A Study of Investigating in Water: Perspective in Organic Chemistry

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Abstract: In recent years, water has gained prominence as a useful solvent for organic chemistry. Using water as the solvent not only results in new reactivity but is also cheap and non-hazardous to the environment. This tutorial review covers a variety of organic reactions that can take place in water, such as oxidations and reductions, radical and carbene formation, oxidation-reduction, and pericyclic reactions. Synthesis of biologically active compounds from carbohydrates as well as reaction conditions of biomolecules are just two examples of the many fields in which aqueous organic reactions find use.

Keywords: Water, Reaction, Hydrogen, Oxidation, Organic chemistry.

Introduction:

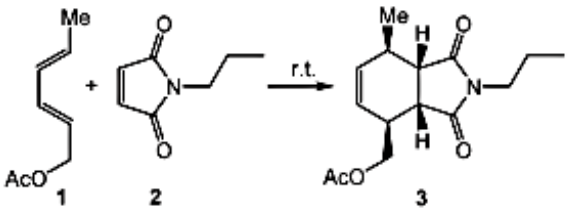
The most complex organic compounds on Earth, which include all forms of life, can only form when chemical bonds are built in water. If we are to learn from nature, we must consider water a universal solvent for organic synthesis [1]. Water has been reported to greatly accelerate Diels-Alder reactions, so there has been a lot of focus on improving organic reactions in water since then. Some of the most important organic reactions, such as Diels-Alder reactions, as well as reactions involving compounds that are sensitive to water, are illustrated by these examples. Water is the most common, accessible, and safe solvent because of these qualities. Because of hydrophobic effects, water often speeds up reaction rates and improves response selectivities, even when the reagents are only slightly soluble or insoluble in this medium. In addition, the air-sensitive transition-metal catalysis can be performed in open air due to the low solubility of oxygen gas in water, which was crucial in the early development of life in anaerobic environments. Because water is used as a solvent, time-consuming protection-deprotection processes are unnecessary for some acidic-hydrogen-containing functional groups, improving the synthetic efficiency of the process as a whole [2]. There is no need to derivatize water-soluble compounds like carbohydrates before use, and water-soluble catalysts could be recycled after being separated from water-insoluble organic foods. The new discipline of chemical biology, which employs chemical methods to investigate living systems, also relies heavily on aqueous organic chemistry. Current organic chemistry school books do not cover aqueous organic chemistry, despite its widespread relevance and promising future. This introductory review will give those who aren't familiar with organic chemistry a basic understanding of the subject to make up for the lack of coverage in textbooks.

Pericyclic reactions:

In organic synthesis, pericyclic reactions play a crucial role in the formation of cyclic structures and the manipulation of stereochemistry. Extensive theoretical and experimental research has been done on the topic of Diels-Alder reactions in water since Breslow's discovery that they proceed faster (by as much as 700-fold) and exhibit a higher endo/exo specificity in water than in organic solvents. Water's small size and high polarity, as well as the three-dimensional hydrogen-bonded wired network of bulk water, grant it a number of unusual characteristics, such as a high surface tension, a low hydrophilicity, and a large cohesive energy density. It is believed that the "on-water" effect and the increased rates and selectivities of pericyclic reactions are due to these distinctive characteristics. There is speculation that hydrogen bonding among oxygen and organic molecules contributes significantly to the rate accelerations of certain organic reactions in water [3].

It's important to note that the "on-water effect," as coined by Sharpless and co-workers, can accelerate the rate of reactions involving both water-soluble and water-insoluble reactants. For instance, compared to homogenous solution, the rate of the Diels-Alder reaction (Figure 1) between water-insoluble trans, trans2,4-hexadienyl acetate (1) & N-propyl maleimide (2) was greatly accelerated in aqueous suspension. Methanol, being a protic solvent, speeds up the reaction time compared to nonprotic solvents like acetonitrile and toluene. This finding points to the importance of both hydrogen bonding & hydrophobic effects in the observed rate acceleration. Water also promotes the rate of Claisen rearrangements, which differ from Diels-Alder reactions

by having negative volume changes of activation. In contrast to the much slower rate at which this rearrangement occurs in organic solvents, naphthyl ether (4) can be converted to the desired product 5, after being suspended in water, in just five days at room temperature. Similar to the aqueous reaction, the neat reaction takes longer to complete.



Solvent	Concentration[M]	Time to completion	Yield (%)
toluene	1	144 h	79
CH_3CN	1	>144 h	43
MeOH	1	48 h	82
neat	3.7[a]	10 h	82
H_2O	3.7[a]	**8 h**	**81**

a. Calculated from the measured density of 1:1 mixture of 1 and 2.

Figure 1: The speed of Diels-Alder reactions can be increased by using water as a solvent.

Additional pericyclic reactions exhibit rate enhancements in water, in addition to Diels-Alder cycloadditions and Claisen rearrangements. For instance, using water as a solvent is much faster than using an organic solvent for the $2\sigma + 2\sigma + 2\pi$ cycloaddition of quadricyclane (6) to azodicarboxylates (7) at room temperature. An increased chemical shift on the ground state, rather than the transition state, may account for the unusual reactivity reported here. Total synthesis of many biologically active compounds has been aided by exploiting the rate enhancements of pericyclic reactions in aqueous solution [4]. Two Claisen rearrangements and a Claisen/Diels-Alder cascade reaction are essential steps in the total synthesis of gambogin (14), a bioactive compound against by the Hela and HEL cell lines. In aqueous solutions, the rate of the Claisen/Diels-Alder cascade reaction increased dramatically between steps 10 and 11. (Table 1). A significant rate increases in Claisen re - arrangement from 12 to 13 is also seen in aqueous solutions.

Solvent	*T*/°C	*t*/h	Conversion [%]
MeOH	65	4	0
Trifluoroethanol	65	4	0
EtOH	65	4	0
$MeOH/H_2O$ (1 : 1)	65	4	100
TFE/H_2O (1 : 1)	65	4	100
$EtOH/H_2O$ (1 : 1)	65	4	100

Table 1: Acceleration of the Claisen/Diels-Alder cascade reaction from a rate of 10 to 11 by aqueous solutions

Multiple experiments show that the hydrogen-bonding effect, in addition to the hydrophobic effect, contributes to the accelerated rates of pericyclic reactions in water. 5 An increase in the mole fraction of liquid in the organic solvents (from 0 to 1) of acetonitrile, acetonitrile, methanol, ethanol, & tert-butyl alcohol at 37 uC accelerates the cycloaddition responses of pyridazinium-dicyanomethanide 1,3-dipole (15) with dipolarophile ethyl vinyl ketone (16). Whenever the mole fraction of water is greater than about 0.90, exponential rate increases begin to take place. There is no evidence of a triggering effect when methanol is used in place of water. This analysis points to the dominance of rate enhancements due to hydrogen-bonding and hydrophobic effects. This conclusion is strongly supported by a calculated value of the transition state structure. It has been observed that both noncatalyzed Diels-Alder reactions and Lewis's acid catalysed Diels-Alder reactions show an increase in the endo/exo specificity of aqueous reactions. For instance, the enantioselectivity of the copper-catalyzed Diels-Alder reaction of 3-phenyl-1-(2-pyridyl)-2-propen-1-one (18) to cyclopentadiene (19) is greatly improved when water is used as the solvent, as opposed to organic solvents. Density functional theory calculations confirm experimental findings that the endo preference increases to 2.4 kcal mol21 when the

molecule is in water. Hydrogen bonding plays a role, but bulk-phase effects like enforcing hydrophobic interactions & anti-hydrophobic co-solvent effects also contribute to the endo/exo selectivity.

Carbanion-equivalent reactions:

One of the most common ways to create CC bonds is through a metal mediated carbanion-based reaction. Many metal-mediated carbanion-based reactions, such as those involving organ magnesium & organolithium reagents, are notoriously difficult to work with because they frequently necessitate low temperature conditions and the strict exclusion of moisture and oxygen. Metals like indium, tin, and zinc have been successfully used as mediators for the reactions of carbonyls & imines with allyl halides in water recently [5].

