Development of Solvent Selection Guides

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Outline

A review of the development of solvent selection guides, focusing on summarizing the work of major pharmaceutical companies as well as several academic groups towards providing guides to facilitate the selection of a more benign solvent for use in synthetic chemistry.

1. Introduction

The sustainability of chemical processes is of increasing importance within the chemical industry and is becoming a key concern for a wider range of practitioners.[1] Historically, Process Chemists have been the leading proponents of sustainable chemistry practices and while this does remain integral to Chemical Development operations, sustainability is now becoming a significant consideration earlier on in the Discovery phase of industrial, as well as academic, research.[2]

In this regard, solvent is one of the largest overall components used within chemical reactions. For example, solvent has been estimated to account for over half of the total material used to manufacture active pharmaceutical ingredients.[3] Based on this, and perhaps unsurprisingly, solvent was identified very early on in the sustainable chemistry revolution as a priority area for research based on the direct and substantial impact that change in this area may have.

Consequently, over approximately the past 15 years, efforts have been made to identify existing solvents that exhibit undesirable properties from an Environment, Health, and Safety (EHS) perspective such that, wherever possible, solvents with an unacceptable profile may be avoided. In addition, considerable research has been invested towards identifying replacements for solvents that are less favourable from a sustainability perspective. These efforts have resulted in a series of solvent selection guides that helpfully describe the alignment of a broad range of widely used solvents with sustainable chemistry principles.

2. Development of Solvent Selection Guides

Two principal approaches have been made towards providing guidelines to assist solvent selection, specifically to assist the practitioner to select a more sustainable solvent for a reaction *a priori* or to allow an existing less favourable solvent to be supplanted with a more benign alternative. A series of reports have emerged over the past 15 years from leading pharmaceutical companies detailing their assessment of what solvents they consider to be favourable or unfavourable (and anywhere in between). This analysis is predominately based on a range of criteria encompassing both EHS

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considerations, as well as those that are related to operational costs and commensurate impact on life cycle management.[4-8] In a more applied approach, several industrial and academic groups have published task-specific guides to help facilitate the replacement of an unfavourable solvent within widely used processes or reactions, such as chromatographic purification[9,10] and common reactions such as amide bond formation,[11] reductive amination,[12] and olefin metathesis.[13]

2.1 General Solvent Selection Guides

As stated above, the development of solvent selection guides has been driven principally by industry, in particular, by several large pharmaceutical companies.[4-8] Accordingly, the guidance delivered is broadly similar, with typically only small variations in the perceived environmental impact of a particular solvent: this is generally related to the nature and number of the variables being used in the assessment. The use of a traffic light-type guide to facilitate solvent selection is also common – this familiar representation is broadly accessible for practitioners and is designed to facilitate movement to a more sustainable solvent choice. Over the years, the depth of analysis relating to the sustainability credentials of a given solvent has increased markedly and in parallel with the best guidance available at the time (Figure 1). In 1999, GlaxoSmithKline (GSK) published the first solvent selection guide,[5a] which has been subsequently embellished with follow-up publications in 2005[5b] and 2011.[5c] In 1999, the level of scrutiny a solvent was subjected to was four-fold: waste, environmental impact, health, and safety. Life Cycle Analysis (LCA)[14] was included in the analysis by 2005 and a further series of considerations in 2011. The most recent guide, from Sanofi in 2013,[7] used an extensive range of factors in the analysis, with at least 11 components constituting this new analysis.

Figure 1. Chronological development of solvent selection guides by pharmaceutical companies: Escalation of analysis detail.

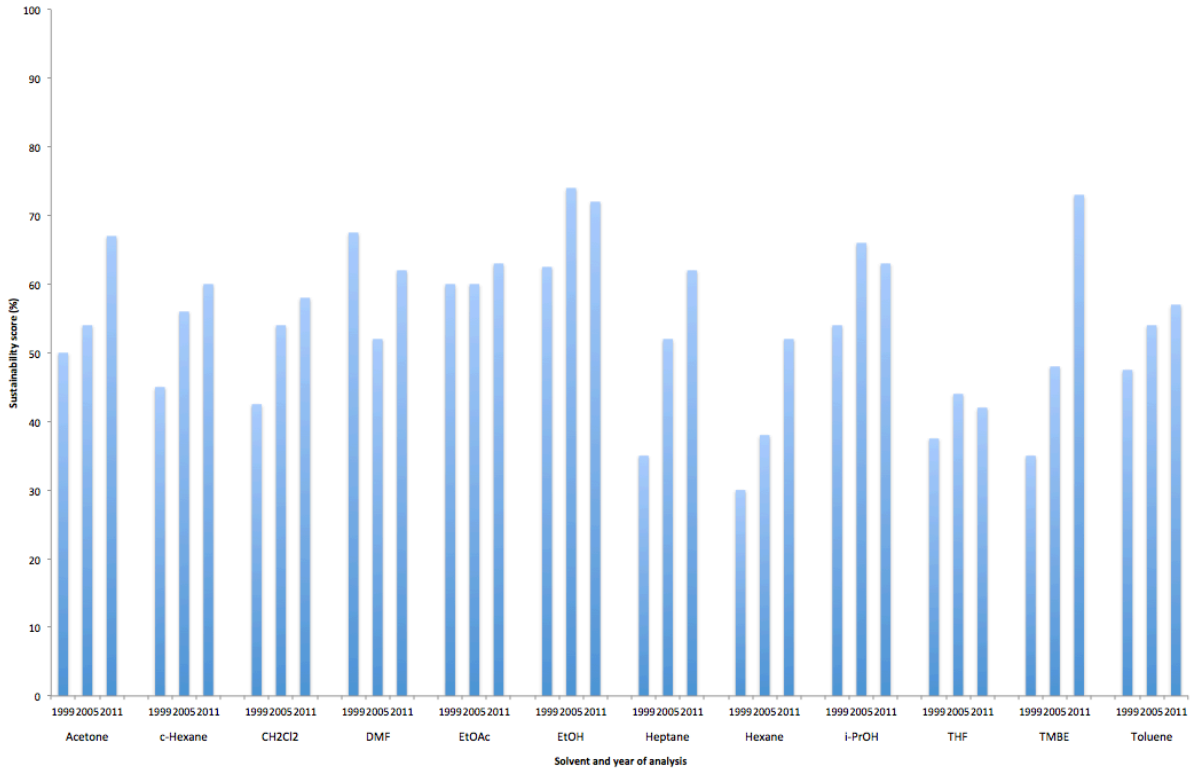
Company (Year)	Considerations
GlaxoSmithKline (1999)	Waste, Environmental Impact, Health, Safety
GlaxoSmithKline (2005)	Waste, Environmental Impact, Health, Safety, LCA
Pfizer (2008)	Environmental/Regulatory Considerations, Worker Safety
GlaxoSmithKline (2011)	Waste, Environmental Impact, Health, Safety, LCA, Flammability/Explosion Reactivity/Stability, Legislation Flag, Physical Properties
Sanofi (2013)	Environmental Hazard Bands, Health, Safety, Physical Properties, Water Miscibility Source, Indistrial/Legal Constraints, ICH Limits, Biodegradability, Resistivity, Cost

The desire to transition away from harmful solvents to more favourable alternatives on industrial scale was clearly demonstrated by GSK in an analysis of its pilot plant operations.[15] For example, in 1999 the undesirable dichloromethane ranked #3 for usage while this dropped to #8 in 2005, a positive movement away from the use of this solvent. Conversely, the more favourable isopropyl alcohol increased in usage from #5 to #1 while heptane (a hexane replacement) increased from #12

to #5, again demonstrating positive movements towards solvents that, following the available guidance, were considered more benign.

