Solvents and Green Chemistry

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Why Are Reactions Performed Using Solvents?

• To dissolve reactants.
• To slow or increase the rate of reactions.
• To act as a heat sink or heat transfer agent.
• To prevent hot spots and run-away reactions.
Issues with Organic Solvents

• Organic solvents are of concern to the chemical industry because of the sheer volume used in synthesis, processing, and separation.
• Organic solvents are expensive
• Organic solvents are highly regulated.
• Many organic solvents are volatile, flammable, toxic, and carcinogenic.
“No Coopora nisi Fluida”

• Aristotle believed that “No reaction occurs in the absence of solvent.”

(This is not true!)
Solvent alternatives

A. Use of solventless reactions

B. Use of “non-organic” solvents

C. Processing technology
Advantages to Solventless Organic Reactions

• There is no reaction medium to collect, purify, and recycle.
• Reaction times can be dramatically shortened.
• Lowered energy usage.
• Considerable reduction in batch size volume.
• Less expensive.
Ways to be Solvent-Free

• **Neat** – reagents react together in the liquid phase in the absence of a solvent.

• **Solid-state synthesis** – two macroscopic solids interact directly and form a third, solid product without the intervention of a liquid or vapor phase.
A Solventless Atom Efficient Reaction: The Crossed-Aldol Condensation

1-indanone
\[ C_9H_8O = 132.16 \]
m.p. 40-42°C

3,4-dimethoxybenzaldehyde
\[ C_9H_{10}O_3 = 166.18 \]
m.p. 42-45°C

2-(3,4-dimethoxybenzylidene)indan-1-one
\[ C_{18}H_{16}O_3 = 280.32 \]
m.p. 183-185°C
Examples - Neat

• Baylis-Hillman reactions\textsuperscript{1}
• Aldol additions\textsuperscript{2}

1. For a review, see: Ciganek, E. *Organic Reactions*, 1997, 51, 201.,
Examples – Solid State

- Oxidations
- Reductions
- Halogenations and Hydrohalogenations
- Michael Additions and Aldol Additions
- Elimination Reactions
- [2+2], [4+2], and [6+2] Cycloaddition Reactions
- Aldol Condensation Reaction

Limitations

• Not all reactions will work in the absence of solvent.

• Function of catalysts.

• Exothermic reactions are potentially dangerous.

• Specialized equipment needed for some procedures.

• If aqueous quench and organic extraction are performed, this reduces green benefits.
Use of non-organic solvents

• Liquid and supercritical CO$_2$
• Ionic liquids
• Fluorous Phase Chemistry
• Water
Supercritical CO₂

• What does it mean to be supercritical?
Properties of scCO$_2$

• Combination of properties from both the liquid and gas state.

• At liquid-like densities, scCO$_2$ exhibits low viscosity and high diffusion rates.

• High compressibility of the supercritical phase allows for solvent properties to be varied by small changes in temperature and pressure.
Properties of scCO$_2$

- Can be handled in standard high-pressure equipment on lab or industrial scale.

- Non-toxic, non-flammable, and inexpensive.

- Non-protic and generally unreactive.

- Product isolation to total dryness is achieved by simple decompression.

- CO$_2$ can be recovered and reused.
Commercial Applications of scCO₂

- Natural product extraction (decaffeination)
- Polymer synthesis
- Dry cleaning
Examples of \text{scCO}_2 as Solvent in Synthetic Organic Chemistry

• Hydrogenation
• Hydroformylation
• Photochemical and radical reactions
• Dies-Alder cycloadditions
• Oxidations
• Palladium mediated couplings
• Biotransformations

Limitations of scCO₂

- Poor solubility of many substrates in scCO₂.
- Modifiers (organic solvents) can be added to regulate solubility, but this move the process away from being green.
- CO₂-philic surfactants are being developed.
  - Are expensive and have to be separated from products.
Ionic Liquids

- Organic salts with melting points below 100°C, often below room temperature.

\[ [NR_xH_{4-x}]^+ \quad [PR_xH_{4-x}]^+ \]

alkylammonium, alklyphosphonium, N-alkykyridinium, and N,N'-dialkylimidazolium cations
Examples of Common Anions

- Octyl sulfate
- 2-(2-methoxyethoxy)ethyl sulfate
- Tosylate anions

- $\text{BF}_4^-$
- $\text{PF}_6^-$
- $\text{SbF}_6^-$
- $\text{CH}_3\text{CO}_2^-$
- $\text{HSO}_4^-$
- $\text{NO}_3^-$
- $\text{NO}_2^-$
- $\text{AlCl}_4^-$
Properties of Ionic Liquids

