

# SOLVENTS: From Past to Present

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Cite This: *ACS Omega* 2024, 9, 7271–7276

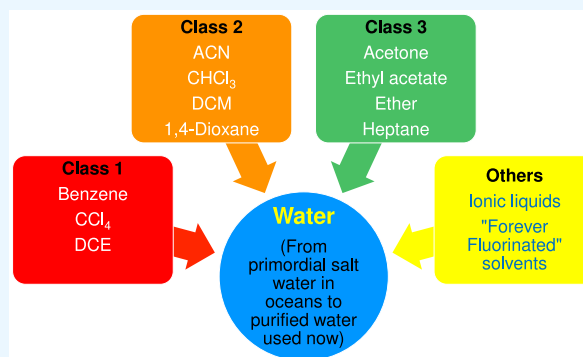
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**ABSTRACT:** Technological advancements in organic chemistry cannot be imagined without solvents, an essential evil due to well-recognized safety, health, and environmental risks and yet an integral part of the value chain for almost all industrially manufactured products intended for human use. A solvent serves as an essential liquid medium for different molecules to interact and react, generating products totally different from the original reactants. Reminiscences reveal water to be the first solvent used in the art of organic chemistry. This Viewpoint attempts to capture anecdotal theories and evidence on the use of this “magic liquid” and the progressive adoption of alternative liquid solvents, which have played a pivotal role in the evolution of synthetic organic chemistry. Synthetic organic chemistry, in turn, has sought to compete with nature in mimicking complex natural product syntheses in the laboratory on minuscule time scales compared with millions of years of evolutionary processes.



## INTRODUCTION

*If there is magic on this planet it is contained in water.*

—Loren Eiseley

*Water is the lifeblood of our bodies, our economy, our nation and our well-being.*

—Stephen Jones

The word “solvent” is derived from Latin, *solvō*—loosen, untie, solve. Solvents can be solids (for instance, in alloys), liquids, gases, and supercritical fluids. A solvent is a material that dissolves a solute (solid, liquid or gas); if the solute dissolves totally, a homogeneous solution is formed. *By this definition, water is most likely the first solvent which dissolved sodium chloride and oceans were formed 3.8 billion years ago.*

Undoubtedly, the emergence of life on our planet was aided by the primordial soup containing methane, ammonia, hydrogen, and oxygen and generated biologically important molecules such as amino acids, sugars, and nucleic acids. The evolution of life forms eventually led to the appearance of humans on the planet. With the passage of time, *Homo sapiens* became the apex species dominating all the areas of the planet. During all of these developments, water served as the critical impeller for the human race to survive and thrive. All major civilizations were established around important rivers, be it the Nile, Indus, or Tigris-Euphrates. Early instances of cures for human ailments record the treatment of patients with natural product extracts. These were extracts of plant or animal origin and used different parts, such as roots, bark, fruits, *etc.* in the case of plants or whole animals, their organs, or specific components of animal organs. The extracts were mostly in water; this humble molecule (two

hydrogens and one atom of oxygen) has been mainly responsible for growth and reproduction of all life on our planet.

A cup of tea without water and an organic reaction vessel without the solvent are almost nonexistent. For two or more substances to react, a liquid medium is required, and solvent plays that role unless both reactants are at least partially miscible liquids. The oldest solution on the planet could be brine solution (ocean) formed 3.5 billion years ago, and water could be considered the first solvent in the universe. AI tools and a Google search did not throw up a definitive answer to the question “What is the first solvent ever used in organic synthesis?” One way to figure that out is to first look at the list of all solvents that are in practice and the available chronology of any documented publications describing the preparation of each solvent in the list. The other way to find a logical answer to this question would be whether any solvent has been used in other fields of science for any purpose and borrowed by organic chemists either by logic, intuition, or serendipity. Besides water, one may surmise from historical references that ethyl alcohol (wine or other liquor) and acetic acid (vinegar) might have been the earliest widely used organic solvents.

**Received:** September 28, 2023

**Revised:** January 3, 2024

**Accepted:** January 16, 2024

**Published:** February 6, 2024



## DISCUSSION

Organic chemists and alchemists continued to depend largely on water until the Industrial Revolution during 1760–1830, even though the search for a universal solvent reached its peak during the heydays of Renaissance alchemy from the 14th to 17th centuries. Notably, Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493–1541), better known in posterity as Paracelsus, made attempts to integrate the practice of medicine with chemistry and devoted much time to the unsuccessful search for Alkahest, the elusive universal solvent capable of dissolving every substance, including metals, without altering the properties of the dissolved material.

During human evolution, alcohol (ethyl alcohol) was identified, but more as a sedative and not as a solvent. One of the major outcomes of the industrial revolution was a large-scale production of chemicals that changed the way humans altered the planet, ushering in the Anthropocene era. Reports of the manufacture of sulfuric acid, sodium carbonate, potash (potassium carbonate), and bleaching powder appear during this period, which started the phase of large-scale manufacturing.

Practical organic chemistry can be thought to have originated when the early humans started cooking their food in vessels ~300 000 years ago using “earth ovens”, beyond the earliest mode of simply roasting food directly in a fire discovered ~780 000 years ago. Cooking in vessels necessitated not just temperature but also a medium-*cum*-solvent—water—to transfer the heat and release flavours. Heating made raw food items more palatable and digestible by fragmentation of starch, proteins, fibers, *etc.*, changing the structure and nature of the ingredients. This may have been followed by cooking of meats in fatty oils, thereby laying the foundation of chemical transformations in water or organic solvents, as early as the Stone Age. The recorded history of solvents, however, goes back to the fourth and fifth centuries, with alchemists from India and China who used natural resources to find better therapeutics. Plants and minerals were extracted in boiling water and alcohol. Later, Egyptian and Greek alchemists worked on colors and dyes. A more serious effort toward the classification of materials appears in the writings of Jabir ibn Hayyan (Geber) in the eighth century, who introduced an early chemical classification system: spirits, which are materials that vaporize when heated; Metals, such as iron, lead, tin, copper, *etc.*; and nonmalleable substances that could be made into powders, such as stones. Synthetic organic chemistry took root in 1828 with the synthesis of urea by Wohler and was quickly followed by the synthesis of many more molecules by scientists like Wohler, Kolbe, Liebig, Chevreuil, Lavoisier, *etc.*, pioneers who laid the foundations of organic chemistry.<sup>1</sup>

The history of solvents starts from the observance of residues of ethyl alcohol (ethanol) in a 13 000 years old brewery near Haifa in Israel. Neolithic people also left traces of alcohol in the pottery that is dated to be 9000 years old. The word alcohol, commonly used for ethyl alcohol, is derived from Arabic “Al-Kohl” or “Al-Kohol”, meaning any substance that can be refined by pulverization, distillation, or sublimation. Ethanol was also called “*alcohol vini*” or subtle part of wine alcohol derived from the origin. Humans had developed the first fermentation processes for getting alcohol, which formed a part of religious rituals for most ancient civilizations. The first report of synthetic alcohol was by Michael Faraday who prepared it by a reaction of sulfuric acid with coal gas. The story of ethanol is intertwined with both sedation and addiction.

