RSC Green Chemistry Series

Francesca M Kerton

Alternative Solvents for Green Chemistry

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Preface

Everyone is becoming more environmentally conscious and therefore, chemical processes are being developed with their environmental burden in mind. Of course, this also means that more traditional chemical methods are being replaced with new innovations. This includes new solvents.

Solvents are everywhere, but should they be? They are used in most areas including synthetic chemistry, analytical chemistry, pharmaceutical production and processing, the food and flavour industry and the materials and coatings sectors. But, the principles of green chemistry guide us to use less of them, or to use safer, more environmentally friendly solvents if they are essential. Therefore, we should always ask ourselves, do we really need a solvent? Chapter 2 explains some of the challenges and successes in the field of solvent-free chemistry, and the answer becomes apparent: not always!

In the introductory chapter, some of the hazards of conventional solvents (e.g. toxicity and flammability) and their significant contribution to waste streams are highlighted. The general properties of solvents and why and where they are used are outlined. Additionally, EHS (Environmental, Health and Safety) assessments and life cycle analyses for traditional and alternative solvents are described. It becomes clear that often a less hazardous VOC is available and that although only "light green" (or at least "less black") in colour, they can be used as an interim measure until a more satisfying option becomes available. In each of the subsequent chapters, where possible, the use of an alternative solvent is described for a range of chemical applications including extractions, synthetic and materials chemistry. At the beginning of each of these chapters, some of the advantages and disadvantages of that medium are laid out.

Water is often described as Nature's solvent; therefore Chapter 3 describes the solvent properties of water. It is already used quite widely on an industrial scale, particularly in emulsion polymerization processes and hydrodistillations. However, some of the most exciting results have come in the field of synthetic

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chemistry. Recently, 'on-water' reactions have shown that hydrophobic (water insoluble) compounds can achieve higher rates dispersed in water compared to reactions in conventional solvents or under solvent-free conditions. Water can also be used at very high temperatures and under pressure in a near-critical or supercritical state. Under these conditions, its properties are significantly altered and unusual chemistry can result. This is further discussed in Chapter 4, which describes supercritical fluids. The focus here is on the non-flammable options, that is, carbon dioxide and water. Modifications that are performed on substrates in order to make them soluble in supercritical carbon dioxide are described. Additionally, the benefits of the poor solvating power of carbon dioxide, e.g. selective extractions, are highlighted and its use in tuning reactivity through its variable density is described.

In addition to water and carbon dioxide, there is an increasing availability of solvents sourced from renewable feedstocks including ethanol, ethyl lactate and 2-methyl-tetrahydrofuran. The properties of these solvents and their potential as replacements to petroleum-sourced solvents are discussed in Chapter 5. Renewable feedstocks and their transformations are a growing area of green chemistry and they have significantly impacted the solvent choice arena. In addition to renewable VOC solvents, non-volatile ionic liquid and eutectic mixture solvents have been prepared from renewable feedstocks and are looking to be very promising alternatives in terms of toxicity and degradation. These and other room temperature ionic liquids (RTILs) will be discussed in Chapter 6. The field of RTILs has grown dramatically in the last ten years and the range of anions/cations that can be used to make these non-volatile solvents is continually expanding. Although some of these media may be more expensive than other alternatives, the chance to make task-specific solvents for particular processes is very exciting. RTILs, alongside fluorous solvents, have also made a large impact in the area of recyclable homogeneous catalysts. Fluorous solvents, as described in Chapter 7, show interesting phase behaviour and allow the benefits of a heterogeneous and homogeneous system to be employed by adjusting an external variable such as temperature. Recent advances in this area will be discussed, for example, supported fluorous chemistry, which avoids the use of large amounts of fluorous solvents and might be more amenable to industrial scale processes.

Possibly the least explored and newest options available to the green chemist are liquid polymer solvents (Chapter 8) and switchable and tunable solvents (Chapter 9). Unreactive low molecular weight polymers or those with low glass transition temperatures can be used as non-volatile solvents. In particular, poly(ethyleneglycols) and poly(propyleneglycols) have been used recently in a range of applications. Probably the most important recent additions to our toolbox are switchable solvents. New molecular solvents have been discovered that can be switched from non-volatile to volatile or between polar and non-polar environments by the application of an external stimulus. Gas-expanded liquids will also be discussed in Chapter 9, as carbon dioxide can be used as a solubility switch and to reduce the environmental burden of conventional solvents.

