentadiene at the transition state (Fig. 4b). We therefore wanted to know the number of hydrogen bonds between water molecules and the carbonyl ($C=O$) oxygen or the thiocarbonyl ($C=S$) sulfur atoms. In fact, the hydrogen bonding to water by the reactants occurs through these atoms only. We applied the same weight shown in eq. 1 to obtain the unbiased number of hydrogen bonds. Our results (Fig. 6) show different trends for the number of hydrogen bonds for the two systems. In the case of the H-bond-"on" reaction, the number of hydrogen bonds is almost constant (within statistical uncertainty), around 1.2, while the number of hydrogen bonds clearly changes along the reaction path for the H-bond-"off" system. It decreases to nearly zero around the transition state (1.9 Å), followed by an increase at 1.8 Å, and finally reaching a value of 0.5 for the product (which is similar to that of the reactants). The evolution of the number of hydrogen bonds in both cases shows a similar pattern as their corresponding evolution of the oxygen or sulfur charge (Fig. 5c). The charge was almost constant for oxygen and peaks around the transition state for sulfur (1.9 Å), coinciding with a drop in the number of hydrogen bonds at the same reaction coordinate. This is in accordance with the trajectories of the transition states we observed, where the sulfur is also bonded to cyclopentadiene and competes with the formation of the second C-C bond. Additionally, we analyzed the distribution of hydrogen bond distances and angles for both systems (, shown in Fig. S1 and S2,), and found no evidence for shorter hydrogen bonds in the transition state.

IV. DISCUSSION

Regarding the role of hydrogen bonds, we have not observed an increase in the number of hydrogen bonds (Fig. 6) for the transition state of the system with a stronger H-bond interaction (the H-bond-"on" system), contrary to the current understanding of the H-bond mechanism^{9,38}.

In the case of the system with a weaker H-bond interaction (the H-bond-"off" system) the number of hydrogen bonds decreased at the transition state. This decrease coincides with the increase in the activation energy of the reaction, and is linked to the competition of C-C bonding with the interaction between the sulfur atom and cyclopentadiene. This added a cost to the cycloaddition reaction of the H-bond-"off" system. We propose that the role of hydrogen bonds, and therefore the role of the water interface, is to stabilize the configurations

FIG. 5. Mulliken charges for different atoms and compared between the H-bond-“on” (red curves) and H-bond-“off” (yellow curves) systems.

FIG. 6. Number of hydrogen bonds between water molecules and the carbonyl (C=O) oxygen or the thiocarbonyl (C=S) sulfur atom along with the reaction coordinate. The red (upper) curve shows the results for the H-bond-“on” system. The number of hydrogen bonds remains constant within the error bars along the reaction path. The yellow (lower) curve shows the results for the H-bond-“off” system. There is a slight decrease in the number of hydrogen bonds around the transition state.

of the reactants in order that the formation of new bonds may occur.

Our results show that the system with a weaker H-bond interaction (as sulfur has a smaller electronegativity compared to oxygen) has to overcome a larger energy penalty caused by the changing conformation of the reactants by interacting via the thiocarbonyl sulfur atom. We have also not found any indication of strengthened hydrogen bonds at the transition states compared to at the reactants or products. Our

hypothesis is that the presence of hydrogen bonds is important as there is a higher penalty for the H-bond-“off” reaction (11 kcal/mol compared to H-bond-“on” reaction). In the H-bond-“off” system, we observed a depletion in the number of hydrogen bonds around the transition state (Fig. 6).

QM/MM studies of the reaction of cyclopentadiene (CPD) with methyl vinyl ketone (MVK) in water suggested that the H-bond is enhanced at the transition states, observing a shortening of the H-bond distance and the influence of water reorientation^{39,40}. We found however, no evidence of a shortening of hydrogen bonds at the transition state (see Figs. S1 and S2) for the Diels-Alder reaction of this work at the interface with water, i.e. on-water. A similar study using QM/MM molecular dynamics showed an acceleration of the same reaction in water compared to methanol⁴¹. The authors assigned responsibility for the acceleration to the H-bond formed between the carbonyl oxygen atom and hydrogen atoms in the solvent at the transition state, which polarized the C=O bond and stabilized the system charge reorganization during the reaction. We found a similar mechanism after analyzing the charge population (Fig. 5), even though our results are from at the interface instead of the bulk, this suggests that there is a stabilization of the transition states through a charge redistribution which contributes to acceleration of the reactions. The role of charge transfer has also been discussed by other authors^{17,41}. Recent studies of the water/oil interface showed significant buildup of surface charge density at hydrophobic interfaces⁴² and the importance of surface electric fields as a source of microdroplet reactivity⁴³. This is, however, not a general statement, as we have studied a single reaction and the wide variety of phenomena occurring at aqueous interfaces may imply different mechanisms for other reactions.

V. CONCLUSIONS

We have studied the Diels-Alder reaction between cyclopentadiene and two cinnamates occurring at the water interface using density-functional based tight-binding (DFTB2²⁰) molecular dynamics. The modeling of a realistic interface was made possible by using an acceleration scheme in the spirit of the second-generation Car-Parrinello method²⁴. The role of the hydrogen bond in the enhancement of the reactivity on-water was investigated by comparing the free energy barrier of the reaction for the two systems, one which is a strong hydrogen acceptor (ethyl cinnamate) and a second weak hydrogen bond acceptor (ethyl thionocinnamate).

We found different reaction mechanisms for the strong hydrogen-bonded and weak hydrogen-bonded system. Namely, a synchronous formation of new bonds in the first case and an asynchronous mechanism in the latter. According to our simulations, the role of hydrogen bonds at the water interface for the systems here studied is the stabilization of the conformations of the reactants. Charge transfer stabilization of the transition states was also observed in our simulations. These results are in agreement with previous studies suggesting the importance of charge reorganization and polarization in the transition states in the presence of water^{17,41} and the buildup of surface charge at water/oil interfaces^{42,43}. Regarding the role of hydrogen bonds, we found no evidence for the increase in the number of hydrogen bonds (with respect to the reactants or products), nor strengthened hydrogen bonds at the transition states as suggested by Jung and Marcus⁹. The free energy barrier of the reaction for the strong hydrogen-bond acceptor system was lower when compared to the weak hydrogen-bond system. A correlation was also observed with the decrease in the number of hydrogen bonds at the transition state for the weak H-bond system. The difference in hydrogen bonding is also observed as a variation of the charge of the sulfur atom at the transition state while the charge of the oxygen atom is constant for the complete reaction profile. All of this suggests that the role of the hydrogen-bond strength is more important than the number of hydrogen bonds. Our conclusions are however, not a general statement as we have studied a single reaction and the wide variety of phenomena occurring at aqueous interfaces may imply different mechanisms for other reactions.

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