Green Chemical Transformations of Bio-sourced Molecules

By

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Abstract

Many modern synthetic organic chemicals and materials are made from non-renewable feedstocks. Given today's environmental concerns, the search for sustainable feedstocks capable of conversion into these chemicals is of increasing importance. In terms of sustainability, the way in which the reaction is carried out is another important consideration. With these concerns in mind, a group of 14 different bio-sourced, renewable feedstocks (homoserine, glutamic acid, aspartic acid, 2,5-furandicarboxylic acid, fumaric acid, oxalacetic acid, tartaric acid, malic acid, succinic acid, levulinic acid, γ-hydroxybutyrolactone, xylitol, mannitol, sorbitol) were examined for their solubility/miscibility in a variety of 'green' solvents, including water, supercritical carbon dioxide, and ionic liquids. Two other bio-based compounds (5-hydroxymethylfurfural and D-xylose) were also studied in selected solvents. Trends in solubility were then assessed so that the data might be extrapolated to help predict solubilities of other related compounds. Some of this work has been published in Green Chemistry: S. M. Payne and F. M. Kerton, *Green Chem.*, 2010, **12**, 1648.

Levulinic acid is a renewable chemical with great potential and has been identified as a 'platform' chemical by the US Department of Energy. Bio-sourced xylitol was transformed into levulinic acid in water using microwave heating at temperatures greater than 200 °C, with yields of up to 45%. This reaction was heterogeneously catalyzed by an acidic sulfonated polymeric resin, Amberlyst-15, which, despite a colour change from grey to black, was easily regenerated with sulfuric acid for reuse in subsequent reactions. Energy-dispersive X-ray analysis of the post-reaction catalyst showed increased carbon, suggesting that carbonaceous materials formed from xylitol

decomposition deposit on the catalyst surface. This reagent decomposition could also explain why maximum yields of 45-50% were obtained despite reactions progressing with 100% xylitol conversion. Even with the moderate yields obtained, the 'green' nature of the system makes this process promising.

Acknowledgements

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In loving memory of Angel

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[BMIm]Cl:	1-Butyl-3-methyl-imidazolium chloride
[BMIm]PF_6:	1-Butyl-3-methyl-imidazolium hexafluorophosphate
[PR_4]DBS:	Tetradecyl(trihexyl)phosphonium dodecylbenzenesulfonate
2-MeTHF:	2-Methyltetrahydrofuran
ACS:	American Chemical Society
AE:	Atom Economy/Efficiency
BPA:	Bisphenol A
Cat:	Catalyst
CBIN:	Canadian Biomass Innovation Network
CEPA:	Canadian Environmental Protection Act
ChoCl:	Choline chloride
CI:	Chemical Ionization
DAI:	Direct Aqueous Injection
DALA:	δ-Aminolevulinic acid
DDT:	Dichlorodiphenyltrichloroethane
DES:	Deep Eutectic Solvent
DI:	Deionized
DMF:	Dimethylfuran
DMSO:	Dimethyl sulfoxide
DOE:	Department of Energy
DPA:	Diphenolic acid
E-Factor:	Environmental Impact Factor
EHS:	Environmental Health and Safety
EI:	Electron Ionization
EQ:	Environmental Quotient
EtOAc:	Ethyl acetate
FFA:	Free Fatty Acid
FIA:	Flow-Injection Analysis
FID:	Flame Ionization Detector

GC:	Gas Chromatography
GC-MS:	Gas Chromatography - Mass Spectrometry
GCCG:	Green Chemistry and Catalysis Group
GHG:	Greenhouse Gas
GSCN:	Green and Sustainable Chemistry Network
GVL:	γ-Valerolactone
HBL:	β-Hydroxy-γ-butyrolactone
HMF:	5-Hydroxymethylfurfural
IL:	Ionic Liquid
LC/MSD:	Liquid Chromatogram/Mass Selective Detector
LCA:	Life Cycle Assessment
LCI:	Life Cycle Inventory
LCIA:	Life Cycle Impact Assessment
LevA:	Levulinic acid
m/z:	Mass-to-charge ratio
M.W.:	Molecular Weight
MS:	Mass Spectrometry
MW:	Microwave
NCW:	Near Critical Water
NMR:	Nuclear Magnetic Resonance
P_c:	Critical Pressure
PA:	Pentanoic acid
PLA:	Polylactic acid
Q:	Unfriendliness Quotient
RB:	Round Bottom
$scCO_2$:	Supercritical Carbon Dioxide
SCF:	Supercritical Fluid
scH_2O:	Supercritical Water
SEM-EDX:	Scanning Electron Microscope – Energy Dispersive X-ray
T_c:	Critical Temperature
TCD:	Thermal Conductivity Detector

TPBS:	Tetrapropylene benzene sulphonate
VOC:	Volatile Organic Compound

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Chapter 1 - Introduction

1.1 Introduction to Green Chemistry

Robert F. Kennedy once said: "Some see things as they are, and ask why. I see things as they should be and ask why not." In today's society, where so many people are asking 'why'- Why is the ozone layer depleted? Why are we experiencing global warming? Why do we have polluted waterways and animal extinction and increased cancer rates? - this is precisely the kind of ideal that modern scientists should be striving for. Why can't we have a world where chemistry and science afford us all the advances and products we're accustomed to without being harmful to human health or the environment? Why can't we find ways of using renewable resources instead of depleting ones on a global industrial scale? Why can't we fix/mitigate some of the damage we've already seen done? These are some of the questions that have lead to the birth of the green chemistry revolution.

1.1.1 Why Green Chemistry?

Modern society has known for some time now that our current way of living is having an adverse effect on the environment. Since the advent of the industrial age, there have been a number of chemistry-related accidents and unforeseen consequences of chemicals, which have impacted our environment, sometimes on a global scale. In the 1950s, the use of surfactants became widespread, largely replacing soap for use in applications such as laundry. Tetrapropylene benzene sulphonate (TPBS), the chemical surfactant (detergent) used at the time, exhibited rather poor biodegradability.[1] Its persistence became problematic as it accumulated in the environment, leading to the

production of large amounts of foam at wastewater treatment plants, and even frothing in rivers and other waterways.[1,2] In addition to being unsettling to look at, this foam was often detrimental to organisms living in the water.

In 1962, Rachel Carson published the book *Silent Spring*, which brought significant attention to the issues associated with the then prominent use of toxic, man-made pesticides.[3] In particular, the extensive use of DDT had led to unanticipated bioaccumulation, adversely affecting certain bird populations through the food chain.[3] These are just two examples of how a lack of understanding and foresight have resulted in unexpected, adverse consequences.

Accidents have also led to public awareness regarding the risks of working with hazardous materials. Tragedies such as the Love Canal incident[4] and 1976's Seveso disaster[5] affected the lives of many people. In 1984, a massive gas leak in Bhopal, India released tons of toxic methyl isocyanate, leading to over three thousand deaths in just the first few hours.[6] The number of subsequent deaths resulting from this exposure are still not accurately known, but are estimated at well over 10,000, while long-term side-effects for survivors include mental impairment, respiratory ailments, and vision problems.[6]

Events such as these undoubtedly played a role in statements made at the 1987 World Commission on Environment and Development, where the global situation was thus described: "Much of the improvement in the past has been based on the use of increasing amounts of raw materials, energy, chemicals, and synthetics and on the creation of pollution that is not adequately accounted for in calculating the real costs of production processes. These trends have had unforeseen effects on the environment. Thus today's environmental challenges arise both from the lack of development and from the

unintended consequences of some forms of economic growth."[7] In the US specifically, 1990 saw the introduction of the Pollution Prevention Act, which recognized that the country was producing billions of tons of pollutants each year, and spending tens of billions of dollars on control and clean-up measures.[8] It stated that "pollution should be prevented or reduced at the source whenever feasible; pollution that cannot be prevented should be recycled in an environmentally safe manner, whenever feasible; pollution that cannot be prevented or recycled should be treated in an environmentally safe manner whenever feasible; and disposal or other release into the environment should be employed only as a last resort and should be conducted in an environmentally safe manner."[8]

Pollution prevention and risk minimization represent two of the principal themes of green chemistry. Everyone knows the old adage 'an ounce of prevention is worth a pound of cure', and this is as true in chemistry as it is in medicine. It is not surprising that these themes have been incorporated into the 12 Principles of Green Chemistry (see later, Figure 1-1).

Another key concern addressed by the green chemistry movement is the extensive industrial use of rapidly depleting petroleum-based feedstocks. By definition, these depleting feedstocks are not renewable on a reasonable time scale, and they are running out. With global supplies dwindling, prices have risen dramatically, making them a less economical feedstock.[9] The need to find suitable alternatives before our supply disappears completely is one of the driving forces of green chemistry. Of course this is not the only issue corresponding to petrochemical use - problems arise even in the early stages of collection and refining.

There are several risks associated with extracting large quantities of crude oil and natural gas from deep within the Earth. Methane gas is highly flammable, and oil spills can be devastating to the local ecology. The Deepwater Horizon disaster in 2010 captured worldwide attention as the terrible explosion, which claimed the lives of 11 people, left an uncapped well spewing gallons of oil into the Gulf of Mexico. The flow continued for nearly three months before the well was capped, at which point an estimated 4 million barrels of oil had been discharged into the surrounding ocean.[10] The extent of the damage to marine life and the surrounding environment is still not fully known, but the effects are likely to be seen and felt for many years to come.[11]

Many of the fuels and chemicals we use today are obtained from the oxidation reactions of petroleum products. These reactions are often polluting, as they entail the use of heavy metal catalysts.[12] Biological feedstocks, conversely, are typically highly oxygenated, and can often be transformed via cleaner methodologies.[13] Additionally, it is now widely known that the burning of fossil fuels contributes to the issues of global warming via the greenhouse effect. Petroleum-based feedstocks are obviously non-ideal, and alternatives are not only desirable, but necessary.

The Brundtland Committee believed that "Humanity has the ability to make development sustainable to ensure that it meets the needs of the present without compromising the ability of future generations to meet their own needs. The concept of sustainable development does imply limits - not absolute limits but limitations imposed by the present state of technology and social organization on environmental resources and by the ability of the biosphere to absorb the effects of human activities."[7] Green chemistry can provide solutions to global challenges such as climate change, sustainable

agriculture, clean energy, toxics in the environment, and depletion of natural resources, making it a valuable tool for achieving worldwide sustainability.[14]

1.1.2 12 Principles of Green Chemistry

One of the most widely used definitions of green chemistry was introduced by Anastas and Warner in 2000: "Green chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products."[13] The twelve principles they subsequently presented (Figure 1-1) have served as a blueprint for chemists striving to carry out reactions in an environmentally responsible manner.

12 Principles of Green Chemistry

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separations agents…) should be made unnecessary wherever possible and, innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided wherever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment, and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Figure 1-1: The twelve principles of green chemistry proposed by Anastas and Warner.[13]

It is important to understand that these principles are not twelve independent goals. Rather, they are meant to be used as a cohesive system. Ideally, all of the principles would be applied in order to realize a truly sustainable process.[15]

As written, these twelve principles are somewhat cumbersome and difficult to remember. They can be simplified into twelve short ideals: (1) Prevention, (2) Atom Economy, (3) Less Hazardous Chemical Synthesis, (4) Designing Safer Chemicals, (5) Safer Solvents and Auxiliaries, (6) Design for Energy Efficiency, (7) Use of Renewable Feedstocks, (8) Reduce Derivatives, (9) Catalysis, (10) Design for Degradation, (11) Real-Time Analysis for Pollution Prevention, and (12) Inherently Safer Chemistry for Accident Prevention.[15] Additionally, a condensed version was developed by Tang *et al.* in 2005, using the acronym: PRODUCTIVELY (Figure 1-2).[16]

P – Prevent wastes
R – Renewable materials
O – Omit derivatization steps
D – Degradable chemical products
U – Use safe synthetic methods
C – Catalytic reagents
T – Temperature, pressure ambient
I – In-process monitoring
V – Very few auxiliary substances
E – E-factor, maximize feed in product
L – Low toxicity of chemical products
Y – Yes, it is safe

Figure 1-2: Condensed 12 principles of green chemistry.[16]

Green chemistry aspires to design chemical products and processes, in order to reduce their intrinsic hazard, across all stages of the chemical life-cycle.[15] While the goal, of course, is to do no harm, one must remember that nothing is truly 100% benign. Everything has an impact, no matter how mild or insignificant it may seem.[17] Even water,

considered to be one of the most benign substances known, can be deadly if consumed in large enough quantities (not to mention if it is inhaled!). And just imagine what would happen if large quantities of fresh water were introduced to a saltwater ecosystem – the results would likely be disastrous for the organisms living within it. Our focus, therefore, must be on continual movement towards 'greener' and more benign processes and chemicals, always seeking improvement. Fortunately, there are many tools available to facilitate this progression.

1.1.3 Tools of Green Chemistry

The specific concept of 'green chemistry' is a relatively new one, with the term having only been used as such in the past two decades. Paul Anastas, current director of the Centre for Green Chemistry and Green Engineering at Yale University, has been credited with the establishment of the field of green chemistry in 1991.[15] He described green chemistry as "an approach to the synthesis, processing and use of chemicals that reduces risks to humans and the environment".[17] Other pioneers in the field include Barry Trost and Roger Sheldon.[18]

Trost introduced the concept of Atom Economy (AE), also known as Atom Efficiency, in 1991.[19] The idea is to maximize raw material use by incorporating the maximum number of reactant atoms into the final product. A quick theoretical calculation can be performed by dividing the molecular weight of the desired product by the molecular weight of the reagents, then multiplying by 100% (Equation 1.1):

$$\%AE = [(M.W.\ Products)/(M.W.\ Reagents)] \times 100\% \quad \text{(Equation 1-1)}$$

Reactions such as the Diels-Alder, which incorporate all reagent molecules into the final product, would be considered 100% atom efficient (Scheme 1-1). Such is an ideal

situation, where none of the starting material goes to waste. However, AE is a very quick and simple approach to waste management and does not take into account factors such as unrecovered solvents, by-products and overall yield, catalysts/co-reagents, and other chemicals associated with synthesis and work-up. In 1992, these deficiencies were addressed when Sheldon introduced the Environmental Impact Factor (E-Factor).[20]

54.06 g/mol
+ 28.05 g/mol
82.14 g/mol

M.W. = 82.14 g/mol

AE = 100%

Scheme 1-1: Diels-Alder cycloaddition as an example of an atom economic reaction.

The E-factor was developed as a metric for quantifying the amount of waste generated with respect to the amount of product made for a given process.[15,20] The higher the E-factor, the less environmentally friendly a process is viewed to be. In an ideal situation, there would be no waste generation, and an E-factor = 0 would be observed. It is calculated by dividing the total mass of waste produced by the mass of the desired product (Equation 1-2):

$$\textbf{E-factor} = \mathbf{M_{waste}\ (kg)/M_{prod}\ (kg)} \quad \text{(Equation 1-2)}$$

When carrying out this calculation, it is important to remember that *all* waste should be taken into account, including lost solvent, unreacted starting material (if not re-used), process aids, and even fuel, ideally. Anastas and Eghbali define waste as the generation of any material that does not have realized value, or the loss of unutilized energy.[15]

However, water as a solvent is not generally incorporated into the calculation for various reasons.[21]

Sheldon also published a table comparing E-factors and waste production in various chemical industries (Table 1-1).[20,21] Upon examination, it can be seen that while the pharmaceutical industry has the lowest total waste of the four major industries investigated, they have the worst overall E-factor. With their comparatively low overall waste production, some might think there is little need to address the problem of waste generated by the pharmaceutical industry, but with such a high E-factor, they have probably the greatest potential for improvement. Given the end-of-pipe costs currently associated with waste treatment and disposal,[22] embracing green metrics can also come with significant economic benefits. In fact, Sheldon's 2007 perspective *The E-Factor: 15 Years On* states that the E-Factor and similar metrics have been embraced and utilized by the pharmaceutical industry with great success in recent years.[21]

Table 1-1: E-factors in the chemical industries.[20,21]

Industry Segment	Product Tonnage (t)	E-Factor (kg/kg)	Waste Production (t)
Oil Refining	10^6-10^8	< 0.1	10^5-10^7
Bulk Chemicals	10^4-10^6	< 1-5	10,000-5,000,000
Fine Chemicals	10^2-10^4	5-50	500-500,000
Pharmaceuticals	10-10^3	25-100	250-100,000

While the E-Factor is undoubtedly a valuable green chemistry tool, it fails to take into account the *nature* of the waste produced. For example, a process producing 1000 kg of sodium chloride as waste and one which generated 1000 kg of chromium salt would be comparable using only the E-Factor as a metric, but would have significantly different environmental effects. To address this deficiency, Sheldon introduced the Environmental Quotient (EQ) in 1994.[23] By introducing an arbitrary Unfriendliness Quotient (Q) to the

E-Factor, a metric able to take into account both the amount and composition of generated waste could be realized. Q values would be assigned arbitrarily to compounds, with higher values corresponding to increased environmental impact, and would be influenced by the ease of recycling and/or disposal. The environmental quotient could then be calculated by multiplying this quotient by the E-Factor[23] (Equation 1-3):

$$\mathbf{EQ = Q(E\text{-}Factor)} \quad \text{(Equation 1-3)}$$

A Q value equal to zero would be consistent with a compound considered to have no significant environmental impact (as used).[21]

Risk reduction through hazard minimization is another key feature of green chemistry. Risk can be described as a function of hazard and exposure[13] (Equation 1-4):

$$\mathbf{Risk} = f\mathbf{(hazard + exposure)} \quad \text{(Equation 1-4)}$$

Therefore, by minimizing either (or both) of these factors, the risk can in turn be reduced. In the past, the dominant approach has been minimization of exposure. This practice has some inherent flaws, however. For one, exposure controls have the potential to fail[13] – a piece of equipment may break or malfunction, a worker may forget to wear an article of safety gear. Conversely, hazard minimization, which has the added benefit of being more economical than exposure control, does not have the same potential for failure – a substance or procedure cannot suddenly become more dangerous.[13] While exposure controls certainly play an important role in risk minimization, focusing on hazard allows for risk limitation even under undesirable circumstances, such as accidental release.[15]

The Environmental Health and Safety (EHS) assessment is a screening method used for the identification of potentially hazardous substances.[24] The simplified EHS procedure involves the assessment of substances in nine different effect categories:

release potential, fire/explosion, reaction/decomposition, acute toxicity, irritation, chronic toxicity, persistency, air hazard, and water hazard. [25] For each category, a grade between 0 and 1 is determined, with an overall score of 0-9 awarded for each substance.[25] Lower scores correspond to lower hazard.

While the EHS method focuses on the inherent hazard of a given substance/process, Life Cycle Assessment (LCA) adopts a broader approach, also taking into account the effects of resource use, emissions, and energy consumption associated with the system.[25] It is used to gauge the impacts of a product or process over its entire life-cycle, from cradle to grave.[26] There are four phases to LCA: (1) Goal and Scope Definition, (2) Life Cycle Inventory (LCI), (3) Life Cycle Impact Assessment (LCIA), and (4) Interpretation.[24] The first phase considers the purpose of the study and the boundary conditions. The second involves gathering emission and resource use data. Phase three is the quantification of resource consumption and potential emissions impact. The final phase is where conclusions are made. LCA can be used to identify which processes contribute most to the particular metrics under study (e.g. environmental persistence, toxicity),[27] and therefore is useful for comparing methods and identifying areas in need of improvement.

While this is most certainly not a comprehensive list of green chemistry tools, those presented can and have had an impact on modern chemistry, especially when used in concert.

1.1.4 Green Chemistry: Past, Present, and Future

In the years since its inception, the field of green chemistry has seen enormous growth. Government, academia, and industry have all recognized the need for more sustainable practices, and have begun taking steps towards the realization of such.

The U.S. Government has instigated many 'green' strategies in the last half-century. In the late 1900s, several pieces of legislation (aside from the previously mentioned Pollution Prevention Act) were enacted including the Clean Water Act, Clean Air Act, Resource Recovery and Conservation Act, Safe Drinking Water Act, and Superfund.[13] Additionally, the U.S. Presidential Green Chemistry Awards were established in 1995, and the Green Chemistry Institute in 1997.[15] More recently (2007), the Energy Independence and Security Act was passed by the United States Congress, implementing the Renewable Fuel Standard.[28]

In Canada specifically, the government has encouraged sustainability through the establishment of Environment Canada in 1971, and by enacting 1999's Canadian Environmental Protection Act (CEPA).[29,30] 2009 saw the founding of GreenCentre Canada, a government funded initiative directed at bridging the gap between academia and industry, thereby facilitating commercialization of 'green' chemistry and engineering breakthroughs.[31] Internationally, the Kyoto Protocol, aiming for a global reduction in greenhouse gas (GHG) emissions, has been ratified by many governments worldwide.

In the academic world, the changing tide is visible in new teaching initiatives: universities all over the globe are offering classes in green chemistry.[15] Memorial University of Newfoundland itself offers an undergraduate/graduate course in green chemistry, and plays host to the Green Chemistry and Catalysis Group (GCCG). The

European Union has hosted a Green Chemistry Summer School annually since 1998,[14] and the ACS has been organizing its own annual Green Chemistry Summer School (for students in the Americas) since 2003.[32,33] The Royal Society of Chemistry published the first issue of Green Chemistry in 1999,[34] a journal which has grown in popularity since, and in Japan, the Green and Sustainable Chemistry Network (GSCN) supports research in the field.[35]

Industry is a key player as well in the green chemistry scheme, one with the potential to make significant and immediate impacts. Even before Paul Anastas had presented the world with 'green chemistry' as a focus for research, industries had begun to incorporate pollution prevention practices into their processes. 3M initiated its 3P program (Pollution Prevention Pays) in 1975,[36] and DOW's WRAP program (Waste Reduction Always Pays) kicked off in 1986,[37] both recognisant of the significant economic advantages associated with pollution prevention. Moving forward to the current century, Pfizer was awarded the 2002 Presidential Green Chemistry Award for their redesign of the sertraline manufacturing process, streamlining to reduce the number of steps while replacing multiple undesirable solvents with a single, more acceptable solvent: ethanol.[38,39] Pfizer was also lauded for having reduced their use of chlorinated solvents by 50% between 2004 and 2006.[18]

Of course there are many other examples of green chemistry principles being realized, both past and present, but they would be far too numerous to list. The bottom line is that green chemistry is happening right now, at all levels, and on a global scale. What is needed now is a concerted effort; government, industry, and academia working together towards a sustainable future. With institutions such as GreenCentre Canada

(supported by government, bridging the gap between academic research and industrial practice) facilitating such cooperation, there is every opportunity for such a collaboration to be achieved.

1.2 Introduction to Biomass

Biomass can be defined as 'biological material derived from living or recently living organisms'.[40] While the term can apply to both animal and plant derived materials equally, the use of plant-based matter is generally inferred, particularly when dealt with in the context of energy development.[40] Forests and crops capture approximately 1% of incoming solar radiation, and this energy is stored in the complex molecules of biomass, such as carbohydrates, lignins, proteins, and glycerides.[41] These highly functionalized molecules afford biomass a high potential for use as a renewable feedstock in the production of bulk and fine chemicals.[42] It has also received much attention in recent years as a source for renewable fuels.

Ten years ago, the US Department of Energy (DOE) Office of Energy Efficiency and Renewable Energy was reorganized to combine the once separate biofuels, biopower, and biobased products programs into a single Biomass Program.[43] This program was established to support integrated biorefineries in the US, with goals of displacing imported petroleum with domestic renewable raw materials, and establishing a robust biobased industry.[44] Such processing facilities extract materials (e.g. carbohydrates, oils) from biomass and convert them into a variety of useful products.[43] In Canada, the Canadian Biomass Innovation Network (CBIN) works to support the development of a sustainable national bioeconomy.[45]

1.2.1 Biomass vs. Petroleum Feedstocks

Petroleum feedstocks such as crude oil and natural gas have been used for many years to generate fuel for lighting, heating, and transportation, and have provided the basis for a wide variety of carbon-based chemicals and polymers.[46] This is not a sustainable system in the long term, however. Concerns are growing because of resource depletion and pollution potential (e.g. net increases in GHGs),[47] as discussed in Section 1.1.1.

Biomass feedstocks, on the other hand, are renewable and (if managed properly) unlikely to run out. Additionally, the utilization of biomass derivatives actually mitigates GHG emissions through the carbon cycle (Figure 1-3).[48] Given efficient processing methods, the use of biobased fuels can even be GHG neutral.[49] Many non-food sources of biomass also have the advantage of being both cheap and abundant, making them a promising source of renewable fuels and chemicals.[50]

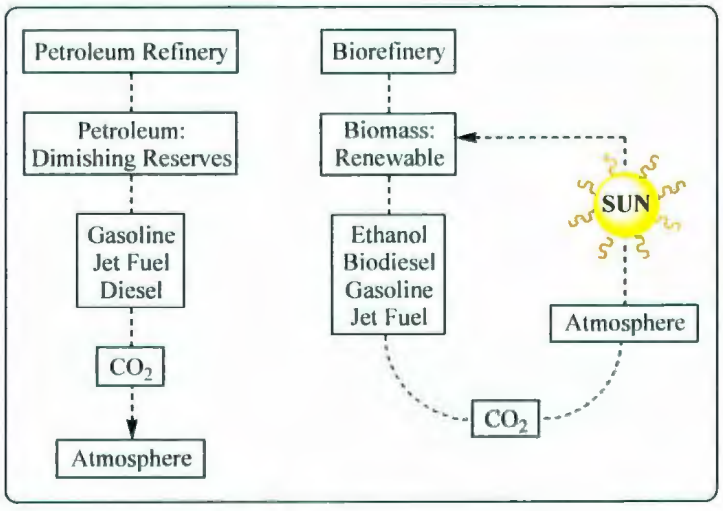


Figure 1-3: Carbon dioxide cycles for petroleum and biomass-derived fuels.[48]

Adoption of biomass feedstocks on an industrial scale requires an economic driving force, given the costs associated with process development and capital investment.[44] While methods for upgrading petroleum feedstocks to useful chemicals and fuels are well established, biomass feedstocks require new and efficient process chains to achieve the same results affordably, as they require a very different approach to upgrading.[41]

Petroleum feedstocks are characterized by a lack of oxygen-containing groups and are underfunctionalized for most applications. Biomass, conversely, has a high concentration of oxygen-containing groups, and is overfunctionlized for many applications.[46] The two feedstocks lie at opposite ends of the functionalization spectrum, with most useful products lying somewhere in the middle (Figure 1-4). Controlled defunctionalizations are therefore required for the efficient processing of biomass.[41]

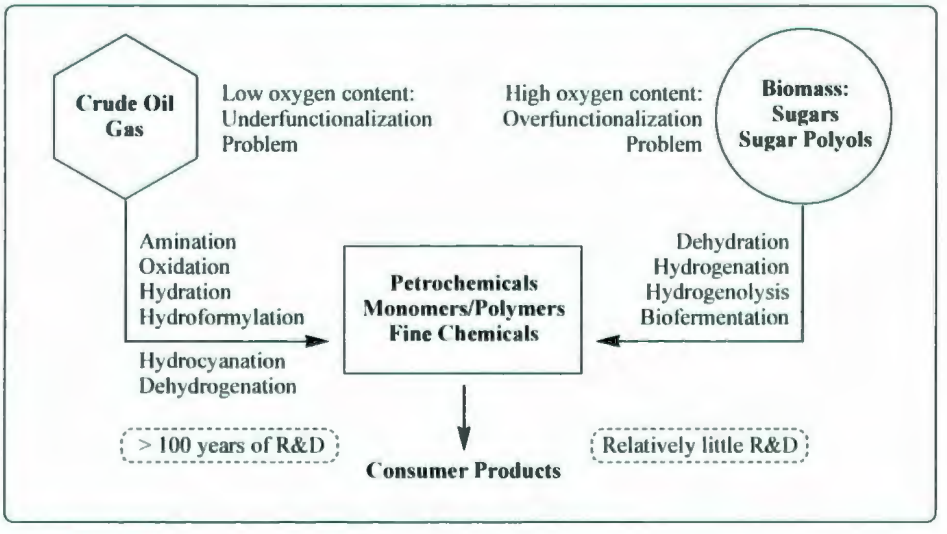


Figure 1-4: Opposing issues of under- vs. overfunctionalization of petroleum vs. biomass feedstocks.[46]

Looking specifically at transportation fuels, biofuels are being developed to first supplement, and eventually replace fossil-based fuels.[51] Because liquid fuels derived

from biomass are similar to the currently preferred petroleum-based fuels, they are compatible with existing infrastructures (e.g. internal combustion engines) and can be implemented on a short time scale.[48] Since the energy released on combustion of a compound is inversely proportional to its oxygen:carbon ratio, a reduction of biomass oxygen content is desirable in biofuel manufacturing.[41] However, complete oxygen removal would actually be detrimental, as the presence of some oxygen allows for more complete combustion, and affords improved anti-knocking properties (traditional gasoline requires additives to improve octane level).[41,52] Another strategy for the upgrading of biomass to fuels is the formation of C-C bonds between derivatives to increase molecular weight.[48] This is important because most fuels are actually made up of a mixture of different compounds that cumulatively provide the desired properties.[51]

Of course, while biofuels are certainly of high importance to achieving sustainability, biomass is useful as much more than just an alternative fuel feedstock. It can act as a starting point for many different reactions, providing the basis for a plethora of useful chemicals and products.

1.2.2 Biomass Reactions

1.2.2.1 – Monosaccharide Extraction

Since many biomass-derived products use monomers derived from polysaccharides (e.g. cellulose) as feedstocks, a discussion of their refining is imperative. While one such monosaccharide (glucose) can be readily obtained from food-crop based starches, the use of non-food sugar sources is desirable. Aside from the societal issues related to the use of edible biomass as a source of chemicals while there are millions of people starving worldwide, the use of inexpensive non-food-sourced biomass is far more

economical.[53,50] Lignocellulose, which can be sourced from materials such as switchgrass, corn stover, bagasse, and other agricultural wastes, is one such alternative.[54]

Lignocellulosic biomass is the most abundant class of biomass, found in all plants as a fundamental element of their structural integrity.[48] It is comprised of three components, in varying amounts: cellulose (~35-50%), hemicellulose (~25-35%), and lignin (15-30%).[48,55]

Lignin is a polymer of phenylpropane-type units, primarily joined via aryl-alkyl-ether linkages.[56] It surrounds the hemicellulose and cellulose fractions, and pre-treatment for lignin depolymerization is generally required to access these carbohydrate segments.[48] Since lignin is not readily amenable to upgrading, it is often burned for heat and electricity.[48]

Hemicelluloses are cross-linked heterosaccharides with compositions and percentages that vary according to species and growing conditions (Figure 1-5).[56] They are bound to lignin and interlaced with cellulose strands.[48] The most abundant variety of hemicellulose consists of D-xylose chains branched with L-arabinose groups, and is particularly prevalent in hardwoods.[56]

Cellulose is a polymer of glucose units joined via β-1,4-glycosidic bonds (Figure 1-5), having a vast network of intra- and intermolecular hydrogen bonding, and held together by the cementing effect of hemicellulose.[42] As a result of these strong intermolecular forces, and because of its high degree of crystallinity, cellulose is insoluble in the majority of common solvents.[56]

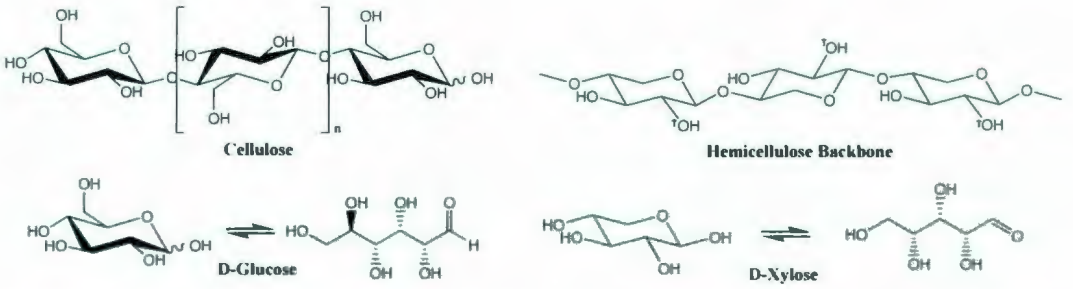


Figure 1-5: The polymeric structures of cellulose and hemicellulose, and the corresponding monomers that make up their backbone († indicates a possible branching site where other sugars can be found).

There are several types of hydrolytic treatments which can be utilized to sever the bonds between lignin, hemicellulose, and cellulose: physical treatment (such as steam explosion), chemical treatment (such as use of acid catalysts), and biological treatment (such as enzymatic hydrolysis).[57] Hemicellulose is more easily hydrolysed than either cellulose or lignin, and dilute acid pre-treatment allows for its hydrolysis while the other two fractions remain largely unaltered.[58]

Because the glycosidic bonds of hemicellulose are weaker than those of cellulose, hydrolysis of hemicellulose to obtain xylose is much more facile than the analogous hydrolysis of cellulose to produce glucose.[57,48] This makes the 5-carbon sugar xylose a promising feedstock for biomass reactions. However, with most sugar-based research focusing on 6-carbon glucose (and its isomer, fructose), there is much potential yet to be discovered for this less-studied compound.

1.2.2.2 – Biofuels

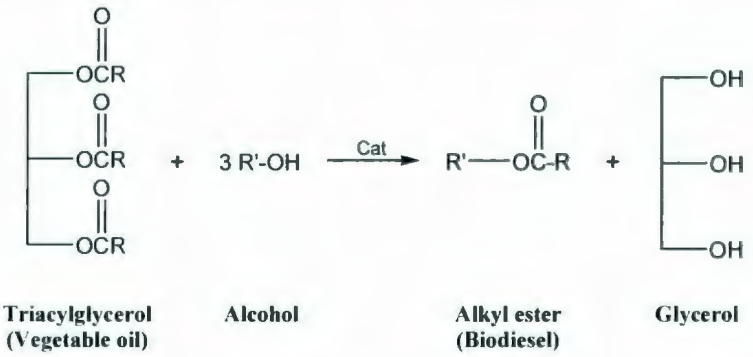
Biofuels are liquid (or gaseous) transportation fuels, which have been predominantly produced from biomass.[59] They can be derived from sugars, starches, vegetable oils, recycled paper/cardboard, or even raw biomass.[51] Currently, bioethanol and biodiesel are probably the two most widely known and utilized biofuels in North

America, if not the whole world. Bioethanol is a petrol additive/substitute which can be blended up to 5% with gasoline in existing gas engines (or in much higher concentrations with appropriately adapted engines), while biodiesel is a renewable fuel for the replacement of petroleum-derived diesel and can be used directly in modern diesel engines without modification.[59]

Bioethanol is produced by the fermentation of sucrose or simple sugars (e.g. glucose).[59] In North America, it is primarily derived from corn-based starch, while sugarcane is the primary feedstock in Brazil.[60] Comparatively, sugarcane ethanol provides significantly greater GHG emission reduction than does maize-sourced ethanol (due to lower energy inputs in growing/harvesting crops), though both have reduced emissions relative to gasoline.[41] However, food-source-based biofuels alone could never even come close to meeting the world's transportation energy requirements.[61] Using waste or low-input biomass (not grown on fertile farmland), such as corn stover, switchgrass, or woody plants, as feedstocks for ethanol synthesis could not only allow for increased and more economical production, but would also improve associated environmental benefits.[61] The main challenge in developing these high cellulose/hemicellulose content feedstocks is the efficient and green depolymerization to isolate the sugars within.[60]

Biodiesel is currently produced via the transesterification of vegetable oil (Scheme 1-2), and has many advantages over traditional diesel in terms of sulfur content, flashpoint, biodegradability, and aromatic content.[59] Glycerol is generated as a byproduct of this process.[62] The commonly used production method utilizes soybean oil, methanol, and an alkaline catalyst, but the high cost associated with using soybean oil (a valued

food product) results in biodiesel costing more than double what its petroleum-based counterpart does.[59] The use of inexpensive, non-edible oils for biodiesel production is desirable, but can be problematic as high free fatty acid (FFA) concentrations are often present: FFAs react with alkali catalysts resulting in soap production.[63]



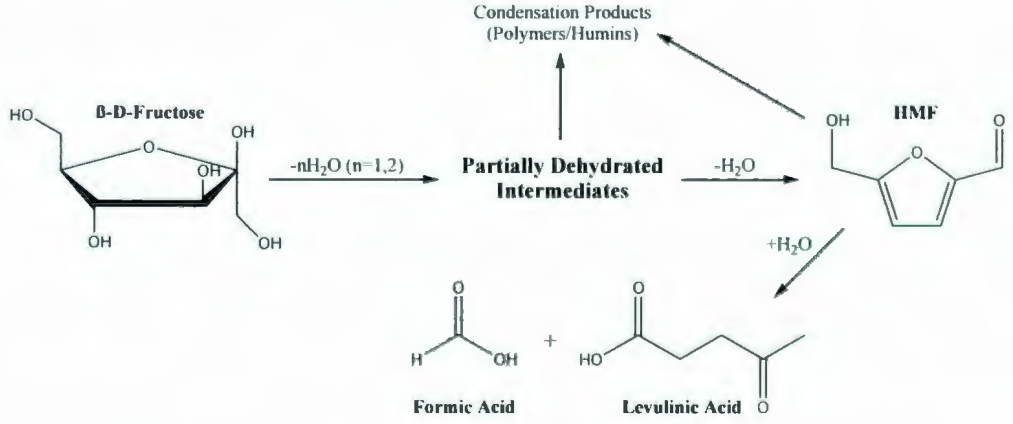
Scheme 1-2: Transesterification of vegetable oil to produce biodiesel.[64]

Other biofuels have been studied to a lesser extent. Biomethanol, for example, has some potential as a possible replacement for conventional motor fuels, but its toxicity is a shortcoming.[59] Another fuel alternative is 2,5-dimethylfuran (2,5-DMF), derived from fructose.[41] Biomass-derived chemicals for use as fuel extenders have also attracted interest in recent years. Regardless of the biofuel under consideration, they all must meet the same viability criteria: providing net energy gain, having environmental benefits, being economically competitive, and must be producible in large quantities without drawing on the food supply.[61]

Of course, the use of biofuels for transportation is a temporary solution, a means of substituting fossil fuels that is realizable on a short time scale. Sustainable transportation options based on electricity (as derived from wind and solar, in particular) are expected to be the way of the future.[65]

1.2.2.3 – Reactions of Sugars

5-Hydroxymethylfurfural (HMF) is an important biomass-derived intermediate for the production of fine chemicals, pharmaceuticals, and biofuels.[66] Current HMF production uses fructose as a starting material, and is limited to small batch operations due to issues with high temperature and pressure, as well as expense.[67] The general process occurs in two steps: initial dehydration(s) to give partially dehydrated intermediates, followed by a further dehydration to yield HMF (Scheme 1-3).[68] Under certain reaction conditions (e.g. prolonged reaction time), hydrolysis of HMF can occur, resulting in the formation of levulinic acid and formic acid.[68] Many catalyst/solvent combinations have been tested in recent years, and HMF yields of up to 100% have been obtained in DMSO (using solid acid catalysts),[68] but efforts to improve the environmental friendliness of the process continue. The use of ionic liquid (IL) solvents (which exhibit reduced flammability compared with organic solvents) to reduce the activation energy of fructose dehydration has been successful, with HMF yields of 83.5% obtained in less time and at lower temperatures.[69] However, ILs are often expensive, and some can be toxic, so this approach is not without drawbacks.



Scheme 1-3: Dehydration of fructose to produce 5-hydroxymethylfurfural.[66]

Glucose is nature's most abundant monosaccharide, directly obtainable from cellulose and starch, making it superior to fructose as a feedstock.[70] While glucose can be isomerised to fructose using a basic catalyst, the use of one-pot reactions to go directly from glucose to product (e.g. HMF) without the need for isolation of fructose provides environmental and economic benefits, conserving time, energy, and solvent(s).[71] Several groups have demonstrated HMF synthesis from glucose, with yields of up to 70% reported.[67,70] Recently, one group has even been successful in transforming not just glucose, but also sucrose and starch, directly into HMF under aqueous (and aqueous/organic biphasic) conditions using microwave irradiation.[72]

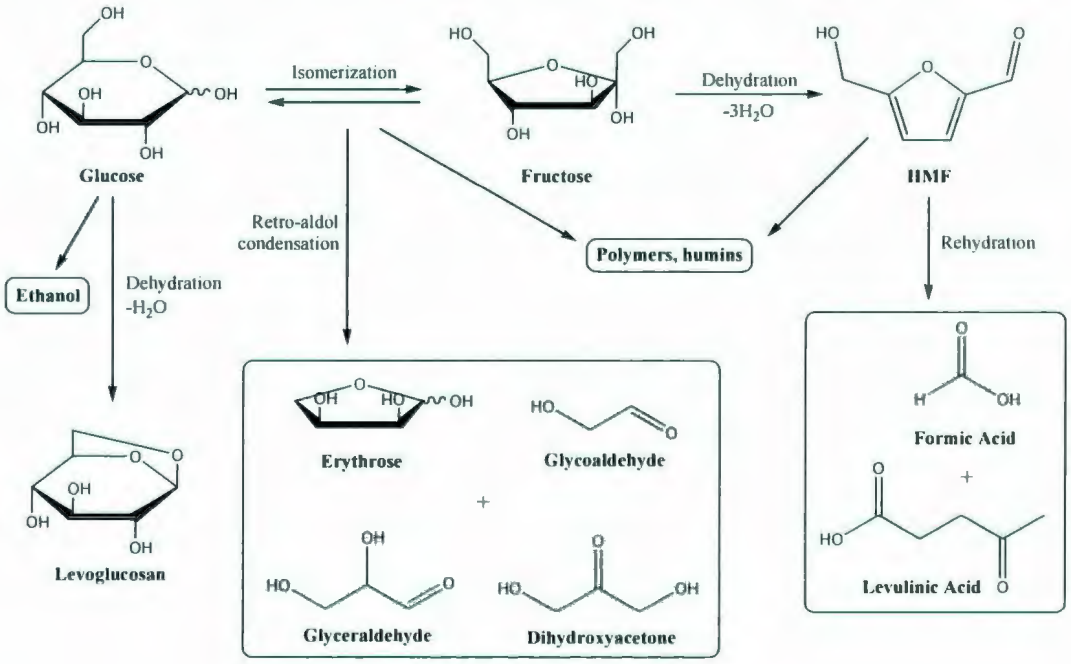
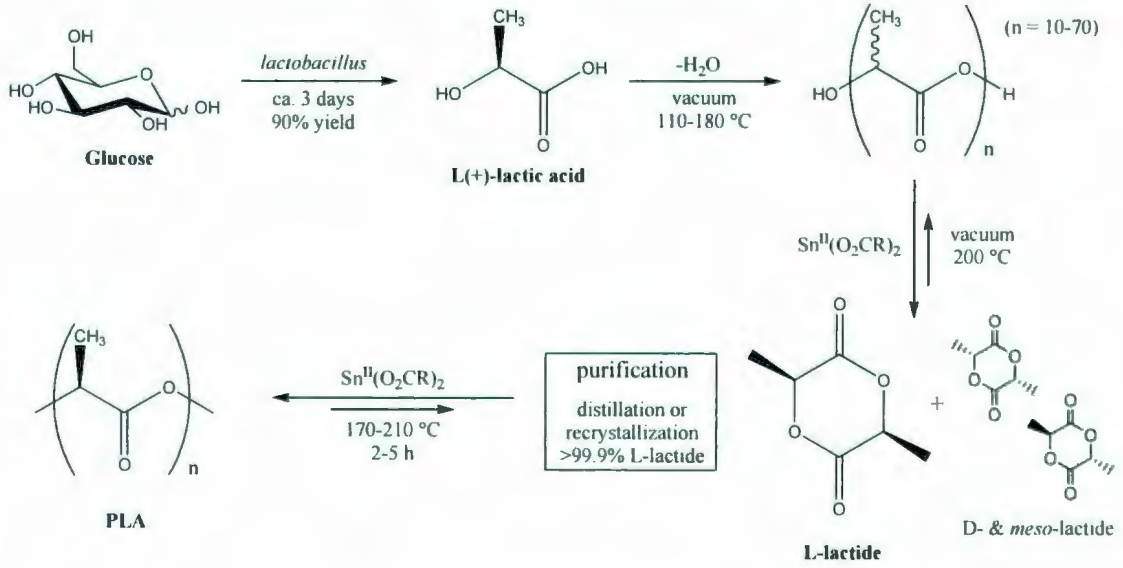