- Good solvents for a wide range of both organic and inorganic materials.
- Have potential to be highly polar yet non-coordinating.
- By varying cations and anions, ionic liquids can be tailored for specific applications.
- Possibility for reaction rate enhancement, higher selectivity and higher yields.
Properties of Ionic Liquids

• High thermal stability
• Often immiscible with organic solvents and/or water
• No measurable vapor pressure
• Non-flammable
• Can be recycled

• Are they safer than solvents?
Ionic liquids have been used as solvents in a variety of reactions:

- Heck Reaction\(^1\)
- Friedel-Crafts reactions\(^2\)
- Diels-Alder reactions\(^3\)
- Hydrogenation reactions\(^4\)

Other Applications of Ionic Liquids

- As biphasic systems in combination with organic solvent or water in extraction and separation technologies.
- For catalyst immobilization and recycling.
- As electrolytes in electrochemistry.
Limitations of Ionic liquids

• Very expensive compared to organic solvents (100 to 1000 x).
• Have to be made, often using solvent.
• Products have to be extracted from ionic liquid using solvent.
• May have to wash with water prior to reuse.
Fluorous Phase Chemistry

• What does it mean to be “fluorous”?

• What does it mean to be “perfluorinated”?
Check out all the fluorine!

**Perfluorous Solvents**

**Perfluorous Catalyst**

**Perfluorous Tags**
Physical Properties of Perfluorinated Organic Compounds

- High affinity for other fluorinated compounds.
- High solubility in scCO$_2$.
- Immiscible in water and most common organic solvents at room temperature.
- Forms homogenous solutions at elevated temperatures with many of these solvents.
- Chemically inert.
  - Is this good or bad?
Uses for Fluorous Chemistry

- For the recovery and recycling of fluorous catalysts and fluorous reagents.

- Fluorous biphasic organic synthesis.
Principle of Fluorous Biphase Catalysis

Homogenous Phase

KEY
- Organic Phase
- Fluorous Phase

Substrates
Catalyst

Heat

Products
Catalysts
Substrates

Cool

PHASE SEPARATION

Products
Catalyst

Catalyst

Organic Phase
Fluorous Phase
Advantages

• Facile recovery of expensive catalysts.
• Complementary to other biphase chemistries.
• More facile separation.
• Design of novel catalysts and reagents.
• Alternative to the solid phase in combinatorial chemistry.
• Non-toxic?
Limitations

• Fluorous solvents and reagents are very expensive.
• 60% fluorine is usually considered the lower cutoff point for efficient fluorous extraction.
• Still requires use of a second solvent for biphase.
Organic Reactions in Aqueous Media

- Water – Isn’t that bad for my organic reaction?
Organic Reactions in Aqueous Media

- Most of the world’s chemistry occur in aqueous media.
Heck Reaction in Water - new for Spring 2009

Oxidative addition

Olefin insertion

Syn beta-hydride elimination

Start Here
Example Aqueous Reactions

- Diels-Alder reactions\(^1\)
- Claisen-rearrangement\(^2\)
- Aldol reactions\(^3\)
- Allylation reactions\(^4\)
- Oxidations\(^5\)
- Hydrogenations\(^6\)

Why Water?

- Cost - water is the world’s cheapest solvent.
- Safety – doesn’t get any safer than water.
- Some reactions work better in water.
Limitations of Water as a Solvent

• Some reactions will never work in water.
• Poor solubility of most organic compounds.
• Solubility may be increased by use of organic co-solvents, pH control, surfactants, and hydrophilic auxiliaries.
Green Concerns of Water

• The product may need to be extracted into an organic solvent to purify it.
• This generates aqueous effluent containing solvent, which must be properly disposed.
Processing Technology

• The use of environmentally sound processing techniques in industrial chemical applications.
Processing Principles

• Greenness through technology
• Goal is to minimize the number of effluent streams generated and the quantity of each stream.
• Organic solvents are not necessarily bad.
Loss of Greenness

• Anytime water is used in an organic reaction, an additional waste stream is created.
  • Solvent
  • Aqueous quench / workup
  • Aqueous wash
Green Process

• A purely organic solvent-based process (with solvent-based workup), with solvent recovery, would generate little waste.

• The use of technology and good environmental practices to reduce VOCs.
Benefits of Organic Solvents

• Cheap relative to ionic liquids and fluorous solvents.
• Volatile – it takes less energy to remove solvents by evaporation.
• Solvents can be recycled by distillation, creating little waste.
• Regulated – Most countries already have industrial requirements limiting the release of VOCs.
• Chemistry is known.