The ancient Mesopotamian civilization recorded the first ever use of alcohol as a sedative for alleviating pain. Observations about alcohol consumption leading to intoxication, addiction, and coma followed by death due to liver complications, including cirrhosis, led to a search to find a better sedative for pain management. Decrease in the use of ethanol for human use laterally provided a class 3 solvent for chemists (the classification of solvents based on their toxicity is provided in Table 1).<sup>2</sup> The

**Table 1. Classification of Solvents**

class 1 (solvents to be avoided, carcinogens)	class 2 (solvents to be limited, nongenotoxic animal carcinogens)	class 3 (solvents with low toxic potential to humans)
benzene	acetonitrile	acetic acid
carbon tetrachloride	chlorobenzene	acetone
1,2-dichloroethane	chloroform	DMSO
	dichloromethane	ethanol
	DMF	ethyl acetate
	hexane	ethyl ether
	methanol	heptane
	THF	methyl ethyl ketone
	toluene	isopropanol
	xylene	

polar nature of ethanol along with its lower boiling point than water made it a well explored solvent. It is still used extensively as a replacement for water in reactions. The ethanol industry grew exponentially in the last century with the development of new processes besides fermentation, hydration of ethylene, *etc.* As understanding of the lone pair of oxygen in solvation and stability of intermediates was established, newer alcohols such as isopropyl alcohol (dominant in the paint industry), amyl alcohol, methanol, *etc.* have been introduced. This class represents a polar group of solvents and dissolve most of the salts or polar compounds.

With the acceleration of developments in organic synthesis, in which a significant proportion of reactants are water-insoluble and/or hydrophobic, a need was felt for nonaqueous solvents; as a result, a range of organic solvents were progressively identified. The advances in physical and mechanistic organic chemistry and the understanding of the role of solvation, the stability of intermediates in a particular medium, viscosity, the ability to form hydrogen bonds, *etc.* necessitated the invention of new solvents and cosolvents. These new solvents naturally performed better in terms of yields and quality of products. This started the trend of moving away from water and ethanol as solvents and further exploring organic molecules as solvents. During the initial stages of development, many molecules were explored and introduced as solvents. They have enjoyed their respective periods of glory, sometimes fading away and many still continuing to get popular support.

Opium alkaloids, cannabis, *etc.* were the next step in pain management, followed by the development of synthetic molecules with the focus on making them nonaddictive to replace ethanol. Ethanol was not serving its purpose for reactions that could not progress in a protic medium. Two major solvents emerged during the search to identify substitutes for alcohol: chloroform and diethyl ether or ether. Both these molecules had a parallel journey of development. Ether as an anesthetic was popularized in 1846, and chloroform was popularized in the year 1847. Chloroform was discovered by Soubeiran in France and Samuel Guthrie in New York in the year 1831.<sup>3</sup> In 1832, Liebig

obtained a purer sample by distilling chloride of lime with alcohol, and in 1834 Dumas named the pure sample as chloroform. Though the discovery of diethyl ether was credited to the alchemist Ramon Llull (1275), it was synthesized in 1540 by Varius Cordus. He called it “*oleum duice vitrioli*”, as ether was obtained by distilling a mixture of wine and vitriol (sulfuric acid).

William T. G. Morton (USA) administered ether for a dental extraction in 1846. Soon, ether became the choice of surgeons to carry out painless operations. James Young Simpson in Scotland took up the challenge of finding a new anesthetic and developed chloroform as an alternative. He administered chloroform to humans in 1847, and its use spread to several countries in Europe. Queen Victoria was given chloroform during child birth and reportedly admired the “painless procedure”. Though established, both of these molecules had issues associated with them. Ether has a very low flash point and catches fire easily, resulting in harm to the patient; hence, handling it is a major concern. Chloroform, on the other hand, is not pyrophoric but is reported to cause cardiac fibrillation, resulting in death in some cases. Both of these were then explored as solvents and are still in use, as chloroform in the deuterated form is used for recording Nuclear Magnetic Resonance spectroscopy (NMR). For application as anesthetics, both of these solvents are replaced with next-generation molecules that combined the desirable properties of both with better outcomes.

During the search for chlorinated (halogenated) anesthetics, carbon tetrachloride was also explored for its activity. Its anesthetic and analgesic properties were briefly explored in the mid-19th century, but this was discontinued after serious medical observations. It caused violent muscle contractions and a negative effect on the heart in some patients. Carbon tetrachloride was first synthesized by Michael Faraday in 1820.

