Water as Organocatalysis

Water is the most abundant substance on earth and an attractive sustainable resource for many applications. In fact, water is the most commonly used solvent by nature for an enormous number of biosynthesis pathways including precise arrangements of multitudes and asymmetric centers, which are highly specific and essential in many biological systems. However, most organic reaction commonly used in both academic laboratories and industry fail in presence of water or oxygen \(^1\). Thus our generations of organic chemists have been trained in such a manner that only pay little attention in considering water as a useful reaction solvent \(^1\).

The only time water is considered as a useful solvent is when it is acted as a non-reaction solvent that involves in separation or purification of the desired product. We rarely use water as a reactant because of the ultimate fear of the detrimental effects of hydrolysis and the influence of the ancient alchimia, which teaches that reactants must be in solution to produce a chemical reaction \(^3\). Furthermore, water is a protic solvent; therefore it is required for protection of all protic functional groups such as amines and alcohol for carrying out specific reaction. However, the situation has been changing because of the early work of Breslow \(^4\) of showing how water enhances the Diels- Alder reaction by acting as a reaction medium \(^4\)\(^5\). This leads to an increasing of interest of water to many organic chemists.

Water can be isolated purely through a reaction called Ideal Green Reaction. Figure 1 shows an ideal green reaction in and on water. The ideal green reaction has an economic benefit of the process that depends on what extra process will be necessary to isolate the product to recover “organic free” water for future use.

![Figure 1: Ideal Green Reaction “in” and “on” water \(^3\). In each case the Product C should have zero solubility and should be formed in quantitative yield by consuming all A and B so by isolating C should leave pure water.](image)

For clear solution of soluble organic reactant “in” water, the effects are (1) the hydrophobic effect, which speeds reaction, (2) hydrogen bonding effects on reactants and transition states, which may add to or oppose the hydrophobic effect, and (3) water polarity effects, which may again increase or decrease reaction rates \(^3\). On the other hand, highly insoluble reactant will be involving two-phase systems that use trans-phase interactions of water with transition states and reactant (Marcus trans-phase H-bonding) \(^3\). However, the extent of insolubility of reactant in water has rarely been quoted to date in accounts which described the
reaction only carried out by on-water because of the two phases (heterogeneous) must be presence in “on” water reaction, and the reaction rate of “on” water is driven by and dependent on the solubility of reactant in water. These characteristics between “in” and “on” water reaction are further discussed.

“In” water effect on organic reactions

The Breslow Hydrophobic Effect

The Hydrophobic effect is an effect resulted from the repulsion between the water molecules and the non-polar substances. In biochemistry, there are many enzymes or proteins that have this phenomenon, which allows them to be fold in the right shape and be stable enough in the presence of water to carry out any catalytic reaction in our body. For example, phospholipid bilayer of cell membrane has choline, phosphate and glycerol head, and fatty acids tail. When it is dissolved in water, the fatty acid tails associate with each other and form bilayer due to hydrophobic effect, leaving the head associate with water. Small organic molecule acts the same way; when there is water present, they are forced to form aggregate in order to decrease the organic surface area exposed to water. This aggregate causes a hydration shell that surrounding the organic molecule with H-bond links run laterally along the hydrophobic surface. (Figure 2). In addition to the large amount of water presence, the larger hydrophobic surface is required with some dangling hydrogen bonds groups are orientated toward the barrier to maximize the packing density of the molecules (Figure 2) [13][14][15].

Figure 2: (i) the hydration shell in small hydrophobic aggregates (ii) large hydrophobic water interface. A and B are organic reactants which are usually insoluble in water. [3]

Because the aggregates are held tightly together by hydrophobic interaction, it allows them to process organic reaction. Forced aggregates of organic reactant tends to raise in energy higher than aggregated ground states and bring it closer to the activated energy of transition state for the reactions. Engberts has shown that the reactive sites of these activated complexes lose their hydrophobic character entirely, a benefit that nature has conferred on water as reaction facilitator [16][17]. Hence, water acts a catalyst that reduces the activation energy and significant rate enhancements. Estimates of lowering the activation energy of Dial-Alder reaction (as
mentioned earlier) by hydrophobic effect shows a direct proportional and agreement with observed rate increases [18][19].

Diels-Alder cycloaddition is a powerful synthetic transformation that has been used widely by organic chemists, and solvent effect of reactions was studied in early 1939 when Hopff and Rautenstrauch disclosed that Diel-Alder reaction could be carried out effectively in an “aqueous dispersion” rather than their patent reaction which were carried out in presence of dispersing or emulsifying agents. [20]. Later in 1980, Rideout and Breslow reported that both rate enhancement and excellent selectivity could be achieved for certain Diels-Alder reaction when the reactions are carried out in diluted aqueous solution [21]. Figure 3, and table 1 and 2 show the rate constant and selectivity of the product for Diels-Alder reaction in addition of water compare to other solvent. Breslow later then hypothesizes the Breslow hydrophobic effect as mentioned.