The perspective of precisely how well aligned a particular solvent is with the ethos of sustainability has closely correlated with the available guidance and this perspective has evolved as the guidance developed and matured. An analysis of the evolution of GSK's solvent guide over 12 years (through the three published iterations) provides an interesting snapshot of how perspectives changed as a function of time (Figure 2).[5] For example, taking a subset of 12 common solvents and tracking the average sustainability score (as a percentage of total possible score) arising from GSK's analysis using all available variables from 1999 (4), 2005 (5), and 2011 (6) illustrates the change in perceived sustainability over this time period (note that legislation issues are not taken into account). In particular, this analysis demonstrates that the impact of the introduction of a larger range of analysed variables serves to generally increase the sustainability score of the solvent. Reasons for this are unclear but may be due to the introduction of additional variables that tend to score highly for most solvents, such as reactivity/stability (GSK 2011: >75% of solvents scored ≥8/10 in this criteria), which may lead to a skewed average sustainability score.

Figure 2. Evolution of GSK's sustainability score of 10 selected solvents from 1999-2011.



Taking the information available in all of these published guides, a more holistic solvent selection guide is shown in Figure 3 along with the suggested alternatives to assist in supplanting a range of less desirable solvents (Figure 4). A point to note that some suggested alternatives are not necessarily desirable themselves but are preferred relative to the progenitor system for which a

replacement is sought. For example, CH_2Cl_2 as a replacement for $CHCl_3$, CCl_4, DCE only where no others options are available.

Figure 3. A summarised solvent selection guide based on the anaysis of GSK, Pfizer, and Sanofi.

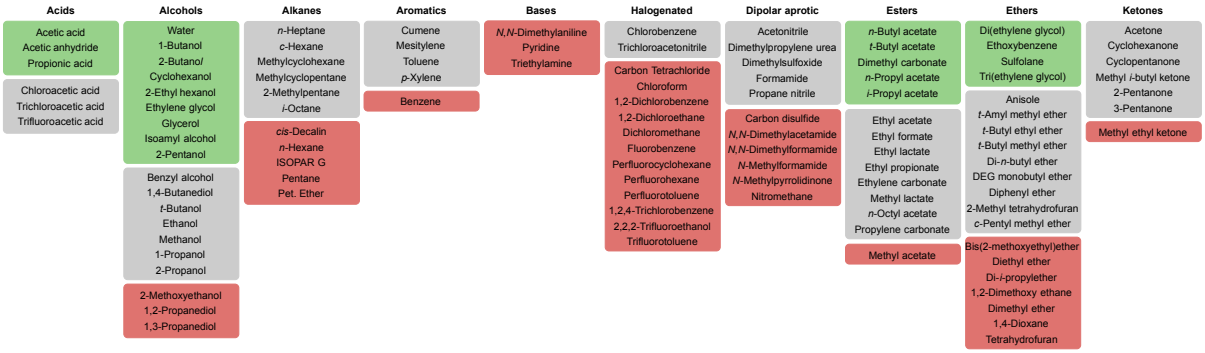
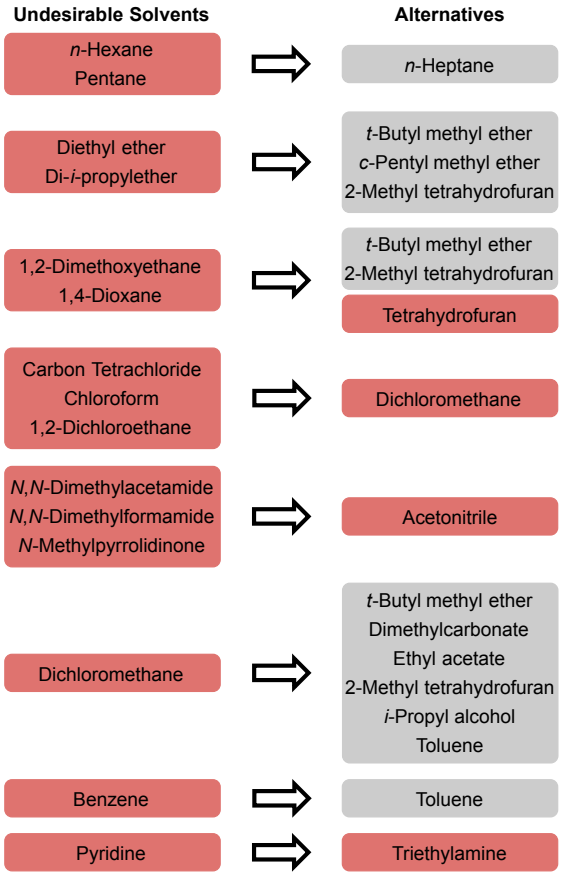