One more solvent in this category is 1,2-dichloroethane. It was called “Dutch oil” as a team of scientists calling themselves “Society of Dutch Chemists” synthesized it from olefiant gas (ethylene) and chlorine. Interestingly, chloroform and carbon tetrachloride also became one-carbon equivalents in modern organic chemistry, though later studies have demonstrated the negative impact of these halogenated solvents toward ozone depletion, leading to exposure of our sensitive planet to UV radiation.

Lampadius of Germany, a pharmacist who later taught chemistry and metallurgy, is credited with the serendipitous synthesis of carbon disulfide in 1796. Kolbe carried out the conversion of carbon disulfide to carbon tetrachloride and finally to acetic acid through a series of intermediates, including an electrochemical reaction. Acetic acid thus became the first organic solvent produced from inorganic sources.

The popularity of ether led to the identification of a class of compounds with the same functionality, some open chain and others cyclic. *t*-Butyl methyl ether, diisopropyl ether, tetrahydrofuran (THF), 1,4-dioxane, and 2-methyl tetrahydrofuran are all examples of the ether class of compounds. Of all these solvents, THF dominated the ether class of solvents due to its pronounced property of better solvation attributed to the lone pair of electrons of oxygen in a cyclic frame. THF, one of the most preferred solvents in organic synthesis, is manufactured by acid-catalyzed dehydration of 1,4-butanediol, which in turn is obtained from acetylene and formaldehyde. DuPont developed a process for oxidizing butane to maleic anhydride followed by catalytic hydrogenation to manufacture THF. Another method of manufacture is through hydroformylation of allyl alcohol and

hydrogenation to get 1,4-butanediol, which yields THF in the presence of acid. In addition, conversion of furan to THF has provided a biomass conversion option for manufacture, avoiding dependency on petrochemicals.

The story of aromatic compounds starts with benzene. Benzene was an enigma and, to some extent, still continues to be. The molecular formula of benzene, C<sub>6</sub>H<sub>6</sub>, prompts a structure with unsaturation. The reactivity of benzene is relatively low compared to that of polyenes, and it is a very stable compound under normal conditions. More than 100 years after its isolation, Kekulé in 1865 suggested a ring structure for benzene. According to accounts, he visualized a snake biting its tail like the “*ouroboros*” of mythology, which, to some extent, satisfied the unique properties of benzene. X-ray confirmation for the proposed structure of the delocalized molecular orbital around the ring was in 1929 by Kathaleen Lonsdale. Benzene as solvent has played a pivotal role in chromatography due to its medium polarity compared to hydrocarbons and halogenated and ethereal solvents before the toxic effects it has on human and animal health were realized. All humans have been exposed to this molecule to varying degrees. The entire family of solvents from oil refineries including BTX (benzene, toluene, and xylene) and low boiling fractions (pentane, hexane, heptane, *etc.*) have dominated the chemical sciences as solvents difficult to replace. Studies about benzene opened a new area for understanding the complex nature of molecules and their reactivities. The principles of aromaticity are defined and expected products can be estimated based on this property of molecules. Use of benzene as a solvent has been curtailed due to its well-established carcinogenic properties, but toluene and xylenes are still used widely.

The discovery of hydrocarbons (so-called because they contain only carbon and hydrogen atoms, hence hydrocarbons) is credited to the Chinese civilization of ~600 B. C. The oil/bitumen that seeped to the surface was used for medication, waterproofing, and warfare. In Azerbaijan, on the silk route, there are seeps that have been on fire for centuries, reports of which are available in Marco Polo's accounts. Petroleum, literally “rock oil”, was first reported in Hit in Iraq as early as 6000 years ago. The asphalt left behind after the evaporation of volatiles was used as a mortar for construction. Bitumen, the tarry residue, was used by the Egyptians for embalming mummies. About 2000 years ago, the Chinese used oil for heating and lights, carrying it in bamboo pipes. The invention of a kerosene lamp in 1854 created a huge demand for the petroleum industry, and the identification of deposits in the Arabian Peninsula has changed the geopolitical scenario of the world.

Acetone, a solvent used in nail polish removers, paints, and varnishes, was initially called “Spirit of Saturn” by alchemists, as it was obtained by dry distillation of lead(II) acetate (also called salt of Saturn).<sup>4</sup> The first isolation was by Andreas Libavius in 1606 by distillation of lead(II) acetate. Most of the historically important chemists of the 17th, 18th, and 19th centuries were associated with this solvent. Jean Baptiste Dumas and Justus von Liebig identified the empirical formula in 1832, and Dumas named it acetone. In 1865, August Kekulé gave the structural formula, and Johann Josef Loschmidt in 1861 established the structure of acetone. Initially it was industrially produced by the Weizmann process, which involved the fermentation of starch to produce acetone, butanol, and ethanol using *Clostridium acetobutylicum*. Later the process was changed to using propylene, and 83% of the acetone produced today is from

propylene. Two major processes are followed for acetone manufacturing: through cumene (synthesized from benzene and propylene) oxidation or the Wacker–Hoechst process of oxidation or hydration of propylene to 2-propanol followed by oxidation. In addition to being a solvent of choice, especially for the removal of water, acetone is an indicator of diabetic ketoacidosis.

Ethyl acetate, a solvent used extensively in extraction and purification of organic compounds, was first synthesized by mixing alcohol with acetic acid. It belongs to the ester class of compounds and thus is liable to hydrolysis in the presence of any strong acid and base. Other esters used are methyl acetate, ethyl formate, *t*-butyl acetate, *etc.*

Another important class of solvents involves nitrogen-atom-containing molecules; formamide, *N,N*-dimethylformamide (DMF), and acetamide were the first series of this class. They represent the amide functionality and have been used extensively, especially DMF, to dissolve molecules that are not easily soluble in other solvents. DMF has also been used as a reactant in reactions such as Vilsmeier–Haack formylation. Nitromethane and nitrobenzene are used for specific reactions, and nitromethane also finds use as a reagent for inducing a 1-carbon and 1-nitrogen moiety in a molecule. Nitrobenzene has a relatively higher boiling point and has not been considered of late, as traces of it may contaminate the product. Solvents containing a nitro group are not used as widely as oxygen-containing solvents. Pyrrolidine and *N*-methyl pyrrolidine represent cyclic *N*-solvents, which were explored due their desirable properties such as polarity, lack of H-atoms, *etc.*

To enhance the potential of heteroatom solvents such as ethers, combinations of solvents have been explored. The most widely used combination has been THF with HMPA. However, HMPA with two heteroatoms, N and P, has adverse toxic effects and is discouraged. Other additives like HMPT, NMP, NMU, *etc.* have proven to be essential add-on solvents for solubilizing the intermediate species for better yields. Fluorine-containing solvents are the latest entry into the vast solvents available, providing alternative to hydrocarbon solvents and offering advantages because of electronegative fluorine atoms. New reactions have been discovered, and many such new reactions demanded novel tailor-made solvents such as perfluoro solvents, ionic liquids, PEG, supercritical carbon dioxide, *etc.* Solvent combinations with HMPA, DMP, and ammonia as additives have also shown utility where a single solvent might not suffice to ensure optimal reactivity and selectivity.