Figure 3: Diel- Alder reaction [1]

\[
\begin{align*}
\text{solvent} & \quad k_2 \times 10^5, \text{M}^{-1} \text{s}^{-1} \\
2,2,4\text{-trimethylpentane} & \quad 5.94 \pm 0.3 \\
\text{methanol} & \quad 75.5 \\
\text{H}_2\text{O} & \quad 4400 \pm 70 \\
\text{H}_2\text{O} (4.86 \text{ M LiCl}) & \quad 10,800
\end{align*}
\]

Table 1: Show the rate constant of reaction in Figure 3 with different solvent [1]

\[
\begin{align*}
\text{solvent} & \quad \text{endolexo ratio (5a/5b)} \\
\text{neat}^a & \quad 3.85 \\
\text{ethanol} & \quad 8.5 \\
\text{H}_2\text{O} & \quad 21.4
\end{align*}
\]

\(^a\text{Excess butenone was used.}\)

Table 2: Show the rate constant of reaction in Figure 3 with different solvent [1]. The hydrophobic effect has a major influence on stereo chemical outcome of reaction, and it often favors product with more compact transition states and normal preference for endo-cyclo addition in Diels-alder [22][23][24][25].
**Hydrogen-bonding effect**

In addition to hydrophobic effect, when organic molecules possess hydrogen bond acceptor site, the water molecules will form H-bonds with them. The hydrogen bonding shows a negative and positive effect in the presence of water by decreasing or increasing the LUMO and HOMO gap in the reaction. The transition state of covalent reaction can be viewed in terms of frontier orbital interaction involving the HOMO-and LUMO pairs of reach molecules A and B for reaction A+B = C shows in Figure 4\[3\]. H-bonding is like electron-withdrawing substituent that lowers the energy of frontier orbital by reducing electron density and inter-orbital repulsion on the substrate (reactant). This activates the substrate to make it become more reactive. Thus the effect of water depends on the presence or absence of H-bonding interaction with the reactants. The simplest case is where the reactant has no H-bond acceptor site. In figure 4, the reaction involving 4π HOMO control in reactant A H-bonding to B will speed the reaction by lowering the HOMO-LUMO gap and the transition state, and the reverse control reaction in 4π LUMO in A with H-bonding at B increasing the frontier gap. Thus when both reactants contain H-bond acceptor site, the effect of water H-bonding on the rate will depend on relative lowering of the dominant frontier to increase or decrease the gap on transition state energy\[3\]. Hence, water can have both negative and positive effect on a substrate.

![Frontier orbitals energies of cycloaddition reactions.](image)

**Figure 4:** Frontier orbitals energies of cycloaddition reactions.\[3\]

**Polarity Effect**

Polarity plays a small impact in water as organocatalysis. Water is highly polar solvent, which is why it has been used as solvent for extraction of non-polar organic compound. Hence, according to thermodynamic, reaction with transition states more polar than initial states will speed in water and slow when the transition states are less polar than initial states\[26][27].
On water

*On water reaction. Marcus trans-Phase H-bonding.*

An important concept difference between “in” and “on” water is phase of reaction. “In” water reaction involves with homogenous condition, and “on” water reaction involves with heterogeneous condition of insoluble reactant in water. Most of “on” water reaction concept might have some overlapped and build from theoretical concept of “in” reaction such as hydrophobic effect of water and H-Bonding, which are main driving force of “in” water catalysis. In 2007, Marcus and Jung proposed that the key to understanding the on-water phenomenon was the unique chemistry that occurs at the water-oil (heterogeneous) phase boundary\(^3\) (Figure 1). Similarly with hydrophobic effect, but at the heterogeneous phase, the large hydrophobic surface about 1 in 4 of water molecules in the final layers has an OH free group that is directed at the boundary in contrast to small hydrophobic aggregates which can be fully enclosed by hydration water cluster with lateral H-bonds along the boundary\(^14\)-\(^28\)-\(^30\). The impact of catalysis depends on the activation energy of H-bonding from water that activates the substrate to decrease the activation energy of the reaction. The catalytic effect of Marcus provides a remarkable insight to the “on” water phenomenon. Thus the concept of both “in” and “on” water catalysis opens a new door to many green organic reactions in a future.

<table>
<thead>
<tr>
<th>solubility ranges (mol/l)</th>
<th>slightly soluble: A</th>
<th>sparingly soluble: B</th>
<th>very sparingly soluble: C</th>
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</thead>
<tbody>
<tr>
<td>active medium</td>
<td>solution</td>
<td>oily droplets</td>
<td>oily regions</td>
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<tr>
<td></td>
<td>small oily droplets</td>
<td>small aggregates</td>
<td>large phase boundaries</td>
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<td>mainly on-water</td>
<td>on-water</td>
</tr>
<tr>
<td></td>
<td>some in-water</td>
<td>some on-water</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3:** Summary table of “in” and “on” water boundaries for water insoluble reactants\(^3\)
Reference: