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‘Organic Chemistry in Water Perspective-An Overview’

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Abstract: Organic transformations that benefit from being performed on water under the conditions defined by Shapeless and co-workers was studied. The Diels-Alder cycloaddition is a powerful synthetic transformation that has been used prolifically by organic chemists, and the effect of aqueous solvents on this large family of reactions. 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 carbine 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.

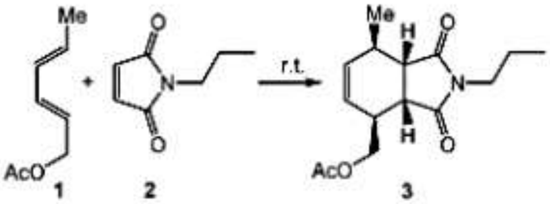
Introduction: The most complex organic compounds on Earth, which include all forms of life, can only form when chemical bonds are built in water. If we are to learn from nature, we must consider water a universal solvent for organic synthesis

[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.

[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.

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.



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.

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.

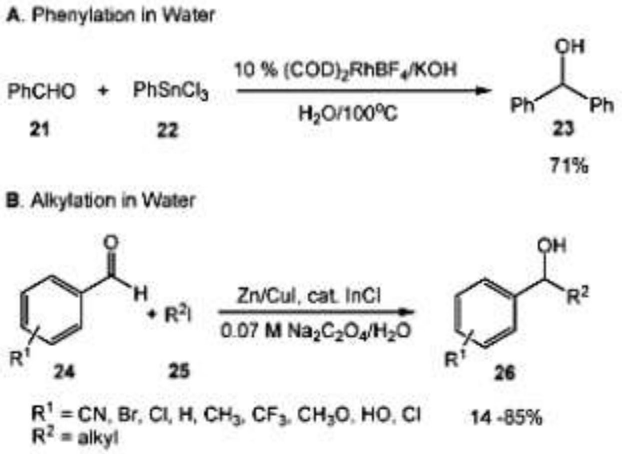


Figure 2: The occurrence of a Barbier-Grifols reaction in water

The a-adduct products are rarely obtained despite the high regio- and stereoselectivity of metal-mediated Barbier-type allylation reactions. One can perform regioselectiveallylation (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.

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) 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.

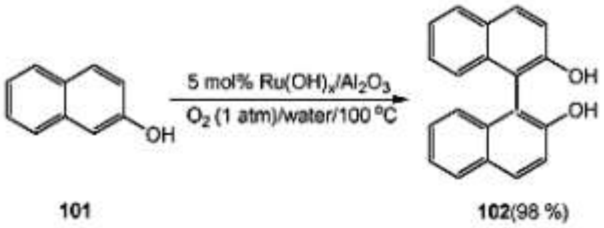


Figure 3: Coupling of 2-naphthol to oxygen in water.

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 .

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.

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. (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 isobtained 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 dinuclearperoxotungstate 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%.

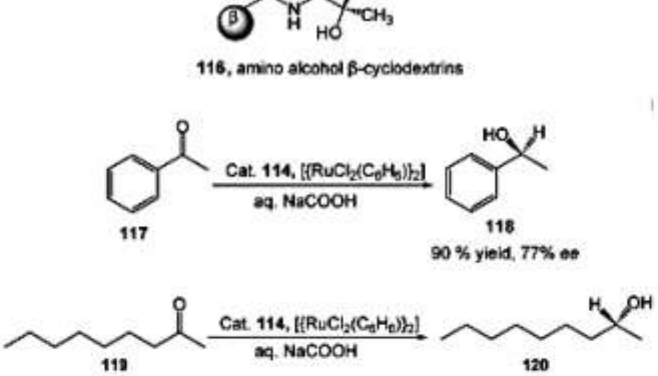


Figure 4: Ketones can be reduced enantioselectively in water.

- 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.

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: The developing discipline of chemical biology, which employs chemical tools to study 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 biological molecules 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.

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 and 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 azaylides in water prevents them from being used to create a novel and useful covalent bond under physiological conditions. A stable amide bond was developed by Bertozzi and colleagues using an aqueous Staudinger reaction and an electrophilic trap. Stable cell surface adducts 146 are made when the biotinylated phosphine 145, which is soluble in water, reacts with azides present on the cell surface.

Conclusion: The science of Organic Chemistry has a broad and diverse past with many investigators from many countries making discoveries that when combined over 200 years led to the field of Organic Chemistry. The intrigue found with substances that contain carbon, organic compounds, arose because so many different substances could be found in nature and many of them had medicinal uses. The discovery of a laboratory synthesis of urea by Frederich Wöhler (1828) showed that organic chemicals did not have to be prepared by the vital forces of nature but could also be prepared by humans, thus opening the way for the field of synthetic organic chemistry. 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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