Rhodium-catalyzed 1,2-addition to aldehydes and aryl or alkenylboronic acid addition to a, b-unsaturated carbonyls were reported by Miyaura. Hayashi and co-workers also reported a related asymmetric conjugate addition. Grignard-type phenylation of carbonyls from trimethylphenylstannane to aldehydes 21 is carried out smoothly in water and in air thanks to Rh(I) [Rh (COD)2Cl or Rh (COD)2BF4]. In order to generate PhSn (OH)nX32n species in situ and increase its reactivity when the methyl groups of organotin substances are replaced by halogens, a base is required (Figure 2). Carbonyl alkylation of the Barbier-Grignard type can be accomplished in water. The desired alcohol products 26 can be obtained in water through the Barbier-Grignard type reaction of different aldehydes 24 with alkyl iodides 25 in the presence of Zn/CuI as well as a catalytic amount of InCl (Figure 2). The hydroxyl group on the aldehyde need not be shielded before the water reaction takes place.

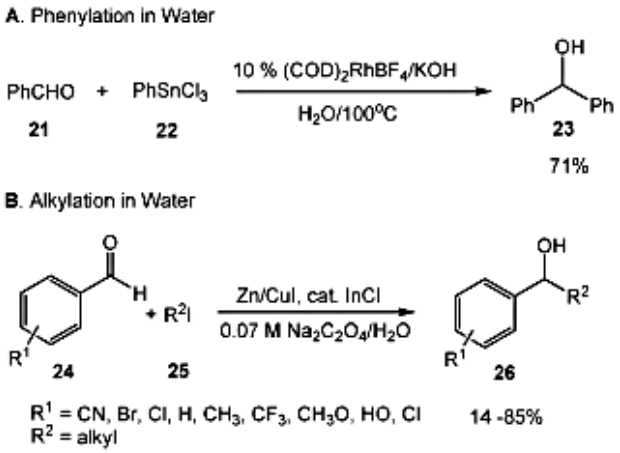


Figure 2: The occurrence of a Barbier-Grifols reaction in water

The a-adduct products are rarely obtained despite the high regio- and stereoselectivity of metal-mediated Barbier-type allylation reactions. One can perform regioselective allylation (a-adduct versus c-adduct) using water as a solvent. The reaction of 1 mmol of aldehyde 27 with 1.2 mmol of allyl bromide (28) in the presence of 2 mL of water solvent gives 100% of the c-adduct 29 in high yield, while in the existence of 6 equiv. of water solvent, 99.9% of the a-adduct 30 is obtained. Here, water is required for the formation of an oxonium ion intermediate that provides a-adduct products, so it serves as a good solvent for the allylation reaction in general [6]. It is thought that the oxonium intermediate cannot form in solutions with too much water as the solvent. Water is also useful for the conjugate addition of unsaturated carbonyls to arylmetallic reagents. The reaction between phenyl tin chloride 32 and conjugated enone 31 proceeds smoothly in the presence of a Rh(I) catalyst, leading to the expected addition good or service 33 in high yield in liquid under basic conditions.

Oxidations–reductions:

Heavy metal reagents (such as potassium permanganate or V2O5) or water oxidants (such as oxalyl chloride or N, N-dicyclohexylcarbodiimide (DCC)) have traditionally been used in stoichiometric amounts to conduct oxidation reactions. Water-compatible oxidizing agents, such as O2 & H2O2, have been used to create new oxidative reactions in aqueous media. Several 2-naphthols and substituted phenols can be converted to the corresponding biaryl compounds in moderate to excellent yields in water using the ruthenium catalyst Ru (OH)x/Al2O3. The only oxidant required is clean, safe, and cheap molecular oxygen. Therefore, the oxidative coupling of 2-naphthol (101) in water yields 1,19-binaphthalene2,29-diol (BINOL) (102)—a crucial building block and ligand—in the presence of 5% mol% Ru (OH)x/ Al2O3 and 1 atm O2. Even after seven recycling cycles, the catalytic activity of a Ru (OH)x/Al2O3 catalyst retains 100% of its initial activity (Figure 3).