Although many advances in the area of alternative solvents have originated in academia, many alternatives are already in use on an industrial scale. For example, supercritical carbon dioxide is used in coffee decaffeination and natural product extractions, as an alternative solvent in dry-cleaning and as a solvent in continuous flow hydrogenation reactions. An overview of these and some other industrial processes that use alternative solvents will be described in Chapter 10.

Unfortunately, as will become clear to readers, there is no universal green solvent and users must ascertain their best options based on prior chemistry, cost, environmental benefits and other factors. It is important to try and minimize the number of solvent changes in a chemical process and therefore, the importance of solvents in product purification, extraction and separation technologies has been highlighted.

There have been many in-depth books and reviews published in the area of green solvents. Hopefully, readers will find this book a readable introduction to the field. However, some cutting-edge results from the recent literature have been included in an attempt to give a clearer picture of where green solvents are today. For more comprehensive information on a particular solvent system, readers should look to the primary literature and the many excellent reviews of relevance to this field in journals such as Green Chemistry and Chemical Reviews.

Certain solvent media can be fascinating in their own right, not just as 'green' solvent alternatives! Therefore, we must not be blind to our overall goal in reducing the environmental burden of a particular process. Hopefully, readers of this book will be able to make up their own minds about the vast array of solvents available for a greener process, or even come up with a new addition for the green chemistry toolbox. Although many advances have been made during the past decade, the most exciting results are surely yet to come.

I would like to thank the editors of the RSC Green Chemistry Series, James Clark and George Kraus, for the opportunity to contribute a book to this important group of books. Also, I would like to acknowledge Merlin Fox (the commissioning editor) and the staff at RSC Publishing involved with this series, particularly, Annie Jacob, who has been advising and helping me all along the way. Finally, I would like to thank my husband, Chris Kozak, for his patience, support and motivational input during the writing of this book.

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CHAPTER 1
Introduction

1.1 The Need for Alternative Solvents

One of the 12 principles of green chemistry asks us to 'use safer solvents and auxiliaries'.[1–3] Solvent use also impacts some of the other principles and therefore, it is not surprising that over the last 10 years, chemistry research into the use of greener, alternative solvents has grown enormously.[4–8] If possible, the use of solvents should be avoided, or if they cannot be eliminated, we should try to use innocuous substances instead. In some cases, particularly in the manufacture of bulk chemicals, it is possible to use no added solvent—so-called 'solvent free' conditions. Yet in most cases, including specialty and pharmaceutical products, a solvent is required to assist in processing and transporting of materials. Alternative solvents suitable for green chemistry are those that have low toxicity, are easy to recycle, are inert and do not contaminate the product. There is no perfect green solvent that can apply to all situations and therefore decisions have to be made. The choices available to an environmentally concerned chemist are outlined in the following chapters. However, we must first consider the uses, hazards and properties of solvents in general.

Solvents are used in chemical processes to aid in mass and heat transfer, and to facilitate separations and purifications. They are also an important and often the primary component in cleaning agents, adhesives and coatings (paints, varnishes and stains). Solvents are often volatile organic compounds (VOCs) and are therefore a major environmental concern as they are able to form low-level ozone and smog through free radical air oxidation processes.[3] Also, they are often highly flammable and can cause a number of adverse health effects including eye irritation, headaches and allergic skin reactions to name just three. Additionally, some VOCs are also known or suspected carcinogens. For these and many other reasons, legislation and voluntary control measures have

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been introduced. For example, benzene is an excellent, unreactive solvent but it is genotoxic and a human carcinogen. In Europe, prior to 2000, gasoline (petrol) contained 5% benzene by volume but now the content is <1%. Dichloromethane or methylene chloride (CH_2Cl_2) is a suspected human carcinogen but is widely used in research laboratories for syntheses and extractions. It was previously used to extract caffeine from coffee, but now decaffeination is performed using supercritical carbon dioxide ($scCO_2$). Perchoroethylene (CCl_2CCl_2) is also a suspected human carcinogen and is the main solvent used in dry cleaning processes (85% of all solvents). It is also found in printing inks, white-out correction fluid and shoe polish. $ScCO_2$ and liquid carbon dioxide technologies have been developed for dry cleaning; however, such solvents could not be used in printing inks. Less toxic, renewable and biodegradable solvents such as ethyl lactate are therefore being considered by ink manufacturers.

Despite a stagnant period for the solvent industry during 1997–2002, world demand for solvents, including hydrocarbon and chlorinated types, is currently growing at approximately 2.3% per year and approaching 20 million tonnes annually. However, when the less environmentally friendly hydrocarbon and chlorinated types are excluded, market growth is around 4% per year. Therefore, it is clear that demand for hydrocarbon and chlorinated solvents is on a downward trend as a result of environmental regulations, with oxygenated and green solvents replacing them to a large extent.[9] It should be noted that these statistics exclude in-house recycled materials and these figures therefore just represent solvents new to the market; the real amount of solvent in use worldwide is far higher. It also means that annually a vast amount of solvent is released into the environment (atmosphere, water table or soil). Nevertheless the situation is moving in a positive direction, as in the USA and Western Europe environmental concerns have increased sales of water based paints and coatings to levels almost equal to the solvent based market. Therefore, it is clear that legislation and public interests are causing real changes in the world of solvents.

The introduction of legislation by the United States Food and Drug Administration (FDA) means that some solvents, *e.g.* benzene, are already banned in the pharmaceutical industry and others should only be used if unavoidable, *e.g.* toluene and hexane. FDA-preferred solvents include water, heptane, ethyl acetate, ethanol and *tert*-butyl methyl ether. Hexane, which is not preferred and is a hazardous air pollutant, is used in the extraction of a wide range of natural products and vegetable oils in the USA. According to the EPA Toxic Release Inventory, more than 20 million kg of hexane are released into the atmosphere each year through these processes. It may seem straightforward to substitute hexane by its higher homologue, heptane, when looking at physical and safety data for solvents (Table 1.1). However, heptane is more expensive and has a higher boiling point than hexane, so economically and in terms of energy consumption a switch is not that simple. Therefore, it is clear that much needs to be done to encourage the development and implementation of greener solvents.

Table 1.1 Properties of some volatile organic solvents, and some possible alternatives.

Solvent	*Boiling point/°C*	*Flash point/°C*	*TLV–TWA[a]/ppm*	*Hazards*	*Green?*
Methanol	64	12	200	Toxic, flammable	Can be renewable
Ethanol	78	16	1000	Irritant, flammable	Can be renewable
Isopropanol	96	15	400	Irritant, flammable	
1-Butanol	117	12	100	Harmful, flammable	
Ethyl acetate	76	−2	400	Harmful, flammable	
Ethyl lactate	154	46	Not yet established	Irritant, flammable	Renewable
THF	65	−17	200	Irritant, flammable	
2-MeTHF	80	−11	Not yet established	Irritant, flammable	Renewable
2-Butanone	80	−3	200	Irritant, flammable	
Dichloromethane	40	none	100	Toxic, harmful, suspected carcinogen	
Chloroform	61	none	10	Possible carcinogen	
Toluene	110	4	50	Irritant, teratogen, flammable	
Hexane	68	−26	50	Irritant, reproductive hazard, flammable	
Heptane	98	−4	400	Irritant, flammable	
Water	100	none	Not applicable		Renewable, non-flammable, cheap
Carbon dioxide	Not applicable	none	5000	Compressed gas	Renewable, non-flammable, cheap
PEG-1000	Not applicable	none	Not applicable		Non-toxic, non-volatile
[Bmim] [PF_6]	Not applicable	none	Not yet established		Non-volatile

[a]TLV–TWA: threshold limit value—time weighted average in vapour.

1.2 Safety Considerations, Life Cycle Assessment and Green Metrics

In recent years, efforts have been made to quantify or qualify the 'greenness' of a wide range of solvents; both green and common organic media were considered.[10,11] In deciding which solvent to use, a wide range of factors should be considered. Some are not directly related to a specific application, such as cost and safety, and these will generally rule out some options. For example, room temperature ionic liquids (RTILs) are much more expensive than water and they are therefore more likely to find applications in high value added areas such as pharmaceuticals or electronics than in the realm of bulk or commodity chemicals. However, a more detailed assessment of additional factors should be performed including a life cycle assessment, energy requirements and waste generation.