Figure 1-6: Transformations of glucose.[71]

Glucose can be used as the starting point for a wide variety of chemicals and products, some obtained via intermediates such as fructose and HMF, others derived directly from the hexose (Figure 1-6). One such compound is lactic acid, also known as

2-hydroxypropionic acid, for which there is a growing market.[73] In particular, it is used to make polylactic acid (PLA) – a biodegradable polymer currently produced on an industrial scale by NatureWorks for use in food packaging, films, bottles, and even apparel.[74] In their process, glucose is fermented to yield lactic acid, which is then converted to dimeric lactide in preparation for ring-opening polymerization (Scheme 1-4).[75] The resultant polymer has several advantages over traditional plastics, including reduced environmental footprint and increased end-of-life options.[74]

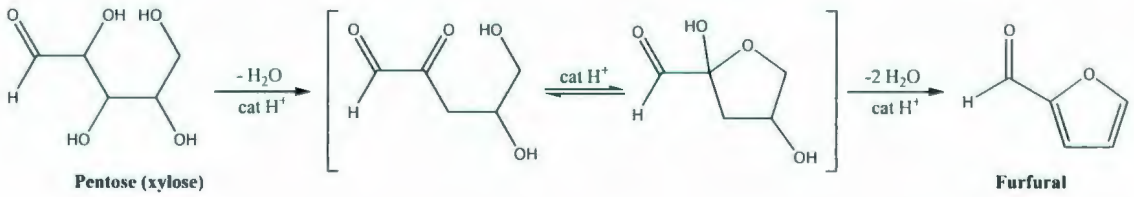


Scheme 1-4: PLA biopolymer synthesis.[75]

Xylose is a 5-carbon sugar derived primarily from hemicellulose, and is itself a useful starting point for many chemicals. Like glucose, xylose can be converted to the biofuel ethanol, though comparatively slower conversion rates and lower yields are observed.[76] Xylose is also the primary source of xylitol, a sugar alcohol that is gaining popularity as an insulin-independent, low-calorie sweetener.[77] Beyond its commercial value, xylitol is also a useful chemical building block, and has been identified by the US

DOE as a 'platform' chemical from which a variety of valuable compounds could be derived.[43] Industrially, it is obtained by the chemical hydrogenation of D-xylose over a metal catalyst.[78] Alternatively, xylitol can be prepared from xylose by fermentation, using yeast, bacteria, fungi, or mixed cultures.[79]

Xylose can also be transformed into furfural, a solvent and a building block for the preparation of furan-based chemicals.[80] Commercial furfural production methods use mineral acids to catalyze the dehydration of pentoses (typically xylose) at high temperature (Scheme 1-5).[81] The past few years have seen some interesting advances in xylose dehydration, however. In early 2011, a group from China reported the use of the IL 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate to catalyze the aqueous conversion of xylose into furfural, and verified catalyst recyclability.[82] Later that same year, Yemiş and Mazza demonstrated the viability of microwave heating for the process.[83]



Scheme 1-5: Dehydration reaction of xylose to yield furfural.[84]

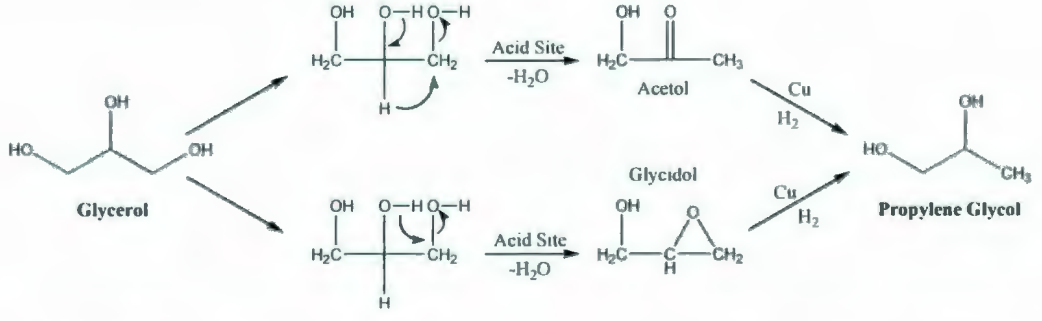
Once furfural has been obtained, it can be hydrogenated to 2-methylfuran, a high octane oxygenate which can be used in gasoline blends.[84] A Canadian group was able to take furfural obtained from xylose dehydrated over (H^+) mordenite zeolite in a continuous plug-flow reactor, and selectively hydrogenate it over a cheap Cu/Fe

catalyst.[84] Such processes are indicative of the wealth of compounds accessible from xylose and its derivatives.

1.2.2.4 – Polyol Reactions

As previously discussed, glycerol is a 3-carbon polyol produced as a byproduct of biodiesel production. As biodiesel production increases, the availability of glycerol as a cheap feedstock increases. Reciprocally, finding adequate uses for this compound would improve the economics of biodiesel production.[85] Unsurprisingly, research into glycerol conversions has seen significant growth.

Glycerol dehydration reactions have been reported in recent literature. Aqueous didehydration to acrolein has been carried out over a variety of catalysts, including $ZnSO_4$ and HSiW, although temperatures greater than 300 °C are generally required.[86] Monodehydration followed by hydrogenation produces propylene glycol, a value-added chemical currently derived from petroleum feedstocks (Scheme 1-6).[87] Hydrogenolysis of glycerol to propane diols is another popular upgrading strategy, with such products being amenable to propanol synthesis.[88]



Scheme 1-6: Proposed bifunctional glycerol hydrogenolysis reaction pathways (with Cu-based catalyst).[87a]

Xylitol, the 5-carbon polyol derived from xylose (as described in *1.2.2.3*), is an optically inactive, low-cost starting material.[89] The US DOE has already identified several potentially valuable derivatives of this pentitol (Figure 1-7), with viable transformation routes to most already known.[43] Acid treatment of xylitol leads to intramolecular dehydration, generating products such as 1,4-anhydroxylitol,[90] while selective deoxygenation yields 1,5-pentanediol, a compound with applications in thermoplastics and polyesters.[46] Xyltiol can also be used as a starting material in rare sugar production.

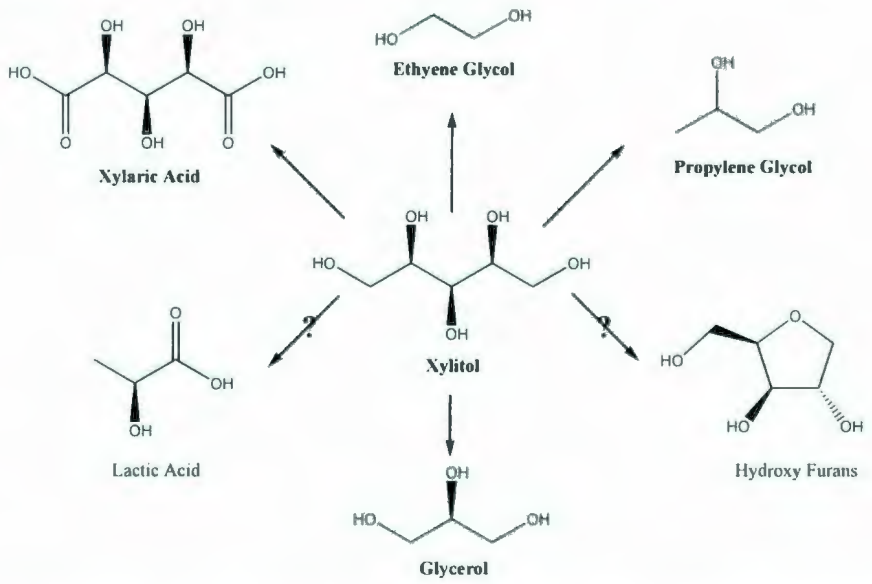
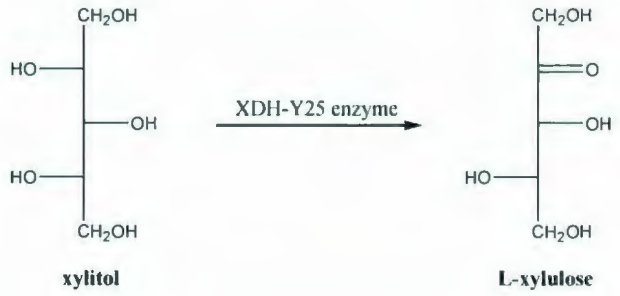


Figure 1-7: Potential derivatives of xylitol. Question marks indicate methods not yet established.[43]

L-xylulose is a rare ketopentose with medicinal applications, which exists in nature only in very low concentrations.[91] Using the thermophilic bacterium *B. pallidus* Y25, xylitol can be converted to L-xylulose at 50 °C, in yields of about 80% (Scheme 1-7).[91] Other rare sugars, such as L-ribulose (an important starting material for various branched sugar molecules) can then be produced via this intermediate (Figure 1-8).[89]



Scheme 1-7: Production of L-xylulose from xylitol.[91]

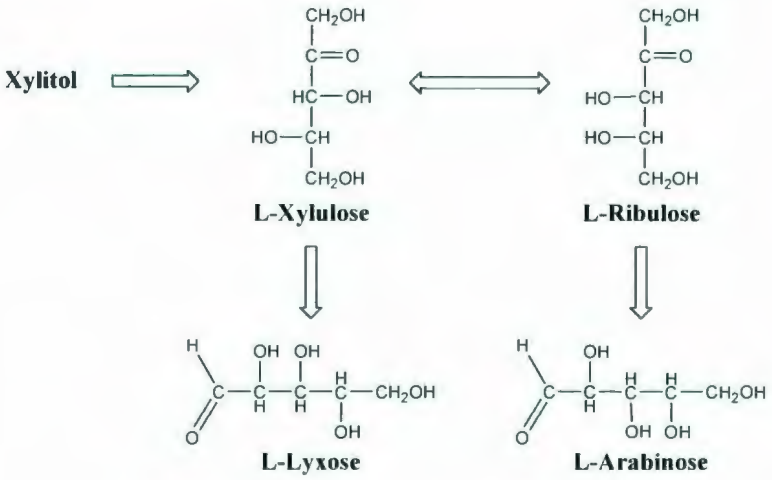


Figure 1-8: Rare sugars derivable from xylitol.[89]

There is a wealth of reactions available for biomass, of which this writing merely scratches the surface, and many more reactions are yet to be discovered. Given sufficient time, ways of making these processes more economical and streamlined will aid in the mass movement of biomass reactions from the research lab into industry, as they evolve from novel to routine processes.

1.3 Introduction to GC-MS

Gas chromatography/mass spectrometry (GC-MS) is a hyphenated analytical technique: gas chromatography, which separates components of a mixture in time, and

mass spectrometry, which aids in the structural identification of each of these components.[92] It is quite possibly the most effective technique available when it comes to the separation, detection, and characterization of complex organic mixtures.[93]

1.3.1 Gas Chromatography

Strictly speaking, gas chromatography (GC) refers to both gas-liquid chromatography and gas-solid chromatography, however, as gas-solid chromatography is relatively uncommon today, GC is generally understood to denote to the former.[94] In this body of work, GC and gas-liquid chromatography may be considered synonymous.

The concept of 'gas chromatography' was first conceived of by Martin and Synge in the early 1940s, though it received little note and wasn't made a reality until years later, in 1951.[95] The first commercial gas chromatograph hit the market in 1955.[94] In the decades since, GC has become one of the most used and successful chromatographic techniques, utilized by almost every type of chemistry-related industry (including hospitals, research establishments, and educational institutions).[93] Though the basic operating principles of a GC have remained the same: sample volatilization in a heated inlet port, separation in a specially prepared column, and subsequent detection of each component upon elution (Figure 1-9),[92] GC offers a large choice of instrumental components.[93]

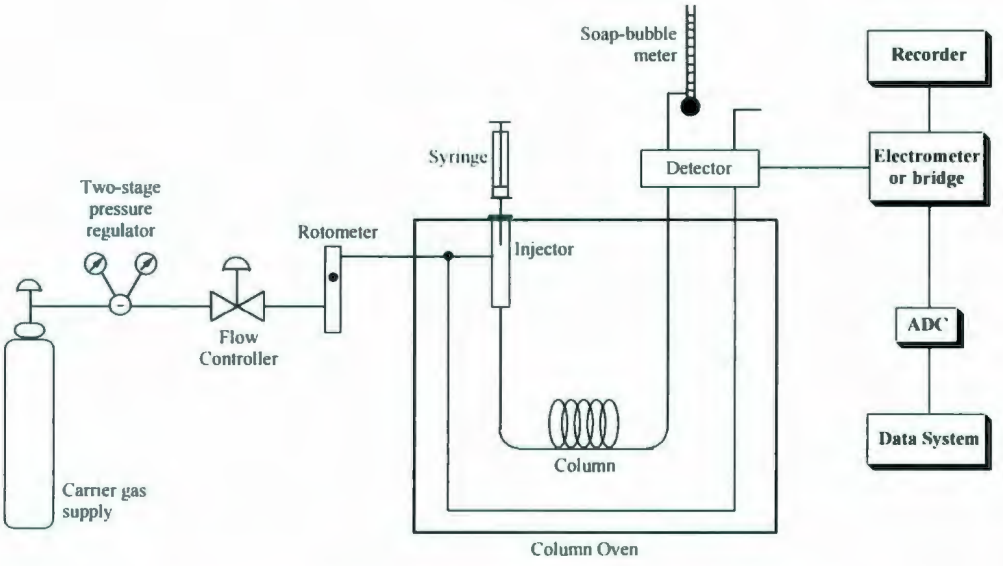


Figure 1-9: Basic schematic of a gas chromatograph.[94]

As would be expected from any chromatographic technique, both a mobile and a stationary phase are required. The mobile phase is comprised of a chemically inert carrier gas, such as hydrogen, helium, or nitrogen.[94] The stationary phase is a non-volatile chemical either found in the column, coated on an inert solid (packed column), or on the column, as a thin layer on the capillary walls (capillary column).[92] The majority of modern GC instruments use capillary columns, as they have much lower flow impedance, can be made significantly longer in length, and can provide much better resolution.[95]

After the column, the detector is the most important component of a GC.[95] The Flame Ionization Detector (FID) is probably the most common detector used in GC.[93] Analytes entering the detector pass through a hydrogen/air flame, forming ions and electrons that cause current to flow in the gap between two electrodes.[92] FID is sensitive to most organic compounds.[93] The Thermal Conductivity Detector (TCD), also known as the 'katherometer detector',[95] is a universal detector capable of discerning any compound with thermal conductivity different from that of the carrier gas.[93] TCD imposes constant

carrier gas flow and filament heating. As compounds of different thermal conductivity elute, differences in gas composition cause heat conduction away from the filament at different rates, resulting in a change in filament temperature and electrical resistance.[92] This detector is widely used, though it suffers from relatively low sensitivity compared to some other detectors.[94] Other detectors, which tend to be used in more specific applications, include the Electron Capture, Nitrogen Phosphorous, Thermionic Specific, and Flame Photometric Detectors.

GC data output is in the form of a spectrum of peaks on an axis of intensity versus retention time. Barring overlap, each peak corresponds to a specific compound, and the area of each peak is proportional to the amount of this compound. As such, GC can be used to determine the amount/concentration of a given component. The most accurate method of quantification is calibration by internal standard. The internal standard used should elute in an empty space in the chromatogram (i.e. at a retention time where no other peaks are present for the sample under study) and, ideally, exhibit chemical similarity to the compound (analyte) being measured.[92] A carefully measured quantity of this internal standard is then added to a series of standards containing varying but known amounts of analyte (in the same solvent/matrix as the sample). Calculating the ratio of peak areas for internal standard to analyte, and plotting against known concentration ratios, gives a calibration curve from which the concentration of analyte in the unknown sample can be calculated.[96]

While GC is useful for both qualitative and quantitative determinations, positive compound identification generally requires the use of a supplementary technique, such as mass spectrometry.[93]

1.3.2 Mass Spectrometry

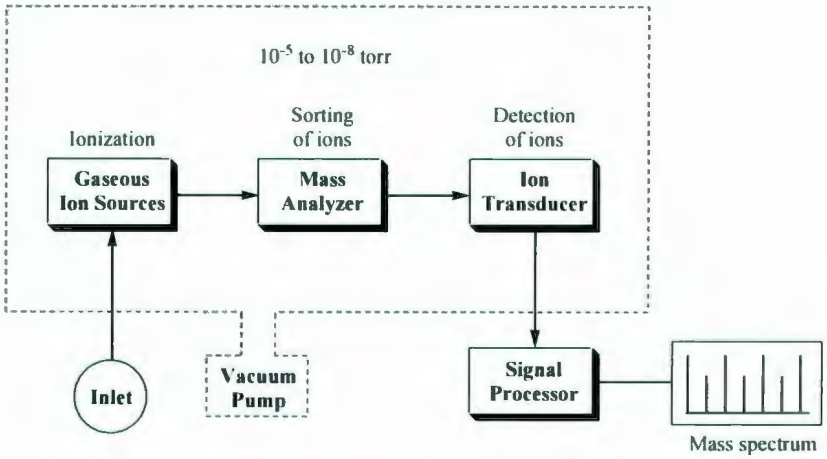


Figure 1-10: Components of a mass spectrometer.[97]

J.J. Thomson is considered to be the father of mass spectrometry (MS), having demonstrated in 1913 that neon actually consists of different atomic species (isotopes) having differing atomic weights of 20 and 22.[92] The modern mass spectrometer is an instrument that measures the mass-to-charge ratio (*m/z*) of gas-phase ions, providing a measure of abundance of each ionic species.[92] It is, perhaps, the most widely applicable analytical tool available.[98] The main components of a mass spectrometer are the ion source, mass analyzer, and detector (Figure 1-10). The system operates under vacuum in order to enable the detection of small amounts of material.[93]

There are two classes of ionization techniques: hard and soft. Hard ion sources impart analyte molecules with enough energy to leave them in a highly excited energy state. Subsequent relaxation results in bond rupture, producing fragment ions with *m/z* less than that of the molecular ion.[98] Conversely, soft ionization causes little fragmentation, resulting in a mass spectrum with few (if any) peaks beyond the molecular ion peak.[98] The most common ionization method is Electron Ionization (EI), in which

electrons produced by a hot filament are accelerated by (typically) 70 eV before entering the ion source through a small aperture.[92] These electrons interact with neutral vaporized sample molecules in the partially enclosed ion source, imparting enough energy to strip the outer shell electrons of some molecules (Equation 1-5). The high energy involved results in most of the molecular ions produced breaking apart into fragment ions (Equation 1-6).[92]

$$M + e^- \rightarrow M^{+\bullet} + 2e^- \quad \text{(Equation 1-5)}$$

$$M^{+\bullet} \rightarrow F^+ + N^\bullet \quad \text{(Equation 1-6)}$$

The second most common ion source is Chemical Ionization (CI), which involves the ionization of sample molecules by collision with ions produced via electron bombardment of excess reagent gas.[98] It is a softer ionization technique, producing significantly less fragmentation than EI (a hard ionization technique).[93] Typically, methane gas is used, producing $CH_4^{+\bullet}$, which can undergo fragmentation (Equation 1-7) to produce reagent ions capable of ionizing sample molecules by proton transfer (Equation 1-8).[92] Negative-ion CI is a variation of this technique, where negative ions are produced by electron capture, generally used for the analysis of highly halogenated molecules (or other compounds with strongly electronegative substituents).[92]

$$CH_4^{+\bullet} + CH_4 \rightarrow CH_5^+ + {}^\bullet CH_3 \quad \text{(Equation 1-7)}$$

$$CH_5^+ + M \rightarrow CH_4 + MH^+ \quad \text{(Equation 1-8)}$$

Two commonly encountered mass analyzers are the magnetic sector analyzer, and the quadrupole mass analyzer. Quadrupole instruments are the most prevalent, being more rugged, compact, and affordable than magnetic sector instruments.[97] This analyzer derives its name from the four rods ions must pass through in order to reach the detector

(Figure 1-11). Ions are sorted by imposing radio frequency potential and dc voltage on diagonally opposed rods: at a given field strength, only a narrow *m/z* range of ions actually reach the detector.[92]

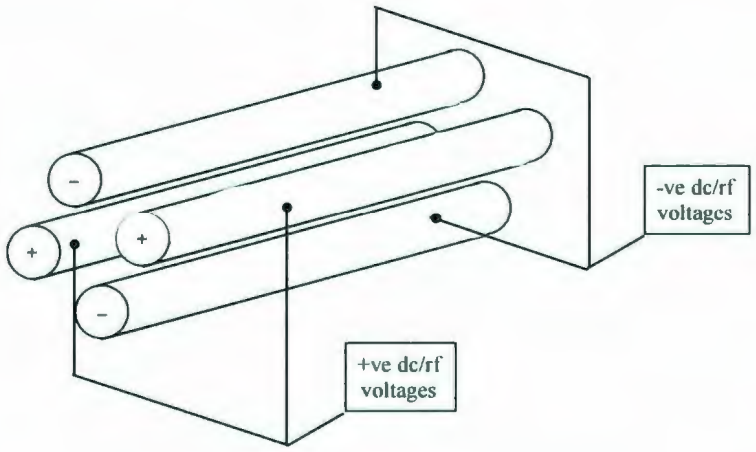


Figure 1-11: Quadrupole mass analyzer.