Using a novel amphoteric resin dispersion of palladium nanoparticles, molecular oxygen can catalyze the oxidation of alcohols in water (ARP-Pd). Water reacts with both primary and secondary alcohols to produce aldehydes and ketones, respectively, in the presence of a nano-palladium catalyst. With minimal degradation in catalytic efficiency over multiple cycles, ARP-Pd is designed for repeated use. Separating products is made easy by aqueous oxidative polymerization. Poly(2,6-dimethyl-1,4-phenyleneoxide) (PPO) 112 is produced through the free radical polymerization of 2,6-dimethylphenol (DMP) 111 in aqueous NaOH solution using molecular oxygen as the oxidant and K3[Fe (CN)6] as the catalyst. 33 Although the DMP monomer can be dissolved in NaOH solution, the PPO polyethylene product cannot. After the reaction, the aqueous solution is re-used for the polymerization process after it has been distilled to remove the precipitated product.

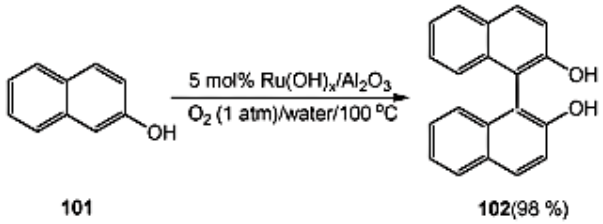


Figure 3: Coupling of 2-naphthol to oxygen in water.

It is common practice to use hydrogen peroxide, another oxidant that is water-compatible, in aqueous oxidation process. Alcohols can be converted into aldehydes and ketones by adding hydrogen peroxide to water in the presence of polyoxometalate which can be prepared in a single step in water from common salts. Water recycling was possible for the in-situ prepared polyoxometalate catalyst [7].

Most oxidizing agents are incompatible with water, so water is rarely used as a solvent in a reduction reaction. To reduce ketones or aldehydes in water, however, sodium/lithium borohydride is frequently employed due to its solubility in water. Ketones can be selectively reduced in water when the hydrophobic lowering agent (LiC6F5BH3) is added to the more hydrophilic lithium borohydride (LiBH4). Qatarized b-keto diamines (113) are reduced almost entirely in water by LiC6F5BH3. On the other hand, when methanol is used, both products 114 and 115 are produced in equal amounts. 35 An improved supramolecular catalyst for selectively reducing ketones is a ruthenium complex of b-cyclodextrin-modified amino alcohols (116). This Ru-base catalyst lessens conjugated (117) & non-activated uninflected ketones (118) to the correlating alcohols in the presence of NaCOOH, with high yields and excellent enantioselectivities in aqueous solution (Figure 4).

Synthetic applications:

Organic synthesis, life science, and chemical biology are just a few of the fields that have benefited from the unique properties of aqueous organic chemistry.

- **Carbohydrate Chemistry:**

Because of the nature of aqueous organic reactions, water-soluble hydroxyl-containing molecules can be employed directly in organic synthesis without the need for time-consuming protection-deprotection processes. Carbohydrate chemistry, in which protection-deprotection processes play a central role, is therefore the most application area for carrying out organic responses in water. C-Glycosides are useful because they can be used as building blocks in the total synthesis of natural products or as enzyme inhibitors, two common examples of their potential utility. C-Glycosidic ketones are typically synthesized from a shielded sugar via the addition of an appropriate nucleophile under anhydrous conditions. A new protocol using water as a solvent greatly improves overall yields by doing away with time-consuming protection-deprotection processes [8]. The b-C-glycosidic ketone 123 can be obtained in one step in almost quantitative yield in aqueous NaHCO3 solution from commercially available D-glucose (121) & pentane-2,4-dione (122). In stark contrast, the b-C-glycosidic ketone 123 is prepared from the protected sugar benzylated D-glucose in seven steps with an overall low yield by using organic solvents. 37 Among the most desirable synthetic targets are polyhydroxylated N-heterocycles, also known as azasugars, because of their wide range of biological activities. Since their structures are so similar to sugars, commercially available carbohydrates have been the usual starting point for azasugar synthesis. Their asymmetric synthesis, on the other hand, is laborious and yields little material. An extremely effective non - symmetric formulation of a pyrrolidine azasugar has been established in only four steps, without any protection-deprotection process, and also in 60% overall yield, with water as the solvent for all the steps. Starting with a low-cost achiral 1,6-dibromodiene 124, a modified Sharpless non - symmetric dihydroxylation yields the enantiopure chiral biselectrophilic diol 125. (70 percent yield, 97 percent ee). Due to the instability of 124 and 125 in organic solvents, it possesses a remarkable and practical reactivity in water [9]. Triol 126 is