A computer-aided method of organic solvent selection for reactions has been developed.[12] In this collaborative study between chemical engineers and process chemists in the pharmaceutical industry, the solvents are selected using a rules based procedure where the estimated reaction–solvent properties and the solvent–environmental properties are used to guide the decision making process for organic reactions occurring in the liquid phase. These rules (Table 1.2) , whether computer-aided or not, could also be more widely used by all chemists in deciding whether to use a solvent and which solvents to try first.

The technique was used in four case studies; including the replacement of dichloromethane as a solvent in oxidation reactions of alcohols, which is an important area of green chemistry. 2-Pentanone, other ketones and some esters were suggested as suitable replacement solvents. At this point, the programme was not able to assess the effects of non-organic solvents because of a lack of available data. However, this approach holds promise for reactions where a VOC could be replaced with a far less hazardous, less toxic or bio-sourced option.

1.2.1 Environmental, Health and Safety (EHS) Properties

The EHS properties of a solvent include its ozone depletion potential, biodegradability, toxicity and flammability. Fischer and co-workers have developed

Table 1.2 Rules used in computer-aided solvent selection for organic reactions.

Establish need for solvents
Liquid phase reactions
The solvent must be liquid at room temperature
Need for solvent as carrier; if one or more reactants are solids
Need for solvents to remove reactants or products; if one or more products are solids
Need for phase split
Matching of solubility parameters of solute and solvent; within ±5% of the key reactant or product
Neutrality of solvents
Association/dissociation properties of solvents
EHS property constraints (based on up to 10 EHS parameters)

Table 1.3 Categories used in EHS assessment of solvents.

Release potential	Chronic toxicity
Fire/explosion	Persistency
Reaction/decomposition	Air hazard
Acute toxicity	Water hazard
Irritation	

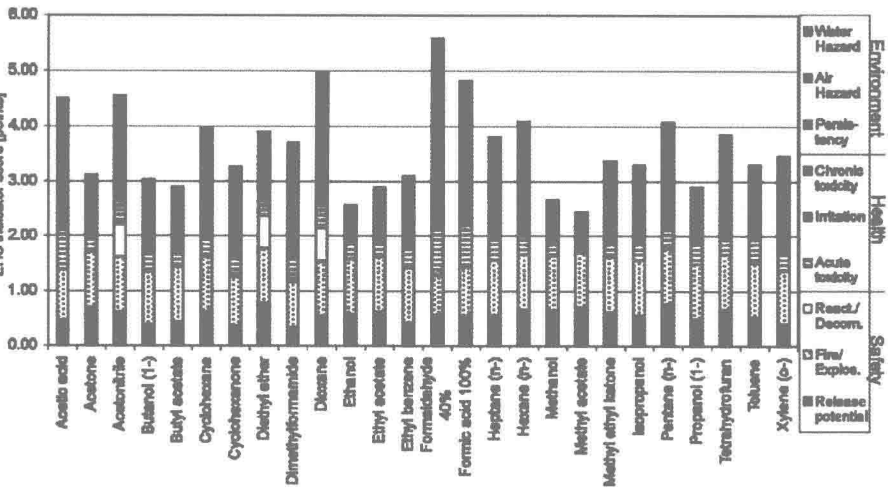

Figure 1.1 Results of an environmental, health and safety (EHS) assessment for 26 common solvents. [Reprinted with permission from *Green Chem.*, 2007, **9**, 927–934. Copyright 2007 The Royal Society of Chemistry.]

a chemical (and therefore, solvent) assessment method based on EHS criteria.[10] It is available at http://www.sust-chem.ethz.ch/tools/ehs/. They have demonstrated its use on 26 organic solvents in common use within the chemical industry. The substances were assessed based on their performance in nine categories (Table 1.3).

Using this EHS method, formaldehyde, dioxane, formic acid, acetonitrile and acetic acid have high (environmentally poor) scores (Figure 1.1). Formaldehyde has acute and chronic toxicity, dioxane is persistent and the acids are irritants. Methyl acetate, ethanol and methanol have low scores, indicating a lower hazard rating.

1.2.2 Life Cycle Assessment (LCA)

The function of life cycle assessment (LCA) is to evaluate environmental burdens of a product, process, or activity; quantify resource use and emissions; assess the environmental and human health impact; and evaluate and