Magnetic sector analyzers use either a permanent magnet or an electromagnet to cause the ion source beam to travel in a circular path (generally 180, 90, or 60 °). Ions of different mass are scanned across the exit slit by varying the magnet's field strength.[98] The most common configuration for magnetic sector instruments in the double-focusing analyzer (Figure 1-12).[93]

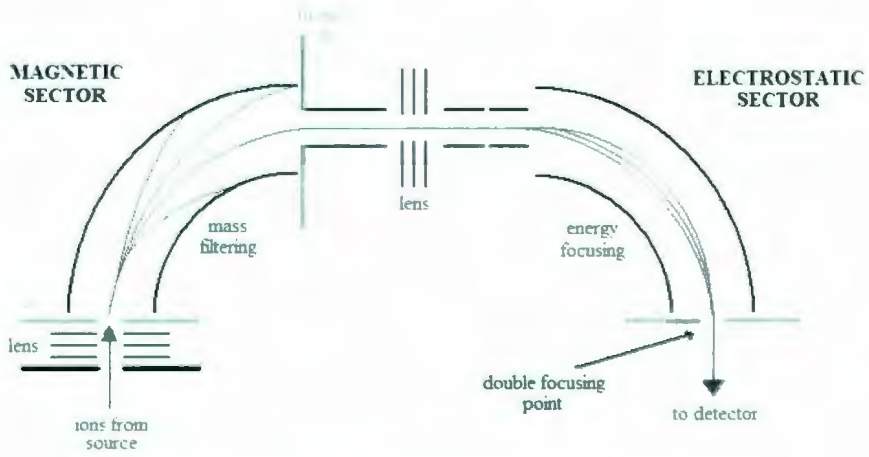


Figure 1-12: Double-focusing magnetic sector analyzer.[99]

The small current that is generated by ions passing through the mass analyzer of a mass spectrometer must be amplified and converted into voltage before it can be digitized and displayed.[93] This is the role of the ion transducer. The most commonly used transducer is the electron multiplier.[97] There are two types, continuous dynode and discrete, but both operate on the same basic principle: ions with sufficient kinetic energy emit secondary electrons upon striking a metal surface.[92]

MS data is displayed in the form of a mass spectrum: peaks representing the molecular ion and any fragment ions are plotted on an axis of intensity versus *m/z*, though the relative intensity of ions will have some variation between instruments.[92] Given that MS can be quite accurate in compound identification, while GC can give highly accurate quantification, a marriage of these two techniques has its obvious advantages.

1.3.3 GC-MS

The first association of a gas chromatograph with a mass spectrometer occurred in 1957, a mere two years after gas chromatographs became commercially available.[100] In the decades since, GC-MS instruments have been used to identify hundreds of components from natural and biological systems.[94] GC-MS instruments almost exclusively use capillary columns and electron multiplier detectors, and the incorporation of EI or CI (or both) ion sources is very common.[92,93] The basic set-up is that of a capillary GC instrument coupled to a MS instrument via a transfer line (Figure 1-13).

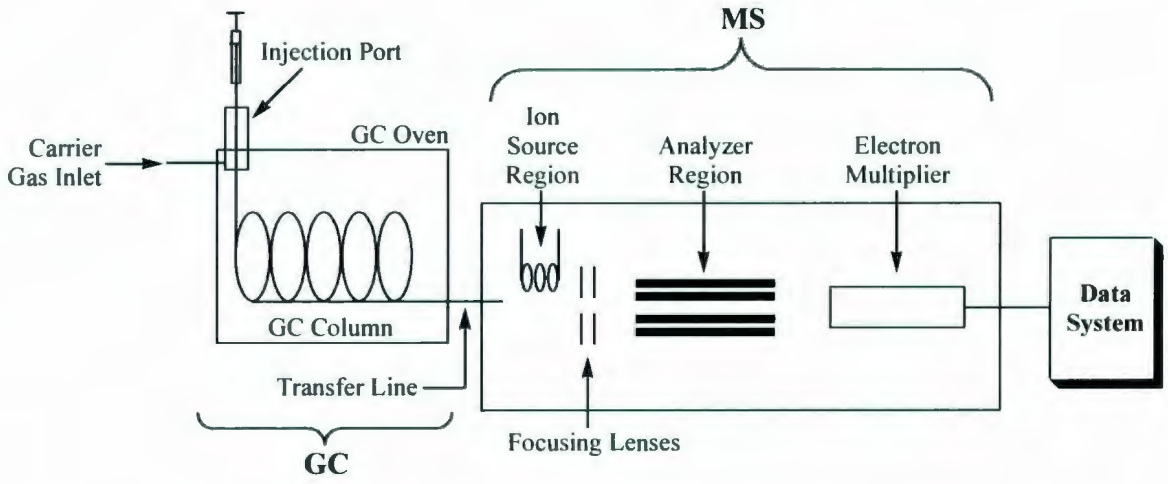


Figure 1-13: Schematic of a typical capillary GC-MS.[94]

The GC-MS interface (transfer line), which links the two instruments, is simply a device to transport GC effluent into the MS ion source.[92] Before the advent of capillary columns, when only packed columns were used, the relatively high carrier gas flow from the GC created problems in terms of low MS pumping rates and necessitated the use of either a split system or a vapour concentrating device to bridge the systems.[95] With capillary columns, it is possible to insert the exit end of the column directly into the MS ion source, ensuring adequate heating between the two systems to prevent cold spots where condensation could occur, as the MS pumping system is capable of handling the effluent in its entirety.[92]

GC-MS is a powerful analytical technique capable of providing reliable qualitative and quantitative data. It is hardly surprising that it has become a staple of scientific institutions worldwide, and as the technology continues to advance, providing access to more affordable, user-friendly instruments with improved sensitivity and resolution, its use can only be expected to increase.

1.4 Summary

Green chemistry is a field in rapid growth. With the promise of triple bottom-line benefits to the economy, environment and society, it is a very attractive area of research. Utilization of biomass is an integral component of this movement, as the use of petroleum feedstocks becomes less and less feasible. Finding methods of applying 'green' methodologies to biomass-based feedstocks is a major theme of the chapters to follow, with GC-MS used as a valuable tool for studying the reactions discussed in Chapter 3.

1.5 References

1. H. A. Painter, P. Reynolds and S. Comber, *Chemosphere*, 2003, **50**, 29

2. http://www.epa.sa.gov.au/xstd_files/Waste/Information%20sheet/soaps_detergents.pdf (Accessed March 2012)

3. R. Carson, *Silent Spring*, Houghton Mifflin Co., New York, 1962

4. http://www.epa.gov/history/topics/lovecanal/01.html (Accessed March 2012)

5. B. Eskenazi, P. Mocarelli, M. Warner, L. Needham, D. G. Patterson Jr., S. Samuels, W. Turner, P. M. Gerthoux and P. Brambilla, *Environ. Health Perspect.*, 2003, **112**, 22

6. E. Broughton, *Environ. Health*, 2005, **4**:6

7. G. Brundtland, ed., *Our common future: the world commission on environment and development*, Oxford, Oxford University Press, 1987

8. http://www.epa.gov/p2/pubs/p2policy/act1990.htm (Accessed March 2012)

9. F. M. Kerton, *Alternative Solvents for Green Chemistry*, The Royal Society of Chemistry, Cambridge, UK, 2009

10. National Commission on the BP Deepwater Horizon Oil Spill and Offshore Drilling, *Deep Water: The Gulf Oil Disaster and the Future of Offshore Drilling: Report to the President*, Government Printing Office, Washington, DC, 2011

11. D. Biello, *Scientific American*, 2010, **303**, 16

12. P. T. Anastas and C. A. Farris, in *Benign by Design: Alternative Synthetic Design for Pollution Prevention*, American Chemical Society, 1994, Symposium No. 577, 2

13. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 2000

14. M. Kirchhoff, *Resour. Conserv. Recycling*, 2005, **44**, 237

15. P. T. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301

16. S. L. Y. Tang, R. L. Smith and M. Poliakoff, *Green Chem.*, 2005, **7**, 761

17. P. T. Anastas and T. C. Williamson, in *Green Chemistry: Designing Chemistry for the Environment*, American Chemical Society, 1996, Symposium No. 626, 1

18. K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31

19. B. Trost, *Science*, 1991, **254**, 1471

20. R. A. Sheldon, *Chem. Ind.*, 1992, 903

21. R.A. Sheldon, *Green Chem.*, 2007, **9**, 1273

22. T. T. Shen, *Industrial Pollution Prevention*, Springer, Germany, 1999

23. R. A. Sheldon, *Chemtech*, March 1994, 38

24. S. Hellweg, U. Fischer, M. Scheringer and K. Hungerbühler, *Green Chem.*, 2004, **6**, 418

25. C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927

26. G. Koller, U. Fischer and K. Hungerbühler, *Ind Eng Chem Res*, 2000, **39**, 960

27. D. Arvizu, *Energy Environ. Sci.*, 2010, **3**, 1378

28. http://www.afdc.energy.gov/afdc/laws/eisa (Accessed April 2012)

29. www.ec.gc.ca (Accessed April 2012)

30. Canadian Environmental Protection Act, 1999 (S.C. 1999, c. 33)

31. http://www.greencentrecanada.com/about-us/ (Accessed April 2012)

32. http://portal.acs.org/portal/Navigate?nodeid=543 (Accessed April 2012)

33. M. Kirchhoff, *C&EN*, 2005, **83**, 50

34. J. Clark, *Green Chem.*, 1999, **1**, G1

35. http://www.gscn.net/indexE.html (Accessed April 2012)

36. http://solutions.3m.com/wps/portal/3M/en_US/3M-Sustainability/Global/Environment/3P/ (Accessed April 2012)

37. http://www.dow.com/sustainability/stories/operations/wrap.htm (Accessed April 2012)

38. G. P. Taber, D. M. Pfisterer and J. C. Colberg, *Org. Process Res. Dev.*, 2004, **8**, 385

39. http://www.epa.gov/greenchemistry/pubs/pgcc/past.html#2002 (Accessed April 2012)

40. http://www.biomassenergycentre.org.uk/portal/page?_pageid=76,15049&_dad=portal&_schema =PORTAL (Accessed April 2012)

41. R. Rinaldi and F. Schüth, *Energy Environ. Sci.*, 2009, **2**, 610

42. M. J. Climent, A. Corma and S. Iborra, *Green Chem.*, 2011, **13**, 520

43. *Top Value Chemicals from Biomass*, US Department of Energy report, August 2004, ed. T. Werpy and G. Petoser, http://www1.eere.energy.gov/biomass/pdfs/35523.pdf

44. J. J. Bozell and G. R. Petersen, *Green Chem.*, 2010, **12**, 539

45. http://www.cbin.gc.ca/index-eng.php (Accessed May 2012)

46. M. Schlaf, *Dalton Trans.*, 2006, 4645

47. L. R. Lynd, J. H. Cushman, R. J. Nichols and C. E. Wyman, *Science*, 1991, **251**, 1318

48. D. M. Alonso, J. Q. Bond and J. A. Dumesic, *Green Chem.*, 2010, **12**, 1493

49. G. W. Huber, S. Iborra and A. Corma, *Chem. Rev.*, 2006, **106**, 4044

50. J. B. Binder and R. T. Raines, *J. Am. Chem. Soc.*, 2009, **131**, 1979

51. S. K. Ritter, *C&EN*, 2011, **89**, 11

52. C. E. Wyman, *Bioresour. Technol.*, 1994, **50**, 3.

53. http://www.fao.org/docrep/012/al390e/al390e00.pdf (Accessed May 2012).

54. S. M. Hick, C. Griebel, D. T. Restrepo, J. H. Truitt, E. J. Buker, C. Bylda and R. G. Blair, *Green Chem.*, 2010, **12**, 468

55. A. Takagaki, M. Ohara, S. Nishimura and K. Ebitani, *Chem. Lett.*, 2010, **39**, 838.

56. E. Chornet, and O. Ralph, *Fractionation of lignocellulosics: teaching manual*, The Centre, Sainte-Foy, Quebec, 1988

57. E. V. Canettieri, G. J. M. Rocha, J. A. Carvalho and J. B. A. Silva, *Ind Eng Chem Res*, 2007, **46**, 1938

58. Ke-Ke Cheng, Jian-An Zhang, E. Chavez and J. Li, *Appl. Microbiol. Biotechnol.*, 2010, **87**, 411

59. A. Demirbas, *Progress in Energy and Combustion Science*, 2007, **33**, 1

60. A. J. Ragauskas, C. K. Williams, B. H. Davison, G. Britovsek, J. Cairney, C. A. Eckert, W. J. Frederick, J. P. Hallett, D. J. Leak, C. L. Liotta, J. R. Mielenz, R. Murphy, R. Templer and T. Tschaplinski, *Science*, 2006, **311**, 484

61. J. Hill, E. Nelson, D. Tilman, S. Polasky and D. Tiffany, *Proceedings of the National Academy of Sciences*, 2006, **103**, 11206

62. E. Arceo, P. Marsden, R. G. Bergman and J. A. Ellman, *Chem. Commun.*, 2009, 3357

63. J. Park, D. Kim, Z. Wang, P. Lu, S. Park and J. Lee, *Appl. Biochem. Biotechnol.*, 2008, **148**, 109

64. G. Knothe, J. H. Van Gerpen and J. Krahl, *The Biodiesel Handbook*, AOCS Press, Urbana, IL, 2005

65. A.Y. Saber and G.K. Venayagamoorthy, *IEEE Trans. Ind. Electron.*, 2011, **58**, 1229

66. J. Wang, W. Xu, J. Ren, X. Liu, G. Lu and Y. Wang, *Green Chem.*, 2011, **13**, 2678

67. B. Zheng, Z. Fang, J. Cheng and Y. Jiang, *Z. Naturforsch.*, 2010, **65b**, 168

68. K. Shimizu, R. Uozumi and A. Satsuma, *Catal. Commun.*, 2009, **10**, 1849

69. X. Qi, M. Watanabe, T. M. Aida, R. L. Smith and Jr., *Green Chem.*, 2009, **11**, 1327

70. X. Qi, M. Watanabe, T. M. Aida and R. L. Smith, *ChemSusChem*, 2010, **3**, 1071

71. A. Takagaki, M. Ohara, S. Nishimura and K. Ebitani, *Chemical Communications*, 2009, 6276

72. S. De, S. Dutta and B. Saha, *Green Chem.*, 2011, **13**, 2859

73. 10 G. Epane, J. C. Laguerre, A. Wadouachi and D. Marek, *Green Chem.*, 2010, **12**, 502

74. http://www.natureworksllc.com/ (Accessed May 2012)

75. S. Mecking, *Angew. Chem. Int. Ed.*, 2004, **43**, 1078

76. X. Zhang, G. Chen and W. Liu, *FEMS Microbiol. Lett.*, 2009, **293**, 214

77. C. Kelly, O. Jones, C. Barnhart and C. Lajoie, *Appl. Biochem. Biotechnol.*, 2008, **148**, 97

78. T. B. Granström, K. Izumori and M. Leisola, *Appl. Microbiol. Biotechnol.*, 2007, **74**, 277

79. J. C. Parajó, H. Domínguez and J. M. Domínguez, *Process Biochemistry*, 1997, **32**, 599

80. S. Lima, P. Neves, M. M. Antunes, M. Pillinger, N. Ignatyev and A. A. Valente, *Applied Catalysis A: General*, 2009, **363**, 93

81. C. Moreau, R. Durand, D. Peyron, J. Duhamet and P. Rivalier, *Industrial Crops and Products*, 1998, **7**, 95

82. F. Tao, H. Song and L. Chou, *Canadian Journal of Chemistry*, 2011, **89**, 83

83. O. Yemiş and G. Mazza, *Bioresour. Technol.*, 2011, **102**, 7371

84. J. Lessard, J. Morin, J. Wehrung, D. Magnin and E. Chornet, *Topics in Catalysis*, 2010, **53**, 1231

85. G. Kharchafi, F. Jerome, J. Douliez and J. Barrault, *Green Chem.*, 2006, **8**, 710

86. (a) L. Ott, M. Bicker and H. Vogel, *Green Chem.*, 2006, **8**, 214; (b) L. Ning, Y. Ding, W. Chen, L. Gong, R. Lin, L. Yuan and Q. Xin, *Chinese Journal of Catalysis*, 2008, **29**, 212; (c) B. Katryniok, S. Paul, M. Capron, C. Lancelot, V. Belliere-Baca, P. Rey and F. Dumeignil, *Green Chem.*, 2010, **12**, 1922

87. (a) S. Wang and H. Liu, *Catalysis Letters*, 2007, **117**, 62; (b) L. C. Meher, R. Gopinath, S. N. Naik and A. K. Dalai, *Ind Eng Chem Res*, 2009, **48**, 1840

88. I. Furikado, T. Miyazawa, S. Koso, A. Shimao, K. Kunimori and K. Tomishige, *Green Chem.*, 2007, **9**, 582

89. T. B. Granström, K. Izumori and M. Leisola, *Appl. Microbiol. Biotechnol.*, 2007, **74**, 273

90. (a) A. Wiśniewski, J. Szafranek and J. Sokołowski, *Carbohydr. Res.*, 1981, **97**, 229; (b) A. Wisniewski, J. Sokolowski and J. Szafranek, *J. Carbohydr. Chem.*, 1983, **2**, 293

91. W. Poonperm, G. Takata, K. Morimoto, T. B. Granström and K. Izumori, *Enzyme Microb. Technol.*, 2007, **40**, 1206

92. F. G. Kitson, B. S. Larsen and C. N. McEwen, *Gas Chromatography and Mass Spectrometry: A Practical Guide*, Academic Press Inc., San Diego, California, 1996

93. P. J. Baugh, *Gas Chromatography: A Practical Approach*, Oxford University Press, New York, 1993

94. D. A. Skoog, F. J. Holler and T. A. Nieman, in *Principles of Instrumental Analysis*, Thomson Brooks/Cole, USA, 1997, pp.701-724

95. R. P. W. Scott, *Introduction to Analytical Gas Chromatography*, Marcel Dekker, New York, 1998

96. D. A. Skoog, F. J. Holler and T. A. Nieman, in *Principles of Instrumental Analysis*, Thomson Brooks/Cole, USA, 1997, pp.696

97. D. A. Skoog, F. J. Holler and T. A. Nieman, in *Principles of Instrumental Analysis*, Thomson Brooks/Cole, USA, 1997, pp.253-271

98. D. A. Skoog, F. J. Holler and T. A. Nieman, in *Principles of Instrumental Analysis*, Thomson Brooks/Cole, USA, 1997, pp.498-534

99. http://orgchemguide.blogspot.ca/2011/04/double-focusing-sector-spectrometers.html (Accessed June 2012)

100. C. Holmes and F. A. Morrell, *Appl. Spectrosc.*, 1957, **11**, 86

Chapter 2 – Solubility of Bio-sourced Feedstocks in 'Green' Solvents

2.1 Introduction

As discussed in the previous chapter, the shift from petroleum-based feedstocks to bio-sourced feedstocks is important from both an economic and environmental point of view. However, as important as the source of reagent is in reaction planning, much of the environmental advantage is lost if the reaction itself is carried out using environmentally unfriendly methods. Solvents are particularly important is this regard, as they often account for the majority of mass waste in reactions/processes.[1]

2.1.1 'Green' Solvents

Since the early 20th century, the world of chemistry has been dominated by the widespread use of solvents belonging to a class of compounds known as Volatile Organic Compounds (VOCs). Representing a wide range of hydrocarbons and other petroleum-derived solvents, including benzene, dichloromethane, chloroform, and pyridine, these compounds have been used in numerous applications.[2] However, they present a variety of environmental and health concerns, such as toxicity, carcinogenity, flammability, and persistence.[3] The use of some VOCs has become such a concern that companies such as Pfizer have compiled a 'red list' of undesirable solvents (Table 2-1) that should be avoided wherever possible, if not banned altogether.[4]

Ideally, all reactions would be performed under 'solvent-free' conditions, altogether eliminating the hazard and waste associated with solvent use. While examples of such chemistry do exist,[5] there are many situations where 'solvent-free' is simply not

an option due to limitations with heat and mass transfer (among others). As such, viable alternatives to these undesirable solvents must be found. Fortunately, a great deal of research in the area of 'green' or alternative solvents has been performed in recent years.

Table 2-1: Red-listed solvents as determined by Pfizer.[4] (HAP = Hazardous Airborne Pollutant, CMR = Carcinogenic/Mutagenic/Reprotoxic)

Red Solvent	FlashPoint	Undesirable Properties
Pentane	-49 °C	Very low flashpoint
Hexane(s)	-23 °C	More toxic than alternative (heptane), HAP
Diisopropyl ether	-12 °C	Powerful peroxide former
Diethyl ether	-40 °C	Very low flashpoint
Chloroform	N/A	Carcinogen, HAP
Dichloroethane	15 °C	Carcinogen, HAP
Dimethyl formamide	57 °C	Toxic, regulated by EU Solvent Directive, HAP
Dimethyl acetamide	70 °C	Toxic, regulated by EU Solvent Directive
N-Methyl pyrrolidinone	86 °C	Toxic, regulated by EU Solvent Directive
Pyridine	20 °C	CMR category 3 carcinogen, toxic
Dioxane	12 °C	CMR category 3 carcinogen, HAP
Dichloromethane	N/A	Regulated by EU Solvent Directive, HAP
Dimethoxyethane	0 °C	CMR category 2 carcinogen, toxic
Benzene	-11 °C	CMR category 1 carcinogen, toxic, HAP
Carbon tetrachloride	N/A	CMR category 3 carcinogen, ozone depleter, toxic, HAP

2.1.1.1 - Water

When it comes to alternative solvents, water is likely the greenest available. It is non-flammable, non-toxic, cheap, renewable, and widely available (most common molecule on the planet).[6] Because of its natural abundance, it does not need to be synthesized, though there may be energy costs associated with its purification before use.[3] Water is an excellent solvent for many inorganic species, as well as some organic ones (e.g. sugars, proteins),[6] and can, in some cases, give enhanced reaction rates via the hydrophobic effect.[1] Its worldwide availability means that it can be readily sourced on- or near-site, thereby minimizing transportation needs.[3]

In addition to its use as an individual solvent, water can be used in conjunction with other (e.g. organic) solvents in biphasic systems.[7] Such systems generally reduce energy costs and improve efficiency.[6] However, even water is not an entirely ideal solvent. It has a number of disadvantages, including low solubility of some compounds, and moisture sensitivity of certain catalysts/reagents.[6] Its high heat capacity and latent heat of vaporization make rapid heating or cooling difficult, and the energy costs associated with its evaporation or distillation are significant.[3] This can make purification of contaminated water difficult, expensive, and energy intensive.[8]

2.1.1.2 – Supercritical Fluids

Supercritical fluids (SCFs) are materials that have been heated and pressurized above their critical temperature (T_c) and critical pressure (P_c) to produce single-phase condensed fluids with densities comparable to liquids and viscosities comparable to gases (Figure 2-1). The ability to fine tune solvent properties simply by varying temperature and pressure conditions makes this class of solvents particularly attractive.[8]

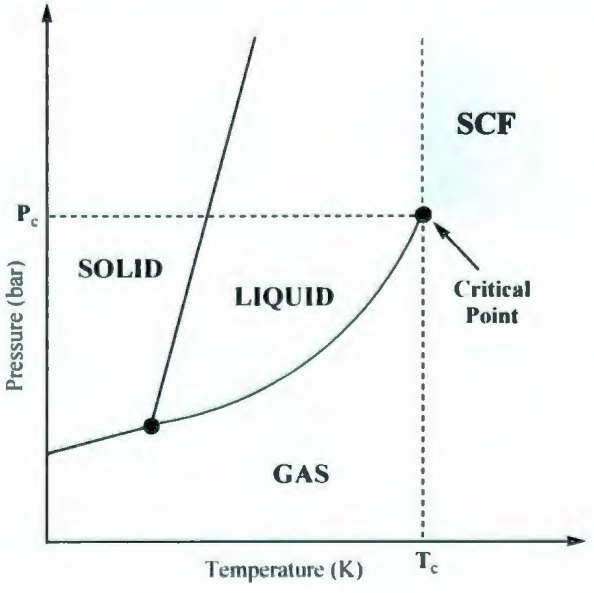


Figure 2-1: Pressure-temperature diagram for a pure compound.

The substance most commonly used as a SCF is carbon dioxide.[9] Next to water, supercritical carbon dioxide ($scCO_2$) is probably the best alternative solvent available.[3] It is environmentally benign, non-flammable, inexpensive, non-toxic, and its relatively mild critical parameters (T_c = 304 K or 31.1 °C, P_c = 7.38 MPa or 73.8 bar) allow for processing at moderate temperatures.[10] One especially attractive feature of $scCO_2$ is the ease with which it can be separated from products or reaction components: complete solvent removal can be achieved simply by lowering the temperature and/or pressure, reverting the SCF to gas-phase.[1] While it is true that CO_2 is a known GHG, CO_2 for solvent use is generally collected from the air or as a by-product of another reaction/process, so there is no net change in atmospheric CO_2.[7] Its disadvantages lie in high equipment costs,[8] the need to work under high pressures,[6] and the poor solubility of many large and/or polar molecules in $scCO_2$.[11]

One way to overcome issues with solubility is through use of a modifier or co-solvent. These are substances added to a SCF in order to change its solvent character, affecting properties such as polarity, aromaticity, and chirality.[9] Methanol and acetonitrile are commonly added to $scCO_2$ in concentrations of up to 10 mol% to increase solvent polarity.[11]

Another SCF that has been attracting significant attention in recent years is supercritical water (scH_2O). Possessing many of the advantages of liquid water, scH_2O has several added benefits, including reduced polarity (allowing for dissolution of many organic compounds) and the ability to act as an acid, base, or acid/base catalyst.[8] Unfortunately, it also exhibits some disadvantages. It has a very high critical temperature

and pressure (T_c = 374.2 °C, P_c = 220.5 bar),[12] and is very corrosive,[8] making large scale use challenging.

2.1.1.3 – Ionic Liquids

The basic definition of an ionic liquid (IL) is a material composed entirely of cations and anions that melts at or below 100 °C.[13] They have a multitude of advantages over traditional VOCs, namely their negligible vapour pressure, extensive liquid range (i.e. they remain liquid through a range of temperatures), thermal and electrochemical stability, favourable solvation behaviour, and recyclability.[14] In particular, the ability to fine-tune their physical and chemical properties simply by varying the anion/cation combination is extremely attractive, gaining ILs a reputation as 'designer solvents'.[15]

Over 200 ILs are already known,[15] but billions of different structures are possible, making this class of solvents difficult to categorize simply.[3] Given that each specific IL has its own varied set of properties (polarity, catalytic ability, acidity, etc.), it is nearly impossible to classify them as a whole, though trends can be observed for ILs with particular anion or cation types.[16,17] Broadly speaking, they tend to possess medium to high polarity and little or no volatility.[3]

A major downfall of ILs is their poorly defined toxicity,[8] though increasing research efforts have been focused on better understanding this.[18] There is little data on their overall environmental impact, and they require expensive, multistage syntheses, making them impractical for most industrial-scale applications.[6] At present, such disadvantages outweigh the 'designer solvent' properties and other benefits of ILs, but as new ones are fashioned with health, safety, and cost concerns in mind, sub-classes of ILs with greater applicability may become viable alternatives.[3]

A Deep Eutectic Solvent (DES) is a mixture of two compounds possessing a freezing point lower than that of either individual component when separate.[19] For example: The DES ChoCl/Urea, formed by combining choline chloride and urea (melting points of 298-305 °C and 134 °C, respectively), has a melting point of 73-77 °C.[19] These solvents can often be derived from benign, bio-sourced materials, making them useful alternative solvents.[13] While they do not strictly conform to the definition of an ionic liquid, DESs and ILs share many of the same properties, and its not uncommon for them to be grouped into a single class.[13]

2.1.1.4 – Bio-sourced VOCs

Sometimes the replacement of traditional VOCs is difficult, and alternative solvents such as those discussed above are simply not viable. In these cases, the use of relatively safe, sustainable, bio-sourced organic compounds like ethyl lactate, ethanol, and methyltetrahydrofuran should be considered.[3]

2.1.1.5 - Outlook

The goal behind 'green' solvents is the minimization of the environmental impacts associated with solvent use in chemical production and other applications.[20] While it is true that there is no one 'universal green solvent', the tools and knowledge to help select the best existing option are available.[6]

2.2 Bio-sourced Feedstock Solubilities

Most modern organic chemicals are made from non-renewable feedstocks, leading to environmental concerns and a need for bio-sourced, renewable feedstocks capable of conversion into these chemicals. Another important consideration is the way

in which the reaction is carried out – how 'green' is the process? With these two factors in mind, an understanding of feedstock solubility in a variety of different solvents would certainly be a valuable asset. The combined use of alternative solvents with bio-sourced reagents would make for greener, more sustainable systems overall.[21]

2.2.1 Bio-sourced Feedstocks

The fourteen compounds studied and described in this chapter (Figure 2-2) are all available from biomass. Many even have the distinction of being identified by the US Department of Energy as being 'platform' chemicals.[22] They are grouped within Figure 2-2 according to functional groups: **1-3** are amino acids, **4-9** are dicarboxylic acids, **10** and **11** are liquids and are an acid and ester respectively, whereas **12-14** are polyols. Their solubility in a variety of solvents was investigated.

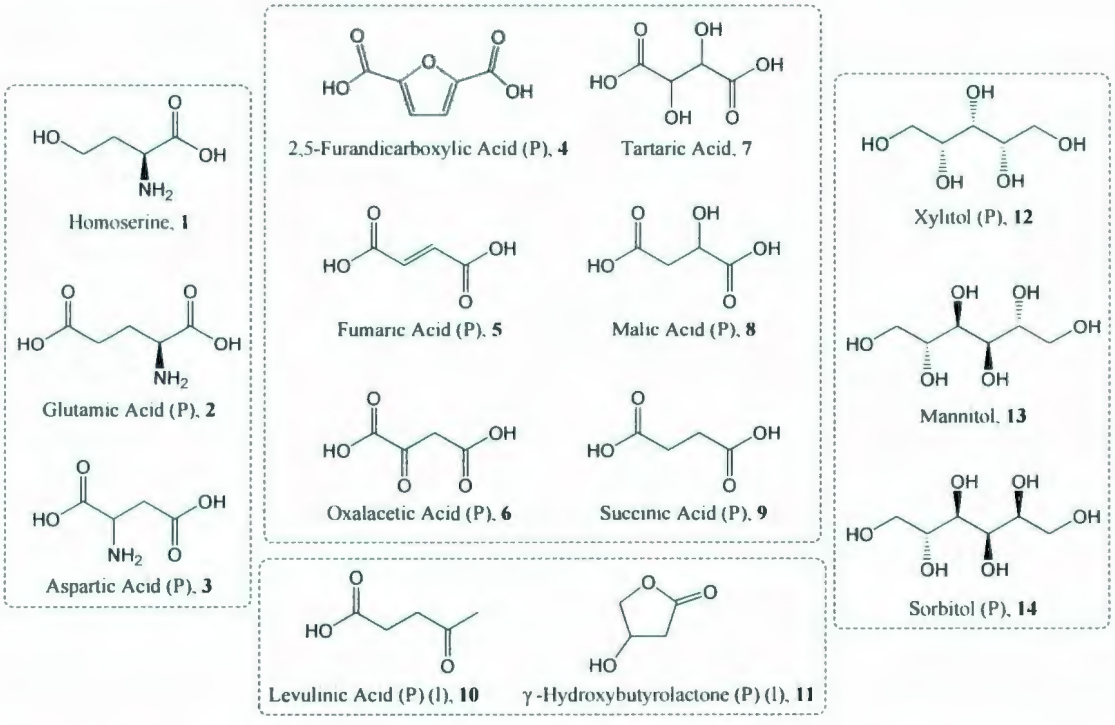


Figure 2-2: Bio-sourced compounds under study including amino acids, carboxylic acids and polyols. Platform chemicals are labelled with (P) and liquids with (l).

The goal in this project was to obtain data for practical purposes, as opposed to obtaining absolute solubility values. A minimum arbitrary solubility level, potentially suitable for extractions or reactions using these green media, was chosen for each solvent system studied. These were 20 mg mL^{-1} (liquid solvents), 1.7 μL mL^{-1} (liquids in CO_2), 0.5 mg mL^{-1} (solids in CO_2/MeOH) and 20 mg g^{-1} (ionic liquid solvents). Although in some cases, absolute data was obtained (*vide infra*).

2.2.2 Solubility in Water and VOCs

As previously discussed, water is a popular green solvent, with solvating properties that can be altered through changes in pH, temperature, and/or pressure. The fourteen compounds under study (Figure 2-2) were all examined for solubility in neutral deionized (DI) water, as well as acidic (acetate) and basic (ammonia) aqueous buffer solutions. Simple alcohols, namely methanol and ethanol, were also examined as they are less hazardous than more commonly used hydrocarbon, ethereal and chlorinated laboratory solvents. Because samples from reaction mixtures are frequently analyzed with NMR or GC-MS, and products are often extracted from aqueous phase reactions using chlorinated or ethereal solvents, data for chloroform and diethyl ether are also reported.

Examination of the solubility data (Table 2-2) revealed several trends. As one might expect from the partition coefficient values for such compounds, the majority of tested compounds proved soluble in neutral water. However, **4** and **5** were insoluble, possibly as a result of available resonance forms of their conjugate bases that are not accessible for the other acids (**6-10**). Also, the amino acids, glutamic acid, **2**, and aspartic

acid, **3**, did not dissolve in neutral water after 24 h. These compounds were also insoluble in the alcohols and organic solvents examined.

Table 2-2: Solubility data for bio-sourced molecules in aqueous solution, alcohols, chloroform and diethyl ether.[a]

			Solvents						
Cmpd	pKa^b	$LogP_{oct\ wat}{}^b$	Water, pH 7	Water, pH 4.7	Water, pH 9.6	Methanol	Ethanol	Chloroform	Diethyl ether
1[d]	2.19, 9.21	−2.785[c]	< 1 min	< 1 min	< 1 min	-	-	-	-
2	2.13, 4.31, 9.58	−3.386	-	-	< 1 min	-	-	-	-
3	1.99, 3.90, 9.90	−3.236	-	24 h	< 1 min	-	-	-	-
4[d]	2.60, 3.55	−0.913[c]	-	2 min	2 min	24 h	-	-	-
5	3.03, 4.44	−0.748	-	2 min	3 min	24 h	24 h	-	-
6	2.22, 3.89, 13.03[e]	−1.600[c]	< 1 min	< 1 min	< 1 min	< 1 min	< 1 min	-	-
7	2.98, 4.34	−2.459[c]	< 1 min	-	< 1 min	1 min	1 min	-	-
8	3.40, 5.11	−1.984	< 1 min	< 1 min	< 1 min	< 1 min	1 min	-	-
9	4.16, 5.61	−0.590	1 min	< 1 min	< 1 min	< 1 min	1 min	-	-
10	4.62	−0.490[c]	Miscible	Miscible	Miscible	Miscible	Miscible	Miscible	Miscible
11	12.87	−1.901[c]	Miscible	Miscible	Miscible	Miscible	Miscible	Miscible	Miscible
12	13.70	−2.068[c]	< 1 min	< 1 min	< 1 min	-	-	-	-
13	13.50	−3.100	< 1 min	< 1 min	< 1 min	-	-	-	-
14	13.00	−2.912[c]	< 1 min	< 1 min	< 1 min	-	-	-	-

a) Time required (at room temperature) to dissolve 100 mg of compound in 5.00 mL of each respective solvent. This corresponds to a concentration of 20 mg mL^{-1}. Entries marked as '-' were not soluble after a 24 h period. *b*) Physical constants obtained from *CRC Handbook of Chemistry and Physics*, 84th edition, CRC Press, Boca Raton, Florida, 2003, and *Data for Biochemical Research*, 3rd edition, Oxford University Press, New York, New York, 1986. *c*) Predicted octanol-water partition coefficient from http://pirika.com/chem/TCPEE/LOGKOW/ourlogKow.htm or ACD/LogP freeware. *d*) 20 mg of compound and 2 mL of solvent were used for studies of homoserine, **1** and 2,5-furandicarboxylic acid, **4**. This corresponds to a concentration of 10 mg mL^{-1}. *e*) pK_{a3} for enolic OH

Changes in pH were expected to have a notable influence on the solubilities of the amino acids. Such expectations did not prove unwarranted, as all of the amino acids studied were soluble in the basic buffer solution (where they would exist as negative ions). All of the other compounds studied were soluble in the basic buffer as well. The acidic buffer solution was successful in dissolving **3** but not **2**. Curiously, tartaric acid, **7**, was the only other compound to be found insoluble in the acidic buffer. The predicted partition coefficient for **7** indicates a higher degree of hydrophilicity (more similar to the amino acids) for this carboxylic acid compared with the other carboxylic acids (**4-6**, **8-10**) studied, which could contribute to this phenomenon. Such behaviour could prove useful for reactions carried out in water, however, where tartaric acid could potentially be

precipitated out of solution simply by acidification. The most significant implication of this work, having shown that all fourteen of the compounds studied (Figure 2-2) can be made readily soluble in water with appropriate pH adjustment, is that water is truly a viable solvent for reactions of bio-sourced compounds.

Each compound was also examined for solubility in the alcohols methanol and ethanol. The amino acids (**1-3**) and sugar alcohols (**12-14**) proved to be insoluble, whilst the remaining carboxylic acid and ester containing compounds (**4-11**) dissolved completely. All of the methanol-soluble compounds were found to be soluble in ethanol as well, with the exception of 2,5-furandicarboxylic acid (**4**), which itself took a long time to dissolve in methanol. Using chloroform and diethyl ether as solvents, all compounds except for the two liquids (**10**,**11**) were determined to be insoluble. This data reflects the weaker intermolecular interactions within **10** and **11**, the moderate intermolecular strength within **5-9** and greater strength within **4**. This is apparent when considering the melting points of these compounds; **4**, T_m 342 °C > **5**, T_m 287 °C > **9**, T_m 185 °C > **7**, T_m 171 °C > **6**, T_m 161 °C > **8**, T_m 139 °C > **10**, T_m 33 °C > **11**, -43 °C.

As previously stated, the goal of this project was not the acquisition of specific and accurate solubility measurements. However, such data could possess significant value, and so a brief survey of these values as could be found in the literature was conducted (Table 2-3). On the whole, this data is comparable with that presented in Table 2-2, though in some cases where we were unable to observe noticeable dissolution, minute quantities have been reported as soluble in the literature (e.g. **9** in chloroform).[23] There were some compound/solvent combinations for which we were unable to obtain literature values, and so several specific solubility experiments were done.

Table 2-3: Specific solubilites of various compounds at room temperature.

Compound	Solvent	Solubility (g/g)	Reference
1	Water	1.1 (30 °C)	24
2	Water	0.023	25
3	Water	0.00785	26
4	Water	0.001	SRC[a]
4	MeOH	0.012	*This work*
5	Water	0.00808	27
5	EtOH	0.0457	27
6	Water	0.1	MSDS[c]
6	MeOH	0.68[b]	*This work*
6	EtOH	0.38[b]	*This work*
7	Water	1.33	MSDS[c]
7	MeOH	0.59	MSDS[c]
7	EtOH	0.33	MSDS[c]
7	$CHCl_3$	Insoluble	MSDS[c]
8	Water	0.56 (20 °C)	MSDS[c]
8	MeOH	0.83 (20 °C)	MSDS[c]
8	EtOH	0.46 (20 °C)	MSDS[c]
8	Et_2O	0.0084 (20 °C)	MSDS[c]
9	Water	0.111 (31 °C)	23
9	$CHCl_3$	0.000933 (29 °C)	23
12	Water	1.8	28
12	EtOH	0.00801	29
13	Water	1.79	30

a) SRC PhysProp Database. *b*) Spontaneous decarboxylation occurs at concentrations greater than these. *c*) Material Safety Data Sheets (MSDS) listed solubility data for some compounds in various solvents.

For 2,5-furandicarboxylic acid (**4**) in methanol, a solubility of 0.0120 (± 0.0015) g/g was observed. This was higher than expected given the low levels of aqueous solubility reported for this compound. The solubility of oxalacetic acid (**6**) was assessed in ethanol and methanol. While a large proportion of the solid dissolved (> 2.7 g in 5 mL MeOH, > 1.5 g in 5 mL EtOH), the solutions began frothing with subsequent additions of solid. This was attributed to the spontaneous decarboxylation of oxalacetic acid under sufficiently acidic conditions.[31]

2.2.3 Solubility in $scCO_2$

The low viscosity and high diffusivity of $scCO_2$ make it promising as a reaction solvent.[32] So after examining their solubilities in water and VOCs, the phase behaviour of the fourteen studied compounds in this medium was investigated. However, of the compounds studied, only the two liquid samples (**10**, b.pt. 30 °C/0.3 mmHg, **11**, b.pt. 100 °C/0.3 mmHg) demonstrated appreciable solubility in pure $scCO_2$ (Figure 2-4, Section *2.2.3.2*). This is likely the result of their comparatively weaker intermolecular interactions. The use of co-solvents for solubilization of solid compounds was also explored.

2.2.3.1 – Solubility Determination

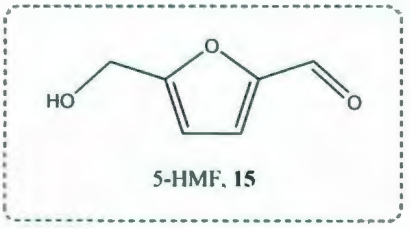
In this work, the Synthetic Method[33] of determining solubility in $scCO_2$ was used. A variable volume view cell, equipped with a camera for visual observation, was utilized for adjusting operating conditions. Within this cell, a fixed amount of solute is dissolved in a known amount of $scCO_2$, and conditions gradually adjusted to reduce its solubility and eventually cause precipitation. The beginning of this precipitation constitutes the cloud point.[33] The temperature and pressure at which the cloud point occurs is recorded as an indication of solubility conditions.

The solute solubility, y, in mole fractions is calculated by dividing the moles of solute by the total moles of solute and CO_2 (Equation 2-1).[33] The moles of CO_2 can be approximated as the product of its volume and molar density. In cases where co-solvent is used, n_{CO_2} is replaced by n_{CO_2+CS}, which is the sum of the moles of CO_2 and co-solvent.

$$y_s = n_s/(n_s + n_{CO_2}) \quad \text{(Equation 2-1)}$$

2.2.3.2 – Solubility in Pure CO_2

Both levulinic acid (**10**) and γ–hydroxybutyrolactone (**11**) were found to be soluble in pure $scCO_2$. Their respective mole fraction solubilities, *y*, were determined as 0.00342 ($y \times 10^3 = 3.4$) and 0.00810 ($y \times 10^3 = 8.1$). These levels of solubility are appreciable, and are comparable with many organic molecules reported in the literature (e.g. acetyl salicylic acid) though notably lower than small molecules such as acetic acid and acetonitrile.[33]



5-HMF, **15**

Figure 2-3: 5-hydroxymethylfurfural

The phase behaviour of 5-hydroxymethylfurfural (Figure 2-3) was also studied because it is produced in the chemical reactions of many sugars.[34] Unlike **10** and **11**, HMF is a solid. However, with a melting point of about 30 °C, it is actually a liquid at all temperatures studied. As such, comparable phase behaviour might be expected. At low temperatures, it did in fact demonstrate behaviour similar to **10**, whereas for temperatures of 70 °C and higher, its phase behaviour was similar to that of **11** (Figure 2-4). The mole fraction solubility of **15** was calculated to be 0.00565 ($y \times 10^3 = 5.7$). Unfortunately, the similarity of phase behaviour for **10** and **15** means that, were a mixture of the two compounds produced in a reaction, $scCO_2$ would not be a viable choice for separation. However, if any of these three molecules (**10**,**11**,**15**) was produced selectively and in good yield in a given reaction, $scCO_2$ would be an excellent choice for the extraction process.

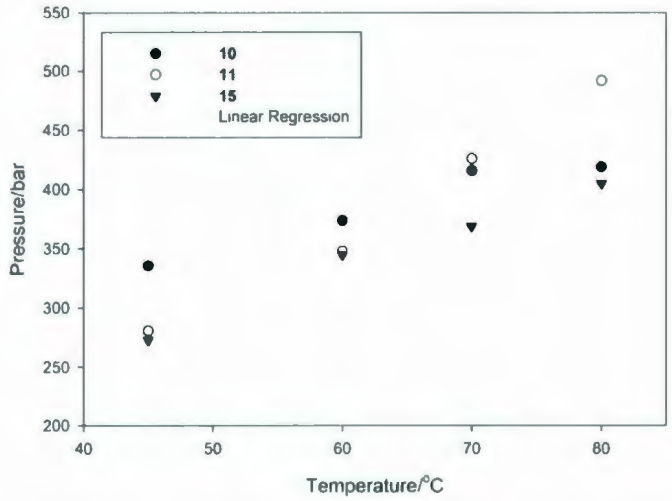


Figure 2-4: Temperature-pressure phase diagram for levulinic acid, **10**, γ-hydroxybutyrolactone, **11** and 5-hydroxymethylfurfural, **15** in neat carbon dioxide. Error bars omitted for clarity, pressure ± 0.3 to 2.1 bar.

2.2.3.3 – Solubility in Modified $scCO_2$

As previously indicated, methanol is a popular $scCO_2$ co-solvent, used to increase its polarity. The solubility of each methanol-soluble, solid compound from the earlier study (Table 2-2) was assessed in this $scCO_2$/MeOH (10% MeOH by volume, 3 mL, x = 0.127) medium (Figure 2-5). Their mole fraction solubilities were ascertained to be: $y = 5.9\text{x}10^{-4}$ (**4**), $y = 9.1\text{x}10^{-4}$ (**5**), $y = 6.4\text{x}10^{-4}$ (**6**), $y = 5.6\text{x}10^{-4}$ (**7**), $y = 6.5\text{x}10^{-4}$ (**8**) and $y = 4.0\text{x}10^{-4}$ (**9**). Interestingly, the most soluble compound was found to be **4**, requiring less CO_2 density (lower P) in order to maintain a single phase. **5** and **6** are less soluble, possibly as a result of their increased flexibility. Conformational changes which may favour inter- and/or intramolecular H-bonding, and therefore disfavour dissolution, are thus possible for these molecules. Compound **7**, possessing a large number of hydroxyl and carboxylic acid groups, retains a reasonably high degree of flexibility making intra-

and intermolecular forces difficult to overcome. Overall, the observed trends correlate well with the intermolecular bonding present within these compounds.

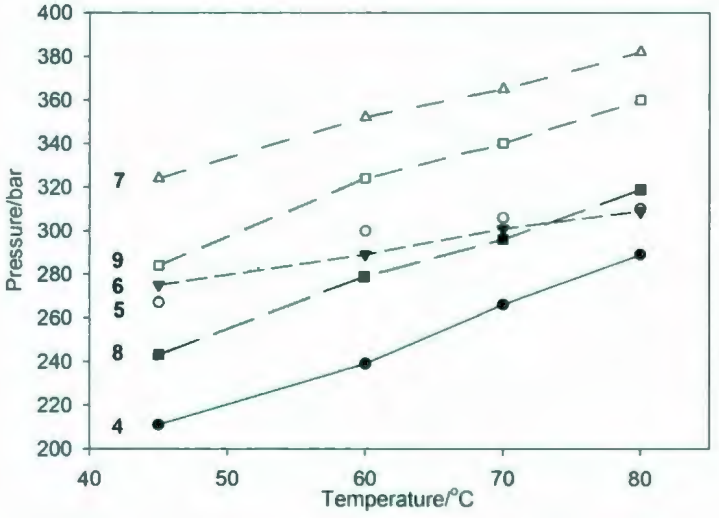


Figure 2-5: Temperature-pressure phase diagram for bio-sourced carboxylic acids **4-9** in carbon dioxide/methanol. Error bars omitted for clarity, pressure ± 0.3 to 3.4 bar.

To confirm that ethanol, a slightly more benign solvent than methanol, would also make an appropriate co-solvent in such systems, **9** was studied in $scCO_2$/EtOH (10% EtOH by volume, 17 mg, x = 0.091). Cloud points were observed at all four temperature points: 45 °C, 179 ± 7.9 bar; 60 °C, 214 ± 4.1 bar; 70 °C, 265 ± 4.3 bar; 80 °C, 293 ± 3.3 bar. These cloud points were generally less distinct than those observed with methanol, but it is worth noting that lower pressures were needed to achieve a homogeneous solution at each temperature. Clearly, $scCO_2$ and $scCO_2$/alcohol mixtures are useful media for investigating chemistry of compounds like **4-11**.

2.2.4 Solubility in ILs

Ionic liquids, as previously referenced, are very versatile, with the potential for tuning of various properties. Their effectiveness in solubilizing carbohydrates has been

detailed in the past decade,[35] and they are also useful for the dissolution of CO_2.[36] Here, a representative compound from each class studied (**2, 5, 7, 9** and **12**) was screened for solubility in tetradecyl(trihexyl)phosphonium dodecylbenzenesulfonate ([PR_4]DBS), a commercially available, hydrophobic IL. After combining 10 mg of compound and 500 mg of the IL in a small (capped) vial, each sample was allowed to stir overnight at room temperature. Compounds **5** and **9** dissolved under these conditions (yielding 20 mg g^{-1} solutions), while **2**, **7**, and **12** did not. These three samples were then heated at 100 °C in a water bath and stirred for 1 hour, allowing for dissolution of 7. Despite heating, **2** and **12** remained undissolved.

Shifting focus to xylitol, **12** and its precursor sugar D-xylose, **16**, specific solubility tests were carried out with several different ILs (Table 2-4). **12** was found to be most soluble in BMImCl, while **16** was most soluble in [PR_4]DBS. Comparing with literature results, both exhibited solubilities less than fructose in BMImCl, but greater than glucose in $BMImPF_6$.[35b] It should be also noted that the solubility of xylose in $BMImPF_6$ observed here was found to be slightly lower than the recently published experimental value of 0.0280 g/g.[35c] Results such as these are promising for the use of xylitol and D-xylose as bio-feedstocks in green reactions.

Table 2-4: Solubility of xylitol (**12**) and D-xylose (**16**) in ILs, in comparison to the solubilities of 6-carbon sugars.

IL	Solubility at 100 °C (g/g)		IL	Solubility at 30 °C (g/g)[35b]	
	12	**16**		Glucose	Fructose
[PR_4]DBS	Not Soluble	0.1294 ± 0.0085	[PR_4]Cl	0.0469	-
$BMImPF_6$	0.0244 ± 0.0095	0.0230 ± 0.0035	$BMImPF_6$	< 0.0004	-
BMImCl	0.1529 ± 0.0083	0.0820 ± 0.0275	BMImCl	-	0.5233
ChoCl/Oxalic Acid	0.0290 ± 0.0014	0.0658 ± 0.0067			
ChoCl/Citric Acid	0.0378 ± 0.0055	Not Soluble			

2.2.5 Conclusions

Analysis of the solubilities of these bio-sourced feedstocks has led to the discovery of several trends, and enabled the grouping of these compounds accordingly (Figure 2-6). Polysaccharides, not studied during the course of this project, were also included in the solubility summary diagram as they are important feedstocks.

The two liquid compounds studied (**10** and **11**) exhibited universal solubility over the entire range of 'green' solvents examined, including pure $scCO_2$. With **15** also demonstrating solubility in $scCO_2$, a useful working hypothesis can be formed: that bio-sourced molecules with low melting points (at or below 30 °C) will dissolve in this green solvent. After the liquid molecules, the next most soluble group of compounds proved to be the dicarboxylic acids, **6-9**, which were soluble in all media except neat $scCO_2$. C-C double bond-containing acids **4** and **5** were also widely soluble, demonstrating solubilities comparable to that of the previous group, with the exception of neutral water. Polyols, **12-14** (and homoserine, **1**) displayed aqueous solubility over a range of pHs, and were also found to be soluble in ILs. The amino acids (**2**, **3**) showed the smallest span of solubility, being insoluble in all solvents studied except for water (and even then only with modified pH), though they may be soluble in different ILs not used in this work.

The presentation of several data sets outlining the solubility of bio-sourced feedstocks in various green solvents could provide valuable insight into the workability of a host of new, green reactions using these compounds, opening the door to a realm of more environmentally friendly procedures.

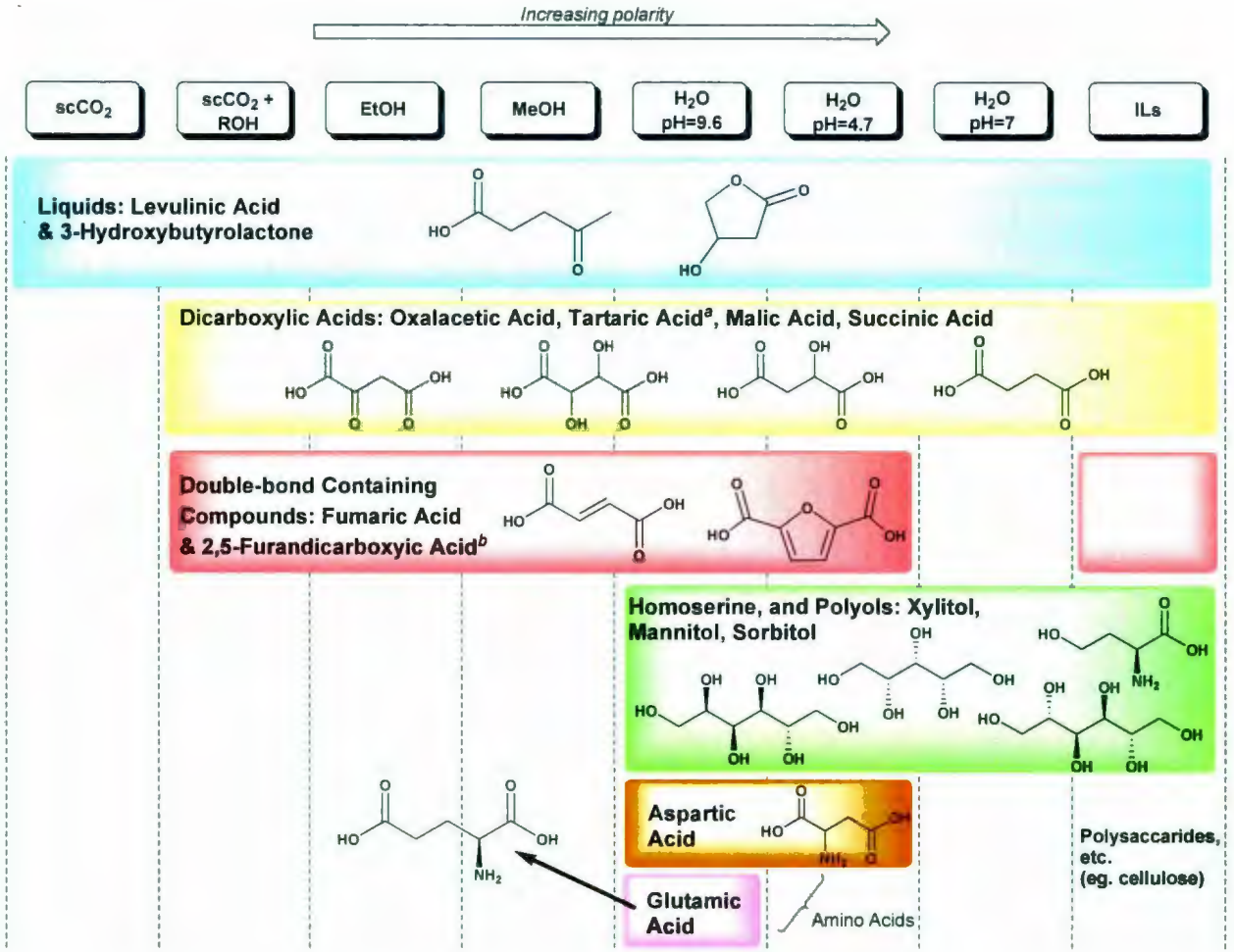


Figure 2-6: Schematic representation of the degree of solubility of classes of bio-sourced molecules in various 'green' solvents. *a*) Not soluble at pH 4.7. *b*) Not soluble in EtOH.

2.3 Experimental

2.3.1 Materials

L-glutamic acid (99%), L-tartaric acid (99%), DL-aspartic acid (99%), DL-malic acid (99%) and cell culture tested fumaric acid were obtained from Sigma-Aldrich. Homoserine, furan-2,5-dicarboxylic acid, oxalacetic acid, levulinic acid, xylitol, D-sorbitol, anhydrous citric acid, anhydrous oxalic acid, and choline chloride were all purchased from Alfa Aesar in 98% or greater purity. γ-hydroxybutyrolactone was also acquired from Alfa Aesar, but in 96% purity. Mannitol (>99%) and D-xylose (>99%) were obtained from ACP Chemical Inc. and Acros Organics respectively.

2.3.2 Solubility Determination

2.3.2.1 – Water and VOCs

100 mg of each compound was added to 5.00 mL of each respective solvent in a small vial (20 mg of compound and 2.0 mL of solvent were used for studies of homoserine, **1** and 2,5-furandicarboxylic acid, **4**). With occasional swirling, vials were observed for several minutes or until complete dissolution occurred. If, after this time period, no apparent dissolution was observable, the sample vial was capped and left to sit overnight. If the sample had not dissolved after 24 hours, it was deemed insoluble.

In determining specific solubilities for **4** in methanol and **6** in methanol and ethanol, small amounts of the compound were added to a vial containing 5 mL of the solvent, followed by mixing and at least 10 minutes to equilibrate. This procedure was repeated until the solid no longer dissolved fully.

2.3.2.2 – $scCO_2$

For the neat $scCO_2$ experiments, a SFT-Phase Monitor II instrument

(Supercritical Fluid Technologies Inc.) was used to record cloud point pressures at four different temperatures. For the first set of experiments, a known amount of compound (0.05 mL **10**, 0.10 mL **11**, and 0.0966g **15**) was placed into the view cell, which was then sealed and filled with liquid CO_2 (30 mL). The system was then brought up to the desired temperature and allowed to equilibrate for 20 minutes, then the pressure was adjusted until a cloud point was observed (as monitored via a CCD camera and a computer screen). The pressure was then increased 50-100 bar and lowered again more slowly to confirm the previous reading. This proceedure was repeated at least once more (depending upon how distinct a cloud point was observed). In this way, a minimum of three cloud point readings were obtained for each temperature/compound condition.

For the second set of experiments, a known amount of compound (10-20 mg) was dissolved in 3 mL of alcohol and placed into the view cell (30 mL in volume), the cell was sealed and filled with liquid CO_2 and then observed under varying temperature and pressure conditions, as described above. Errors in the cloud point data were typically 0.3 to 2.1 bar for neat $scCO_2$ and 0.3 to 3.4 bar for $scCO_2$/MeOH.

2.3.2.3 – Ionic Liquids

10 mg of compound and 500 mg of $[PR_4]$DBS were combined in a small vial, which was capped and left to stir overnight at room temperature. The undissolved samples were then heated to 100 °C in a water bath and stirred for 1 hour. Any sample remaining undissolved after heating were deemed insoluble. The specific solubilities for xylitol (**12**) and xylose (**16**) were determined by the addition of small amounts of solid to a vial of IL (known mass), stirred continously at 100 °C, in 2 hour intervals

until it no longer dissolved.

2.3.3 IL Synthesis

2.3.3.1 – [BMIm]Cl

(Method based upon literature procedure.[37])

Approximately 50 g (54 mL) of 1-chlorobutane and 44 g (43 mL) of 1-methyl-imidazole were combined in a pre-weighed 250 mL RB flask, equipped with a stir bar and condenser, and refluxed overnight. After cooling, two distinct layers were visible. These were separated and the top layer discarded. The cloudy orange IL layer was washed with 3 × 40 mL EtOAc, the washings discarded, and the solution transferred back into the RB, capped, and left to sit overnight. The RB was then placed in an oil bath and stirred under vacuum to remove solvent – temperature gradually increased to 90 °C and held there, forming a dark brown solution. This solution was re-washed (at 70 °C) with EtOAc, followed by solvent removal under vacuum. The IL was then allowed to cool, yielding 48.71 g of light orange crystalline solid.

2.3.3.2 – [BMIm]PF_6

(Method based upon literature procedure.[38])

10.17 g of [BMIm]Cl and 50 mL of acetone were combined in a 150 mL flask, capped, and stirred for several minutes until a cloudy suspension was formed. 9.20 g of sodium hexafluorophosphate ($NaPF_6$) was added to the flask, followed by an additional 30 mL of acetone, rinsing down the sides. The flask was then stoppered and stirred vigorously for ~24 hours. The cloudy white suspension formed was filtered by suction through a frit with 1.5 cm of Celite, into a 150 mL RB flask. The clear, pale yellow filtrate was dried over sodium sulfate overnight, then filtered to remove the solid. The

solution was concentrated on a rotary evaporator to remove excess solvent, and placed under vacuum for several hours to ensure dryness, yielding a pale yellow oil.

2.3.3.3 – ChoCl/Oxalic Acid

(Method based upon literature procedures.[39])

Choline chloride (10.04 g) and oxalic acid (7.42 g) were combined in a stoppered Erlenmeyer flask, equipped with a stir bar, and heated to 80 °C. The mixture was stirred at 80 °C until a homogeneous liquid formed, roughly 30 minutes. After being left to stand at room temperature overnight, it remained liquid, therefore it could be assumed to be a eutectic mixture.

2.3.3.4 – ChoCl/Citric Acid

(Method based upon literature procedures.[39])

Choline chloride (10.07 g) and citric acid (6.94 g) were combined in a Parafilm covered Erlenmeyer flask, equipped with a stir bar, and heated to 115 °C. The mixture was stirred at 115 °C until a viscous, homogeneous solution formed, approximately 1 hour. After being left to stand at room temperature overnight, it formed a very viscous liquid (almost gel-like, but viscosity could be reduced with moderate heating), and was assumed to be a eutectic mixture.

2.4 References

1. P. T. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301

2. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 2000

3. J. H. Clark and S. J. Tavener, *Org. Process Res. Dev.*, 2007, **11**, 149

4. K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31

5. (a) G. Epane, J. C. Laguerre, A. Wadouachi and D. Marek, *Green Chem.*, 2010, **12**, 502; (b) S. M. Hick, C. Griebel, D. T. Restrepo, J. H. Truitt, E. J. Buker, C. Bylda and R. G. Blair, *Green Chem.*, 2010, **12**, 468; (c) G. Epane, J. C. Laguerre, A. Wadouachi and D. Marek, *Green Chem.*, 2010, **12**, 502; (d) M. Kurszewska, E. Skorupowa, J. Madaj and A. Wiśniewski, *J. Carbohydr. Chem.*, 2004, **23**, 169

6. F. M. Kerton, *Alternative Solvents for Green Chemistry*, The Royal Society of Chemistry, Cambridge, UK, 2009

7. D. J. Adams, P. J. Dyson and S. J. Tavener, *Chemistry In Alternative Reaction Media*, John Wiley & Sons, West Sussex, England, 2004

8. W. M. Nelson, *Green Solvents for Chemistry: Perspectives and Practice*, Oxford University Press, New York, 2003

9. T. Clifford, *Fundamentals of Supercritical Fluids*, Oxford University Press, New York, 1999

10. K. Matsuyama and K. Mishima, *Fluid Phase Equilibria*, 2006, **249**, 173

11. T. S. Reighard, S. T. Lee and S. V. Olesik, *Fluid Phase Equilibria*, 1996, **123**, 215

12. M. A. McHugh and V. J. Krukonis, *Supercritical Fluid Extraction: Principles and Practice*, Butterworth-Heinemann, Newton, MA, 1994

13. S. Hu, Z. Zhang, Y. Zhou, J. Song, H. Fan and B. Han, *Green Chem.*, 2009, **11**, 873

14. J. Pernak, F. Stefaniak, and J. Węglewski, *Eur. J. Org. Chem.*, 2005, **2005**, 650

15. C. Chiappe and D. Pieraccini, *J. Phys. Org. Chem.*, 2005, **18**, 275

16. J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker and R. D. Rogers, *Green Chem.*, 2001, **3**, 156

17. C. Capello, U. Fischer and K. Hungerbuhler, *Green Chem.*, 2007, **9**, 927

18. (a) J. Ranke, S. Stolte, R. Stormann, J. Arning and B. Jastorff, *Chem. Rev.*, 2007, **107**, 2183; (b) D. Coleman and N. Gathergood, *Chem. Soc. Rev.*, 2010, **39**, 600

19. E. R. Parnham, E. A. Drylie, P. S. Wheatley, A. M. Z. Slawin and R. E. Morris, *Angew. Chem. Int. Ed.*, 2006, **45**, 4962

20. C. Capello, U. Fischer and K. Hungerbuhler, *Green Chem.*, 2007, **9**, 927

21. S. M. Payne and F. M. Kerton, *Green Chem.*, 2010, **12**, 1648

22. *Top Value Chemicals from Biomass*, US Department of Energy report, August 2004, ed. T. Werpy and G. Petoser, http://www1.eere.energy.gov/biomass/pdfs/35523.pdf

23. X. Sun, H. Jin, X. Luan, W. Jin and G. Lui, *J. Henan Normal University (Natural Science)*, 2009, **37**, 105

24. M. D. Armstrong, *J. Am. Chem. Soc.*, 1949, **71**, 3399

25. P. Ji and W. Feng, *Ind. Eng. Chem. Res.*, 2008, **47**, 6275

26. A. Apelblat and E. Manzurola, *J. Chem. Thermodyn.*, 1997, **29**, 1527

27. L. Dang, W. Du, S. Black and H. Wei, *J. Chem. Eng. Data*, 2009, **54**, 3112

28. H. Hao, B. Hou, J. Wang and G. Lin, *J. Cryst. Growth*, 2006, **290**, 192

29. S. Wang, Q. Li, Z. Li and M. Su, *J. Chem. Eng. Data*, 2007, **52**, 186

30. S. Cohen, Y. Marcus, Y. Migron, S. Dikstein and A. Shafran, *J. Chem. Soc. Faraday Trans.*, 1993, **89**, 3271

31. C.S. Tsai, *Can. J. Chem.*, 1966, **45**, 873

32. (a) J. M. DeSimone and W. Tumas, *Green Chemistry Using Liquid and Supercritical Carbon Dioxide*, Oxford University Press, Oxford, 2003; (b) R. S. Oakes, A. A. Clifford and C. M. Rayner, *J. Chem. Soc., Perkin Trans. 1*, 2001, 917

33. R. B. Gupta and J. Shim, *Solubility in Supercritical Carbon Dioxide*, CRC Press, Boca Raton, Florida, 2007

34. (a) G. Yong, Y. Zhang and J.Y. Ying; *Angew. Chem. Int. Ed.*, 2008, **47**, 9345; (b) X. Tong and Y. Li, *ChemSusChem*, 2010, **3**, 350; (c) B. Zheng, Z. Fang, J. Cheng and Y. Jiang, *ChemInform*, 2010, **41**, 27

35. (a) R. P. Swatloski, S. K. Spear, J. D. Holbrey and R. D. Rogers, *J. Am. Chem. Soc.*, 2002, **124**, 4974; (b) A. A. Rosatella, L. C. Branco and C. A. M. Afonso, *Green Chem.*, 2009, **11**, 1406; (c) M. E. Zakrzewska, E. Bogel-Lukasik and R. Bogel-Lukasik, *Energy Fuels*, 2010, **24**, 737

36. P. J. Carvalho, V. H. Álvarez, I. M. Marrucho, M. Aznar and J. A. P. Coutinho, *J. Supercrit. Fluids*, 2010, **52**, 258

37. J. G. Huddleston, A. E. Visser, W.M. Reichert, H. D. Willauer, G. A. Broker and R. D. Rogers, *Green Chem.*, 2001, **3**, 156

38. P. Suarez, J. Dullius, S. Einloft, R. De Souza and J. Dupont, *Polyhedron*, 1996, **15**, 1217

39. (a) S. Hu, Z. Zhang, Y. Zhou, J. Song, H. Fan and B. Han, *Green Chem.*, 2009, **11**, 873; (b) A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Chem. Commun.*, 2003, 70

Chapter 3 – Acid Catalyzed Dehydration of Xylitol to Form Levulinic Acid

3.1 Introduction

Literature reports of pentitol dehydrations first emerged in 1945 and were devoted to xylitol, which could be converted to 1,4-anhydro-D,L-xylitol via mild acid treatment.[1,2] Other reports concerning acid catalyzed dehydrations of xylitol have since been published.[3]

Industrial xylitol production generally involves the reduction of pure D-xylose, obtained from hardwood hydrolysates, using a Raney-Ni catalyst. However, this approach requires multiple purification steps and typically results in yields of less than 60%.[4] Fortunately, hemicellulose with high xylan (xylose oligomer) content can be found in a variety of biomass sources. Additionally, it has the potential to be coupled with other processes in order to reduce overall cost and waste.