Figure 4. Suggested alternatives to undesirable solvents.



2.2 Task-specific Solvent Selection Guides

2.2.1 Chromatography

Chromatographic purification has been identified as the largest consumer of solvent within common synthetic processes.[3] Accordingly, adopting green chemistry principles within chromatography could be expected to have a significant impact on the overall sustainability of a chemical process without requiring substantial investment in terms of reaction development/optimization. In the 1960s, Neher published the first widely used equielutropic series that assisted in the identification of equipolar eluent systems for chromatographic purification;[16] however, sustainability was not necessarily the zeitgeist and so this was largely based upon solvents that are not in keeping with current green chemistry principles (for example, chlorinated solvents, hexane).

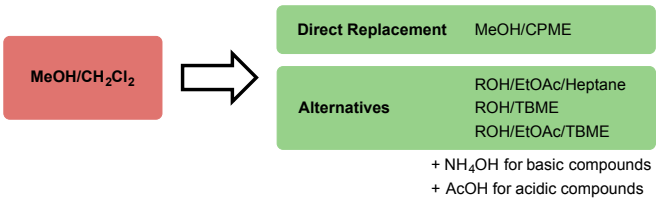
In the last few years, two studies, one from a group of industrial chemists at Amgen[10a] and the other a collaboration between an academic group at the University of Strathclyde, GlaxoSmithKline (GSK), and Sigma Aldrich (SA),[9] sought to provide some guidance towards improving solvent selection in this area. These studies specifically targeted the replacement of CH_2Cl_2, which is commonly used in conjunction with a MeOH modifier for the purification of relatively polar compounds.

The Amgen study focussed on the use of alcohol- (MeOH, EtOH, *i*-PrOH) and additive-modified (AcOH, NH_4OH) mixtures of heptanes, EtOAc, and *tert*-butyl methyl ether (TBME) for the purification of a range of 26 drug-like molecules on silica and helpfully presented a modern equielutropic series based on these mixtures in comparison to MeOH/CH_2Cl_2.

The Strathclyde/GSK/SA group adopted a slightly different approach and focussed on establishing a direct replacement for CH_2Cl_2 while retaining MeOH as the modifier. Ultimately, cyclopentyl methyl ether (CPME) was identified as a potential greener surrogate for CH_2Cl_2, providing comparable and, in some cases improved, chromatography on normal silica gel. Similar to the Amgen approach, this study also evaluated their suggested replacement solvent system on a 95-member library of drug-like and fragment compounds.

Both of these studies provided the first guidance dedicated towards identifying eluents that can be used to replace CH_2Cl_2 within chromatography in a practical sense (i.e., using a broad range of real examples). A summary of this guidance is provided in Figure 5.

Figure 5. Replacement of dichloromethane within chromatographic purification.



2.2.2 Reaction Specific Solvent Selection Guides

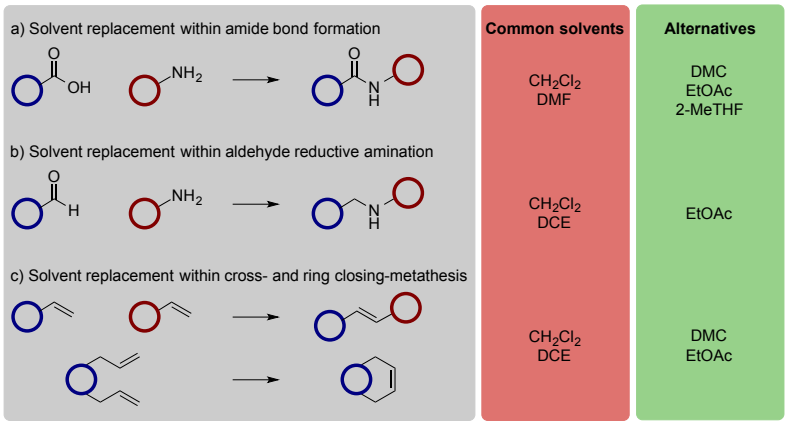
Over the past few years, several studies have emerged that evaluate the performance of a range of established or emerging alternative solvents within widely used chemical transformations.[11-13] Many of the most common organic reactions employ solvents that have considerable issues from the sustainability perspective – DMF and chlorinated solvents in particular. As such, the primary aim of these reaction-specific investigations has been to establish the best alternative media without compromising the chemistry either from an efficiency perspective (i.e., yield) or from a practical viewpoint (i.e., set-up, temperature, time, etc.).

Amide bond formation is one of the most widely practiced organic reactions.[17] Indeed, a 2011 survey of the types of reactions used by industrial practitioners found that amidation accounted for approximately 16-17% of all transformations carried out in a Medicinal Chemistry environment.[17] In addition, DMF remains the solvent of choice for the majority of amide bond forming processes. Based on this, in an effort to provide a general alternative to DMF (as well as CH_2Cl_2) for amide bond forming reactions, a comprehensive survey of eight alternative solvents within four benchmark reactions (aryl acid-aryl amine, aryl acid-alkyl amine, alkyl acid-aryl amine, and alkyl acid alkyl amine) and using five common amidation reagents found that DMC, EtOAc, and 2-MeTHF were viable alternatives (Figure 6a).[11] This study also compared the reaction time, indicating how long the reaction took to reach completion as well as demonstrating the utility of the proposed replacements, alongside CH_2Cl_2 and DMF for comparison, in a representative application phase using amines and carboxylic acids that displayed the functionality common to Discovery Phase Medicinal Chemistry.

A similar analysis from the same research team was performed for another staple of industrial organic synthesis – reductive amination.[12] Similar to amidation processes, reductive amination is broadly used[17] but has a heavy reliance on the use of chlorinated solvents, such as CH_2Cl_2 and DCE.[12] A thorough investigation of 12 benchmark reactions employing representative examples of 12 amine classes in reductive amination with both alkyl and aryl aldehydes using three different reductants and 10 solvents found EtOAc to be a suitable replacement solvent for these reactions (Figure 6b). Once more, the generality of these alternative conditions was exemplified through application to a set of 21 amine syntheses with an indication of reaction efficiency.

The replacement of chlorinated solvents within key reaction continues to be a strong theme for research. Olefin metathesis is another key organic transformation that routinely employs chlorinated solvents. It was recently shown that CH_2Cl_2 could be replaced, once more, with EtOAc and DMC for cross-metathesis and ring-closing metathesis reactions (Figure 6c).[13]

Figure 6. Solvent replacement in common organic reactions.



3. Conclusions and Outlook

Over the past 15 years, a combination of industrial and academic research has provided a series of guides that have been designed to assist the practitioner with the selection of a more sustainable solvent for synthetic transformations. Of particular interest has been the replacement of solvents that are viewed as particularly problematic from a sustainability perspective – especially DMF and chlorinated solvents. As new guidance emerges and new alternative solvents researched and discovered, identification of alternative solvents suitable to supplant other problematic media will no doubt continue.

Indeed, beyond the guides described above, Grignard additions have recently been shown to be effective using deep eutectic solvents as a replacement for conventional ethereal solvents as well as requiring a less stringent reaction set up – room temperature and using air as the atmosphere.[18] Moreover, a series of specific guides and more general information on the selection of greener reagents for reactions have are beginning to emerge, allowing facile selection not only of greener solvents for reactions but also for the reagents selected.[6,19]

4. Acknowledgements

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