With the evolution of modern structure–property elucidation and computational techniques, the capabilities of synthetic organic chemists to identify optimal solvents or mixtures thereof have increased significantly. Mabeoone et al.<sup>5</sup> demonstrated that supramolecular polymers can be used to amplify solute–solvent effects and enable deeper understanding of solvation phenomena at molecular levels. At larger industrial scales that might additionally involve gas–liquid (G-L) interactions in reactive media, Ganguly et al.<sup>6</sup> recently presented a simplified model of optimal G-L contact regimes that can guide the optimization of agitation conditions for ensuring intimate mixing of gas–liquid reactants without excessive energy use. Integration of these different approaches that can enable discernment and optimization of thermodynamic and kinetic aspects of reaction mixtures are likely to yield significant benefits in industrial uses of solvents for organic reactions,

The focus of the usage of these solvents has been on the efficiency at which the products are made, including cost

economy. Both academic and industrial researchers, knowingly or unknowingly, were oblivious to the impact of these solvents to human health and the environment, which is now creating havoc, and many course correction measures are under way.

Toward the goals of ensuring alignment with Green Chemistry Principles, aiming to minimize environmental impact and health hazards associated with traditional solvents and increased recyclability of solvents postreaction, a range of alternatives have emerged in recent decades.

1. **Biobased Solvents:** Derived from renewable resources such as plants, vegetable oils, or biomass, biobased solvents offer a sustainable alternative in terms of fossil carbon source avoidance. For example, ethyl lactate, derived from corn, has gained attention for its low toxicity and biodegradability.<sup>7</sup>
2. **Ionic Liquids:** Ionic liquids (ILs) have begun to reach mainstream use as green solvents due to their low volatility and wide temperature range in the liquid state. Their tunable properties make them versatile in various applications, including catalysis and extraction.<sup>8</sup> The first ever ionic liquid would be sodium chloride, which fits into the definition of ionic liquid with its melting point at 801 °C. An interesting observation of ionic liquid in nature has been the curious case of tawny crazy ants attacking fire ants. Fire ants spray toxic alkaloid-based venom that is neutralized by tawny crazy ants by exuding formic acid, thus forming an ionic liquid that is liquid at ambient temperature.<sup>9</sup>  
Timken et al.<sup>10</sup> have described a commercial high-octane gasoline production technology using an IL catalyst. ILs were initially expected to be the game changers,<sup>11</sup> delivering improved selectivity for desired product formation compared to nonionic solvents and allowing products to precipitate out/separate from the reaction medium so that recycling of components from the mixture would be facile. However, ILs have yet to receive widespread acceptance due to the complexity involved in industrial-scale synthesis of all but a select few ILs. It was also observed that quaternary salts were harmful to living systems, including nucleic acids and multicellular organisms. In addition, effects of ILs on air, water, and humans as contaminants in drug molecules have not yet been studied in detail. Safe disposal of waste generated from IL-based reactions also remains work-in-progress for the most part.
3. **Supercritical Fluids:** Utilizing supercritical carbon dioxide as a solvent has gained popularity, especially in extraction processes. Its low toxicity, nonflammability, and ease of removal make it an attractive green alternative.<sup>12</sup> Increasing interest in the utilization of captured carbon dioxide as a climate change mitigation strategy also strengthens this application, as the life cycle carbon footprint associated with the solvent being replaced by supercritical CO<sub>2</sub> can be offset. Wai et al.<sup>13</sup> were among the first to highlight its potential as a reaction medium.
4. **Deep Eutectic Solvents:** A review by Alonso et al.<sup>14</sup> referred to deep eutectic solvents (DES) as “The Organic Reaction Medium of the Century”. While this may be premature hyperbole, DES have emerged as a promising class of solvents with unique properties, evolving from the exploration of eutectic mixtures. Unlike traditional solvents, DES are typically composed of two or more

components that form a eutectic mixture with a melting point lower than those of each individual component. The vast array of possible combinations among various components enables tailoring of DES properties to meet specific requirements. Common components include quaternary ammonium salts, hydrogen bond donors (such as carboxylic acids, amides, or alcohols), and metal halides. DES typically exhibit low volatility, reducing the release of harmful vapors into the atmosphere. For example, Khandelwal et al.<sup>15</sup> refer to a one-pot four-component domino protocol for the synthesis of structurally diverse spirooxindoles using a DES medium. DES, too, have their limitations. The viscosity of these systems tends to be high because of the significant intermolecular ionic interactions. The availability of ecotoxicity data is limited. Contaminant removal after a reaction could be potentially challenging.