In China, xylitol is produced from corncob waste.[5] Recent research has shown that after the corncob hemicellulose has been hydrolysed to obtain the xylose necessary for xylitol production, the remaining cellulosic corncob residue can be easily broken down into glucose, a valuable precursor for a range of chemicals.[6] Additionally, the use of biocatalysts for xylose hydrogenation has been shown to give yields of xylitol greater than 90% in some cases.[7,8] Production possibilities such as these make xylitol very viable as a feedstock, from an environmental as well as economic point of view.

3.1.1 Levulinic Acid

Levulinic acid (LevA) is an underutilized chemical with great potential, having had the distinction of being identified as a 'platform' chemical by the US Department of Energy.[9] It is a colourless compound with a melting point of 37 °C, a boiling point of 246 °C, and is readily soluble in a range of solvents including water, ethanol, diethyl ether, and acetone.[10] Each molecule possesses two highly reactive functional groups, allowing it to react as both a carboxylic acid and a ketone, and permitting a vast number of synthetic transformations.[11] LevA and its derivatives (Figure 3-1) have applications in a variety of industries, such as food, fuels, chemicals, cosmetics, and medicine.

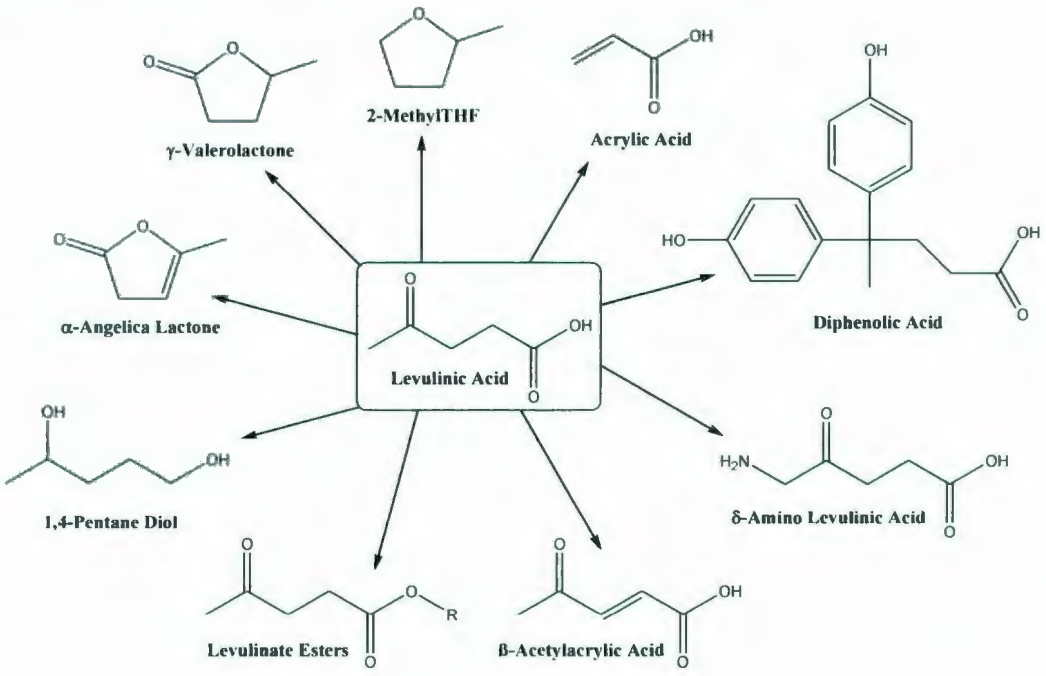


Figure 3-1: Some potentially useful derivatives of LevA.[12]

LevA can be transformed to γ-valerolactone (GVL) by reduction over a metal catalyst, or by reaction with sodium dithionate in aqueous dioxane.[10] GVL is an important precursor for the polymer industry, and has use as a gasoline blending agent.[13]

Additionally, aqueous solutions of GVL can be further converted to pentanoic acid (PA), a compound whose esters find applications in the perfume industry, over a bi-functional catalyst (Figure 3-2).[13] 5-nonanone (itself an industrial solvent) can be derived from PA, and can be further developed into hydrocarbon fuels and blendstocks.[13]

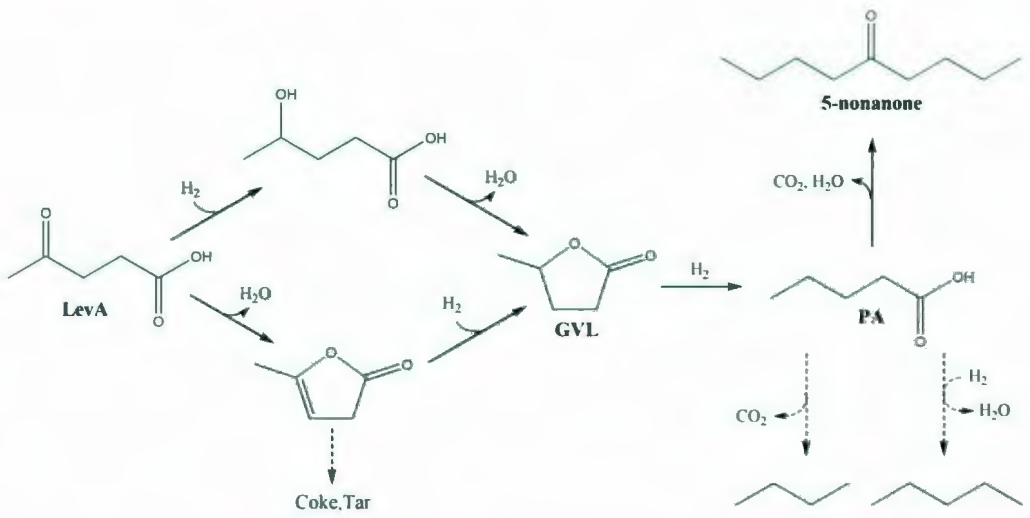


Figure 3-2: Upgrading of LevA via dehydration/hydrogenation and C-C coupling.[13]

Another valuable LevA derivative is 2-methyltetrahydrofuran (2-MeTHF). Due to the low yields associated with direct conversion of LevA to 2-MeTHF, indirect methods (eg. through GVL) are commonly used.[11] 2-MeTHF is useful as a fuel additive, as it has favourable oxygenate and vapour pressure properties.[14] It can be added to petroleum in amounts of up to 30% by volume with no adverse effects, and without requiring engine modifications.[11] Alternatively, levulinate esters have the potential to be used directly as stand-alone fuels.[15] Notably, 2-MeTHF is also used as a 'safer' substitute for the lower boiling solvent THF.[16]

Other functional derivatives of LevA include diphenolic acid (DPA) and δ-aminolevulinic acid (DALA). DPA is prepared by the reaction of LevA with two

molecules of phenol, and has applications in lubricants, adhesives, and paints.[11] It can also act a substitute for BPA in polymer manufacture.[14] DALA, a biodegradable, broad-spectrum herbicide/pesticide, is formed from the amination of LevA.[14] Additionally, it has found use in some cancer therapies.[11] A list of selected LevA derivatives and their applications is presented in Table 3-1.

Table 3-1: Applications of levulinic acid and selected derivatives.[11]

Pharmaceuticals and Specialty Chemicals	**Solvents and General Chemicals**	**Monomers and Specialty Polymers**	**Agricultural Products**	**Transport Products**	**Fuels and Fuel Additives**
Angelica Lactone	Formic Acid	DPA	DALA	Sodium Levulinate	MeTHF
Levulinic Acid	GBL	GVL	DPA	Succinic Acid	Ethyl Levulinate
DALA	Pentanediol	Butanediol	Formic Acid		Methyl Levulinate
5-Bromolevulinic acid	THF	THF			GVL
	MeTHF	Succinic Acid			
	Succinic Acid				

LevA has been produced since 1870,[17] but commercial US production was not realized until the 1940s when A.E. Stanley Manufacturing began converting starch to LevA using HCl.[18] Today, LevA is generally formed by the heating of hexoses with mineral acids for an extended period of time.[19] The maximum theoretical yield of LevA via this route is 71.6% w/w, as formic acid is co-produced as a by-product.[11] However, current processing technology limits the cost-effective large-scale production of LevA from biomass, and high purity LevA is still produced from maleic anhydride via a petrochemical route, which have thus far limited levulinic acid to a fairly small, specialty market.[20] Much work has been done in recent years to make the process more economically viable, however, because of the many potential applications of levulinic acid and its derivatives.

While levulinic acid is typically produced from 6-carbon sugars (hexoses) such as glucose and fructose, via a hydroxymethylfurfural intermediate, its production from 5-carbon sugars has also been shown possible. Pentoses such as xylose can be converted, via a furfural intermediate, to furfuryl alcohol, which can then be transformed into levulinic acid (Figure 3-3).[20] However, this is a multi-step synthesis as opposed to a direct conversion, and is rarely used due to processing complexity and cost. Xylose (and even xylan) can also be converted directly into furfural via an acid catalyzed reaction under microwave heating, with furfural itself being useful both as a solvent and as an alternative to petrochemicals for the production of a variety of other chemicals.[21]

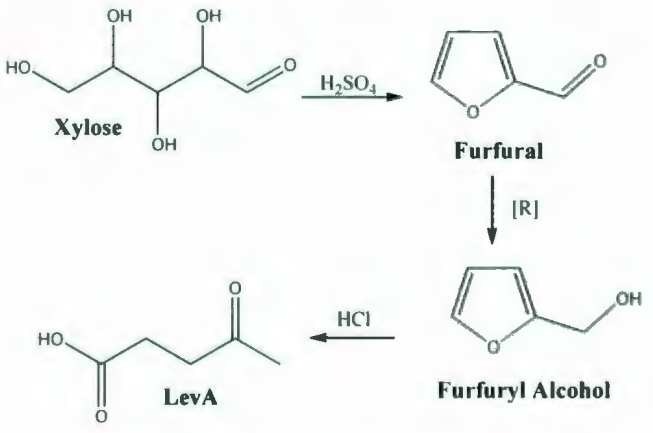


Figure 3-3: The synthetic route for production of levulinic acid from xylose.

3.1.2 Microwave Irradiation

Modern domestic microwave ovens and laboratory microwave reactors run at a frequency of 2.45 GHz in order to prevent interference with various telecommunications devices.[22] They operate via two dielectric heating mechanisms: dipolar polarization and ionic conduction.[23] With dipolar polarization, molecular dipoles align with the applied electric field, and are forced to move as it oscillates – the resulting friction heats the

solution.[24] In ionic conduction, ions quickly migrate back and forth with the electric field polarity. Both mechanisms result in much faster heating of solutions than more traditional conduction or convection methods.[24]

The use of microwave (MW) energy for heating and/or driving reactions is growing rapidly, as evidenced by numerous literature reports on the subject in recent years.[25] It has been described as a 'cold' in situ process, as heat is only produced when the sample/solution absorbs the MW energy.[24] MW heating is associated with many potential benefits, including reduced processing times, increased product yields, enhanced product purities, and improved material properties (as compared with conventional heating).[26] Such benefits have made the use of MWs popular, especially in the field of green chemistry where efficiency and waste minimization are a premium. In addition to saving time, MW heating is often touted as being more energy efficient than traditional methods.[26] While recent research has shown that this is not always the case (some MW-assisted reactions can be rather energy inefficient), energy savings can be realized when multi-mode reactors are used under favourable conditions.[26]

3.2 Xylitol Dehydration to Levulinic Acid

Water is a popular 'green' solvent because it is both abundant and benign.[16] It is one of the few solvents in which sugar alcohols are highly soluble,[27] and is quite amenable to MW heating.[23] Combining the use of MW heating (using an efficient multi-modal instrument) with this 'green' reaction medium for xylitol (itself a renewable feedstock) dehydrations would make for an environmentally benign process overall, particularly where heterogeneous (and therefore easily separable) catalysts are employed.

The use of the sugar alcohol xylitol as a starting material for levulinic acid production has never (to the knowledge of this author) been previously reported. An alternate route to this valuable platform chemical would not be unwelcome, especially if carried out in an environmentally friendly matter. During the course of the studies described herein, the novel conversion of xylitol to levulinic acid in a single step, with water as a solvent, using microwave heating and a solid acid catalyst was successfully demonstrated (Figure 3-4).

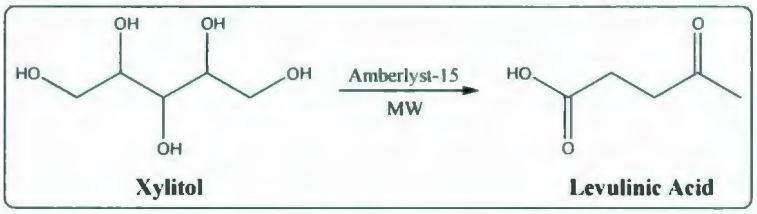


Figure 3-4: Xylitol conversion to LevA.

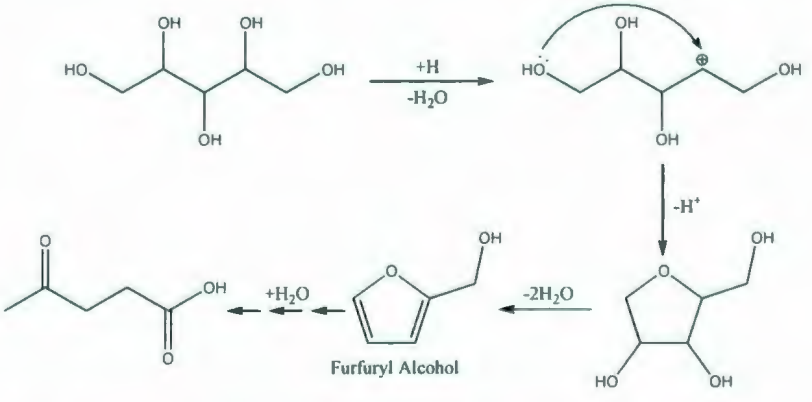
3.2.1 Catalyst Screening

A variety of acidic catalysts were screened for use in the conversion of xylitol to levulinic acid in water: $Zn(OTf)_2$, $La(OTf)_3$, $Yb(OTf)_3$, Al_2O_3, Nb_2O_5, sulfated ZnO, H-Y zeolite, H-β zeolite, Dowex 50WX2, Nafion SAC-13, Amberlite CG-120, Amberlite IRC-50, Amberlite IRP-64 & 69, hydrochloric acid, *p*-toluene sulfonic acid, camphor sulfonic acid, and Amberlyst-15 (both wet and dry). Most of these afforded trace or no levulinic acid. The sulfated zirconium oxide gave a low yield (13%), while the sulfonic acids gave slightly better yields (15-20%). Amberlyst-15 gave superior yields, in the range of 20-40%. This is not particularly surprising, given that it has been known to catalyze dehydrations of sugars.[28]

Amberlyst-15 is a solid polymeric resin containing sulfonic acid groups. Given that all the active catalysts possessed a sulfonic acid group, it was hypothesized that this

group was key for the reaction. To confirm, pure sulfuric acid was also screened (0.5:1 acid:xylitol mol ratio), which demonstrated activity comparable to Amberlyst (34% yield). Finally, to examine what effect increased surface area might have on the catalytic activity of Amberlyst-15, several reactions were attempted with Amberlyst which had been ground to form a smaller particle size. No improvements were observed.

Looking into potential reasons why a sulfonic group might be critical to this reaction, a possible reaction mechanism (Scheme 3-1) was taken into account. In the initial step, when water is lost, coordination of the hydroxyl group with the sulfonic acid group may afford a better leaving group. It is worth noting that this step is likely the rate determining, high energy step for this process, given that the conversion of furfuryl alcohol to levulinic acid has been previously reported with a wide range of acids including hydrochloric acid (which was not useful for xylose dehydration under the studied conditions).[29] Moreover, the minimum reported reaction temperature for obtaining levulinic acid from furfuryl alcohol was only 60 °C while a minimum temperature of 210 °C (Figure 3-8, Section **3.2.5**) was required to obtain levulinic acid from xylitol in this study.



Scheme 3-1: Proposed mechanism for the conversion of xylitol to levulinic acid.

3.2.2 Catalyst/Reagent Ratio

Given the good results obtained using Amberlyst-15, and the advantages associated with using a heterogeneous catalyst,[30] this material was selected for use in further reactions. Varied catalyst and reagent amounts were assessed in a 20 mL solution under consistent reaction conditions (45 min at 250 °C) in an attempt to optimize yields. Unfortunately, no obvious trends were apparent, nor were yields greater than 37% achieved (Table 3-2).

Table 3-2: Yields for the Amberlyst-15 dry catalyzed conversion of xylitol to LevA in water, with 45 min of MW heating at 250 °C. Effect of varying catalyst/reagent amounts.

Entry	Amberlyst (mg)	Xylitol (mg)	Levulinic Acid (mg)	% Yield
1	393	508	116	30
2	493	491	131	35
3	604	500	125	33
4	526	300	59	26
5	505	418	99	31
6	499	600	155	34
7	509	703	167	31
8	594	399	113	37
9	620	596	132	29
10	605	811	207	33

To determine which was acting as the limiting reagent, catalyst or xylitol, a series of reactions was performed in which more of one or the other was added midway through the reaction (Table 3-3). It is apparent from this data that further Amberlyst-15 addition (entry 2) does not initiate any further reaction – no improvement in overall yield was observed. Conversely, the addition of more xylitol did encourage further reaction (entry 1). While the total % yield remained roughly the same for the overall reaction, an increased mass yield of levulinic acid was observed, indicating that a portion of the added xylitol was indeed converted to the desired product. This would suggest that the limiting factor in the reaction is xylitol.

Table 3-3: Effect of adding more xylitol (1) or Amberlyst (2) midway through a 60 min MW reaction, in water, at 250 °C. Entry 3 is a control reaction: 30 min + 30 min of heating with no additional reagent or catalyst added.

Entry	Amberlyst (mg)	Xylitol (mg)	Levulinic Acid (mg)	% Yield
1	601	397 + 302	151	28
2	599 + 401	401	77	25
3	613	460	111	32

To confirm xylitol as the limiting factor, a sample of solution was taken immediately following reaction and, without any pre-treatment or work-up, was subjected to direct-aqueous-injection (DAI) GC-MS (Figure 3-5): No xylitol was detected post-reaction. Flow-injection analysis comparing a sample of xylitol dissolved in water to a post-reaction aqueous solution was also carried out (Figure 3-6), and the mass peak at *m/z* 151 corresponding to xylitol was no longer found to be present in the post-reaction solution. The peak at *m/z* 115 can be attributed to levulinic acid, while those at *m/z* 97 and 195 are the result of chemicals leaching from the Amberlyst resin.