obtained by selective hydrolysis of 125, with a 98 percent yield. After that, the preferred epoxy alcohol 127 is obtained in 99.7 percent yield via a novel liquid epoxidation of 126 using dinuclear peroxotungstate as a catalyst & H2O2 as an oxidant (92 percent ds). Finally, azasugar 128 is produced in a yield of 88% via an intramolecular ring opening of the epoxide after the bromide has been displaced nucleophilically by ammonia. As a result, the total yield of 128 is 60%.

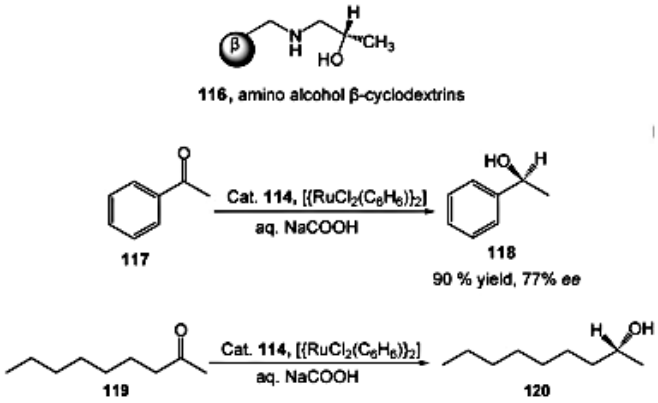


Figure 4: Ketones can be reduced enantioselectively in water.

- **Biomolecules that have been chemically modified:**

The developing discipline of chemical biology, which employs chemical tools to research biology, relies heavily on aqueous organic chemistry. Chemical biology has recently come to recognize the power of selective chemical changes designed to modify biomolecules, as life is known to build chemical bonds in aqueous environments. They help scientists understand how cells work and lead to novel approaches in protein engineering. The functional groups involved must be relatively unreactive and inert toward biomolecules if this is to be accomplished. Furthermore, the selective chemical changes must take place in an aqueous physiological environment at room temperature.

Extremely energetic functional groups like azides and alkynes are nearly non-bioactive. In terms of thermodynamics, the Huisgen cycloaddition of azides 129 & alkynes 130 is preferential by about 30-35 kcal mol12. But the reaction calls for hotter conditions. Newly developed by Sharpless and colleagues, a copper(I)-catalyzed version is efficient at physiological temperature changes and also in aqueous solutions. This reaction allows for the targeted engineering of a wide range of biomolecules, including virus particles, nucleic acids, & proteins. The cowpea mosaic virus (CPMV) is a good example; it has a single-stranded RNA genome encased in 60 identical copies of a two-protein unit. CPMV (132), which is adorned with azides, is efficiently combined with the dyealkyne (133) in the presence of Cu(I) catalyst. 39 A further chemoselective reaction developed for biomolecule modification is the modified Staudinger reaction. In the Staudinger reaction, phosphines and azides combine to form azaylides. At room temperature, phosphines & azides react effectively to produce amines & phosphine oxides in the presence of water. Phosphines & azides are both extremely non-toxic to living things. Because of this, the classical Staudinger reaction is a promising option for the chemo-bio modification of bio-molecules. However, the instability of the aza-ylides in water prevents them from being used to create a novel and beneficial chemical bond under physiological circumstances. A stable amide bond was developed by Bertozzi and colleagues using an aqueous Staudinger reaction and an electrophilic trap. Steady cell surface adducts 146 are made when the biotinylated phosphine 145, which is soluble in water, reacts with azides present on the cell surface.

Chemical manipulation of biological macromolecules:

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Conclusion:

Over the past decade, organic reactions in water have received unprecedented study and development in this field. This survey serves as a primer for the subject area. There is now as much variety in organic reactions that can take place in water as there is in organic solvents. Notably, new in for of reactions in water have been discovered. The future of this field is buoyed by the widespread interest in aqueous organic reactions.

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