While new generation solvents such as biobased solvents, ionic liquids, supercritical carbon dioxide, deep eutectic solvents, perfluoro solvents, *etc.* have contributed to some but as yet insubstantial improvements at global scale, it is high time chemists reorient their approach to design experiments using solvents that do not cause any damage to the planet. Volatile organic solvents (VOCs) similarly need to be replaced, wherever possible, due to their adverse health and occupational hazard implications despite the best precautions that may be advised in use. Though perfluoro solvents are being considered now, they are labeled as “forever molecules” as they can never be disintegrated and get accumulated in human body.<sup>16</sup>

The concern of extensive use of solvents, which contribute to 50–80% of the waste generated during a reaction, has prompted researchers to consider options that will provide alternatives to VOCs. A major concern about the use of water in reactions has been that it reacts with molecules in many different ways, which prevents good yields from being obtained out of the complex reactions. A recent article by Lipshutz et al.<sup>17</sup> highlights some of the advances made to use water as a preferred solvent for carrying out reactions and highlighting the limitations encountered. Some of the reactions being carried out in water are olefin cross-metathesis, Suzuki–Miyaura coupling, photocatalytic reactions, and one of the most important reactions of amide bond formation. The techniques used are surfactants, micelles, droplet formation, *etc.* Even if the reaction is carried out in water, the solvent used for extraction nullifies the efforts.

Another attempt is to develop solvent-free reactions with techniques such as ball-milling, where the reactants are made to react using mechanical forces.<sup>18</sup> Ultrasonic irradiation- and microwave-accelerated reactions,<sup>19</sup> preferably in water, are also being developed. European authorities have introduced a new initiative REACH (registration, evaluation, authorization, and restriction of chemicals) to encourage industries to stop use of common organic solvents.

The use of water for carrying out reactions is being emphasized;<sup>20</sup> however, the expenditure of purification of water after the reaction has not been considered. The water layer will have starting materials, reactants, reagents, surfactant, and product in varying ratios. The byproducts are also part of the aqueous system. It will be a major challenge to remove all of the contaminants and make the water as pure as drinking water.

## CONCLUSION

Solvents will continue to remain indispensable in organic chemistry for at least the next few decades. Ironically, when scientific knowledge was at its nascent stage, the practitioners of chemistry in general and organic chemistry in particular favored naturally biocompatible solvents like ethanol and water. The next solvents invented based on ethanol were diethyl ether and acetic acid, which also have minimal adverse impact on the environment. As documentation of scientific knowledge and investments into research gained momentum, understanding of mechanistic organic chemistry has been progressively advanced, and knowledge in physical, chemical, and biological sciences has begun to be integrated. While new solvents discovered have served the purpose of facilitating reactions with increasing ease, despite the progress made in understanding the impact of chemicals on life processes, these new solvents ended up in the undesirable class 1 and 2 categories rather than in class 3 (ethanol being perhaps the best example of this benign class). It appears in hindsight that we have heavily compromised the impact of these convenient reaction media on life, the environment, and sustainability. It is essential that collective wisdom of all branches of science, including industrialization, will prevail sooner than later, leading to focused efforts of resources in research that will result in solvents that can be sustainably produced at large scales, are friendly to the planet, and do not adversely impact the health of all living beings. It is believed, with highest optimism, that optimized new reactions will be developed in class 3 solvent media and water or “no solvent” as the ultimate goal.

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### Notes

The authors declare no competing financial interest.  
<sup>†</sup>Pursuant to retirement from CSIR-Indian Institute of Petroleum, A.R. now operates as an independent consultant at Sustainable Energy, Safety and Supply Chains based at I-1784 Second Floor, Chittaranjan Park, New Delhi, Delhi 110019, India.

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