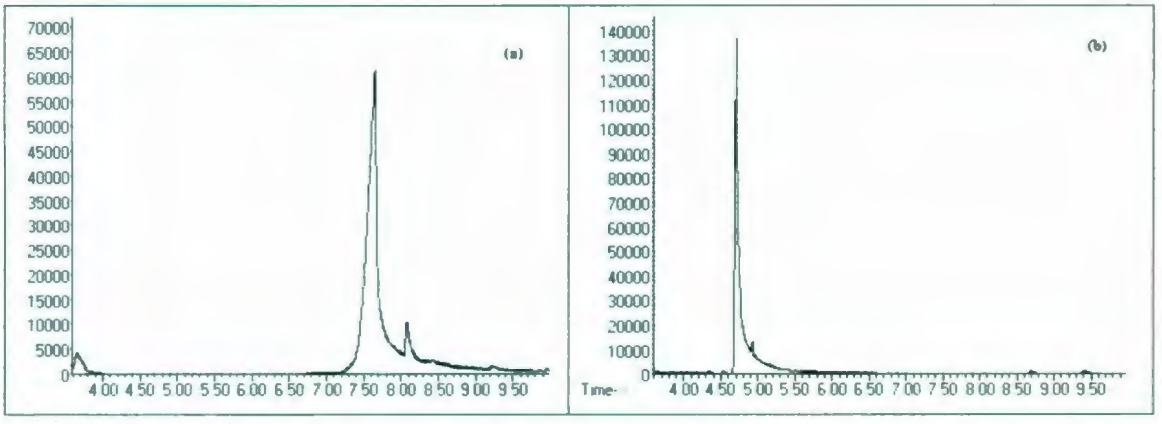


Figure 3-5: Direct aqueous injection GC analysis of (a) an aqueous sample of xylitol, as compared to (b) a sample of post-reaction aqueous solution containing levulinic acid.

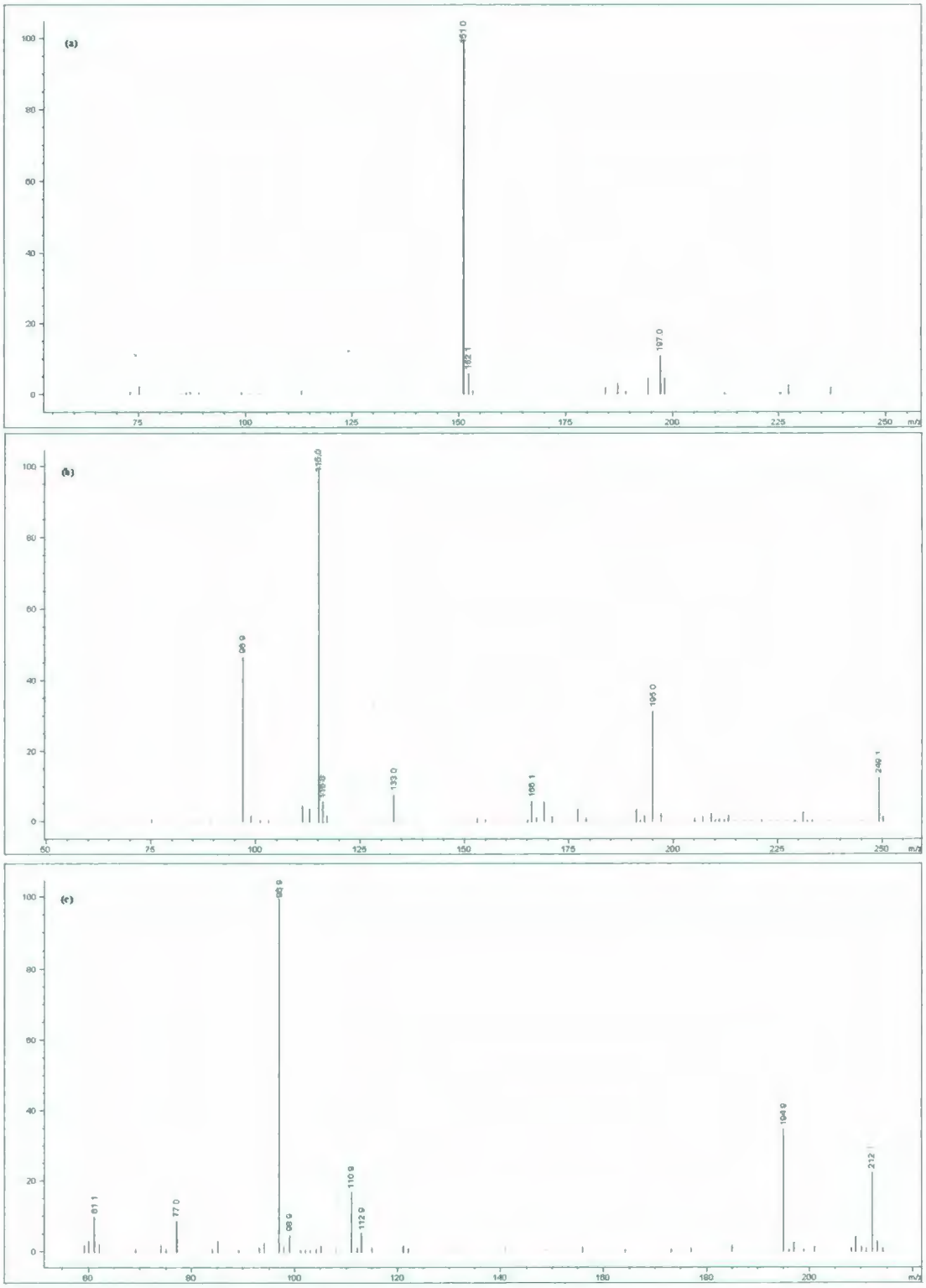


Figure 3-6: APCI mass spectra (negative mode) of (a) aqueous xylitol, (b) post-reaction solution, and (c) aqueous solution resulting from soaking Amberlyst-15 overnight.

Although all of the xylitol was consumed in these reactions, to date, the exact nature of the by-products formed has not been unequivocally identified. However, it is proposed that some of the xylitol may be undergoing over-dehydration to form carbon (Section **3.2.3**).

3.2.3 Catalyst Blackening

In the course of these reactions, a curious phenomenon was observed. In cases where levulinic acid was successfully produced, the Amberlyst-15 turned black. This change could not be attributed to a high temperature catalyst/support degradation process, however, as heating the Amberlyst alone, under the same reaction conditions and without any xylitol present, did not lead to a blackening of the resin. The only circumstances under which Amberlyst-15 blackening has been reported to occur in the literature involved metal complexation (e.g. Pd(0)) with the resin.[31] Since no metals were employed in this reaction set-up, such complexation was deemed unlikely. There have also been reports of zeolite blackening during carbohydrate dehydration reactions, as a result of coke formation on the catalyst surface.[32] Though the catalyst differs, this seems to better agree with the implemented reaction methodology, and it was hypothesized that carbon from xylitol degradation was likely depositing on the catalyst surface.

In order to further investigate this theory, samples of catalyst were taken before and after reaction, and subjected to SEM-EDX analysis. While the surface morphology of the particles from the micrographs did not show any differences, the EDX spectra (Figure 3-7) suggest increased carbon in the post reaction sample, which would lend credence to the reagent degradation hypothesis.

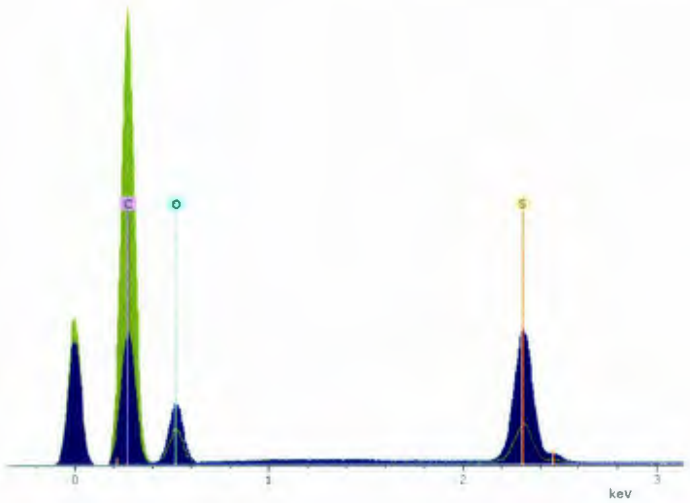


Figure 3-7: Energy dispersive X-ray analysis of pre- (blue) and post-reaction (green) Amberlyst-15, illustrating the increase in carbon and decrease in sulfur and oxygen after reaction.

3.2.4 Catalyst Recycling/Regeneration

Aside from easy separation, one of the most attractive qualities of a heterogeneous catalyst is its potential for re-use/recycling, and so catalyst reusability in this system was examined. Initially, direct use of spent catalyst from a previous reaction in a new reaction (after washing with water and drying) was attempted. This was unsuccessful. It was determined that this was most likely the result of one of two phenomena: either the catalytic sites were being blocked by the carbon deposition, or the high heat was promoting the loss of acidic groups. Assessment of the pH of several post-reaction aqueous solutions revealed highly acidic character (pH $\approx$ 1), suggesting that the latter effect is responsible, at least partly, for the loss of catalytic activity. Further support may be gleaned from the EDX spectra (Figure 3-7), as it shows some reduction in S and O concentration.

In previously reported biomass transformations where Amberlyst was utilized, catalyst regeneration via treatment of Amberlyst resin with a sulfuric acid solution was demonstrated.[33] After subjecting the spent catalyst from previous reactions to this treatment, the resultant 'regenerated' Amberlyst was able to successfully catalyze new reactions with yields comparable to that generated by fresh (unused) Amberlyst-15.

3.2.5 Effect of Reaction Temperature and Time

The effect of shortening or lengthening the reaction time on overall yield was then studied (Table 3-4), all previous reactions having been run for the same 45 min time period. Reducing the reaction time to 30 min reduced the yield of levulinic acid, while increasing to 60 min led to a moderately improved product yield. Increasing the reaction time further, to 90 min, saw the yields decrease, possibly as a result of product decomposition.

Table 3-4: Comparison of levulinic acid yields with varying reaction times at 250 °C.

Entry	Amberlyst (mg)	Xylitol (mg)	Reaction Time (min)	LevA (mg)	% Yield
1	591	514	30	102	26
2	504	501	30	120	31
3	499	600	45	155	34
4	594	399	45	113	37
5	1139	795	60	232	38
6	807	807	60	261	42
7	806	796	90	176	29
8	599	396	90	93	31

The effect of varying the reaction temperature was also examined (Figure 3-8). No levulinic acid production was discernable at 200 °C, but gradually increasing yields were observed moving from temperatures of 210 °C up to about 250 °C. Due to pressure limitations of the microwave reactor used (80 bar maximum), it was not possible to maintain temperatures much higher than 260 °C, thereby imposing a cut-off point.

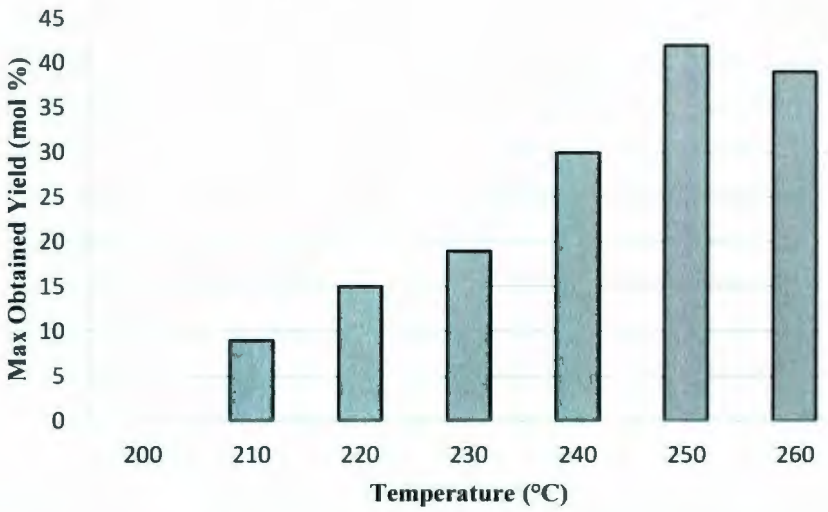


Figure 3-8: The effect of reaction temperature on maximum yields of levulinic acid production (Reaction time: 60 min, except at 260 °C, 45 min).

Obviously, high temperature and/or pressure are critical for this reaction, possibly as a result of achieving near-critical water (NCW) conditions.[34] NCW has some very interesting and different properties compared with traditional liquid water, including reduced polarity and increased K_w, making it simultaneously a better acid and base.[16] The likelihood of the change in polarity having a significant effect on this reaction scheme is small. However, the increased K_w could certainly be influencing the outcome.

3.2.6 Effect of Solvent Volume

To determine the effect of water volume on the yield, a series of reactions were carried out using 15, 20, 30, and 40 mL of H_2O (Table 3-5). Maintaining a reaction temperature of 250 °C, a trend was observed: product yield decreased with increasing solvent volume (Figure 3-9). This would suggest a significant influence of xylitol concentration on product yields, with more concentrated solutions affording higher yields.

Table 3-5: Comparison of levulinic acid yields with varying solvent volumes, in the range of 15-40 mL, after 45 min of microwave heating at 250 °C (In 40 mL, the yield of levulinic acid was too low to accurately calculate, as so those results are not included in this table.

Entry	Amberlyst (mg)	Xylitol (mg)	Solvent Volume (mL)	LevA (mg)	% Yield
1	692	592	15	203	45
2	596	518	15	78	20
3	497	396	15	41	13
4	703	599	20	65	14
5	613	516	20	51	13
6	503	402	20	32	10
7	697	597	30	37	8
8	606	521	30	28	7
9	501	405	30	12	4

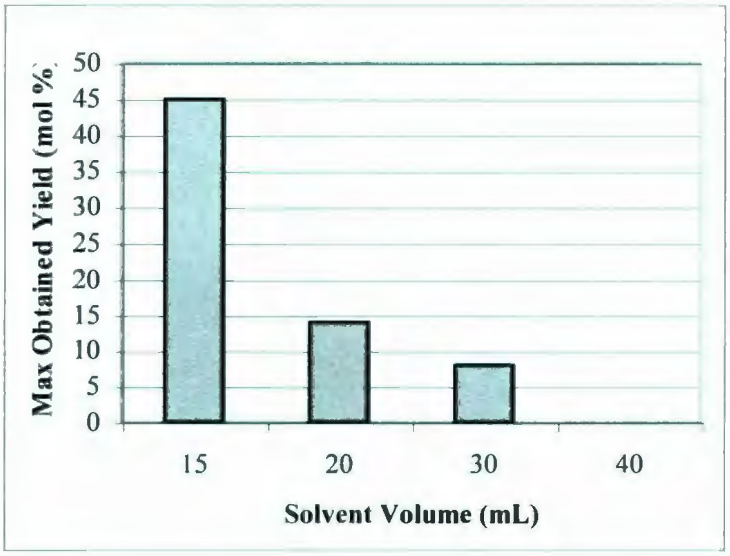


Figure 3-9: The effect of solvent volume on levulinic acid production - best yield (out of 3) obtained after 45 min at 250 °C.

3.2.7 Conclusions

A novel synthetic route for the production of levulinic acid from the bio-sourced, renewable feedstock xylitol has been discovered, which utilizes 'green' methodologies. While high temperatures seem to be vital to success, the use of water as the only reaction solvent certainly lends a green aspect to the process. The polymeric resin Amberlyst-15

possesses the required catalytic sulfonic acid group, and (after relatively facile separation from the reaction mixture) can be regenerated with sulfuric acid post-reaction for use in subsequent runs. The fact that this regenerated catalyst shows activity comparable to that of unused catalyst is especially promising. The combined use of benign reaction solvent, microwave heating, a heterogeneous and reusable catalyst, and a renewable feedstock make for a relatively environmentally friendly process overall.

While levulinic acid yields of up to only 45 mol % were obtained, 100% conversion of xylitol and good selectivity were observed: Extracted EtOAc fractions contained only levulinic acid and added internal standard according to GC-MS analysis. Even so, given typical LevA yields from glucose of ~ 62 mol%,[35] after years of research and more in-depth study, 45% is certainly significant.

3.3 Experimental

3.3.1 Materials

Xylitol (≥ 99%), Amberlyst-15 dry, Amberlyst-15 wet, n-dodecane (≥ 99%), and (±)β-hydroxy-γ-butyrolactone (96%) were all obtained from Alfa Aesar and used as received unless otherwise indicated. HPLC grade ethyl acetate for extractions was obtained from EMD Chemicals, and used without further purification. Nano-pure water was used in all cases, purified by passing distilled water through ion exchange resin and activated carbon cartridges. ACS reagent grade sulfuric acid was obtained from Fisher Scientific.

3.3.2 Microwave Reactions

Reactions were carried out in an Anton Paar Synthos 3000 Microwave, using an SXQ80 rotor equipped with T-probe S. Quartz reaction vessels were used in all cases. The desired amounts of catalyst and reagent were added to the vessel, which was equipped with a stir bar, then 20 mL of water was added. Vessels were sealed, placed in the rotor, then run for the desired length of time at the required temperature. After reaction, the vessels were vented while still in the rotor and then carefully opened. After decanting off the pale yellow aqueous solution, the catalyst was either discarded or (if needed for further study/reuse) washed with water, transferred to a vial, and placed in a fumehood to dry. The solution itself was saturated with NaCl and then spiked with dodecane (as an internal standard). After extracting with 3×10 mL EtOAc, a 1 mL aliquot of the organic phase was taken for GC-MS analysis. A calibration curve with dodecane (Appendix 1) allowed for not only identification of the product, but quantification as well. Finally, to ensure reproducibility, as well as to assess the precision associated with calculated yields, a set of 5 reactions were run under virtually identical conditions and the standard deviation in the resultant yields calculated: a value of $2\sigma = 0.7$ was obtained. As such, a reported yield of 25% would indicate with confidence an actual yield in the range of 24.3-25.7%.

For evaluating the impact of solvent volume, the microwave experiments were carried out as above (with varying amounts of water) up until separation of catalyst from aqueous solution. The aqueous solutions were then spiked with internal standard β-hydroxy-γ-butyrolactone (HBL) and a 1 mL aliquot taken for DAI GC-MS analysis. A new calibration curve, with HBL, was used for quantification in this case (Appendix 4).

For the Catalyst/Reagent Ratio, Catalyst Blackening, Catalyst Recycling/Regeneration, and Effect of Reaction Time and Temperature studies, Amberlyst-15 dry was used. For the Effect of Solvent Volume study, Amberlyst-15 wet was used. No difference in reactivity between wet and dry Amberlyst-15 was observed in this study.

3.3.3 Catalyst Regeneration

The regenerated catalyst was prepared as follows: 0.6 g of used, blackened catalyst (previously washed with water and air dried) was weighed into a vial. 3 mL of concentrated sulfuric acid was diluted with 2 mL water and this solution (5 mL total) was added to the vial with the catalyst. After soaking for 3 h, the solution was filtered off and the resin washed with water, then left to air-dry in a fumehood for 48 h. The resultant catalyst was used directly in catalyst recycling experiments.

3.3.4 Characterization

GC-MS spectra were obtained using an Agilent 7890A GC System equipped with an autoinjector, coupled to a 5975C MSD (EI). The column used was a DB-5 capillary column. Flow-injection analysis (FIA) was carried out using an Agilent 1100 series LC/MSD, bypassing the column, and run using negative mode APCI. For SEM-EDX analysis, an FEI Quanta 400 environmental scanning electron microscope equipped with an energy dispersive X-ray analytical system from Roëntec was used.

3.4 References

1. J. F. Carson and W. D. Maclay, *J. Am. Chem. Soc.*, 1945, **67**, 1808

2. E. Skorupa, B. Dmochowska, L. Pellowska-Januszek, W. Wojnowski, J. Chojnacki and A. Wiśniewski, *Carbohydr. Res.*, 2004, **339**, 2355

3. (a) B. G. Hudson and R. Barker, *J. Org. Chem.*, 1967, **32**, 3650; (b) A. Wiśniewski, J. Szafranek and J. Sokołowski, *Carbohydr. Res.*, 1981, **97**, 229; (c) A. Wiśniewski, J. Sokołowski and J. Szafranek, *J. Carbohydr. Chem.*, 1983, **2**, 293; (d) A. Wiśniewski, E. Skorupowa, J. Sokołowski, D. Glod and G. Descotes, *J. Carbohydr. Chem.*, 1989, **8**, 59

4. T. B. Granström, K. Izumori and M. Leisola, *Appl. Microbiol. Biotechnol.*, 2007, **74**, 273

5. A. Wang, Y. Wang, T. Jiang, L. Li, C. Ma and P. Xu, *Appl. Microbiol. Biotechnol.*, 2010, **87**, 965

6. Ke-Ke Cheng, Jian-An Zhang, E. Chavez and J. Li, *Appl. Microbiol. Biotechnol.*, 2010, **87**, 411

7. S. Kim, J. Yun, S. Kim, J. Seo and J. Park, *Enzyme Microb. Technol.*, 2010, **46**, 366

8. N. U. Nair and H. Zhao, *Metab. Eng.*, 2010, **12**, 462

9. *Top Value Chemicals from Biomass*, US Department of Energy report, August 2004, ed. T. Werpy and G. Petoser, http://www1.eere.energy.gov/biomass/pdfs/35523.pdf

10. B. Timokhin V., V. Baransky A. and G. Eliseeva D., *Russ. Chem. Rev.*, 1999, **68**, 73

11. D. J. Hayes, S. Fitzpatrick, M. H. B. Hayes and J. R. H. Ross, in *Biorefineries-Industrial Processes and Products,* ed. B. Kamm, P. R. Gruber and M. Kamm, Wiley-VCH, Weinheim, Germany, 2008, 139

12. B. Girisuta, L. P. B. M. Janssen and H. J. Heeres, *Chem. Eng. Res. Design,* 2006, **84**, 339

13. J. C. Serrano-Ruiz, D. Wang and J. A. Dumesic, *Green Chem.*, 2010, **12**, 574

14. J. J. Bozell, L. Moens, D. C. Elliott, Y. Wang, G. G. Neuenscwander, S. W. Fitzpatrick, R. J. Bilski and J. L. Jarnefeld, *Resour. Conserv. Recycling,* 2000, **28**, 227

15. S.K.Ritter, *C&EN*, 2011, **89**, 11-17

16. F. M. Kerton, *Alternative Solvents for Green Chemistry*, The Royal Society of Chemistry, Cambridge, UK, 2009

17. J. Y. Cha and M. A. Hanna, *Industrial Crops and Products,* 2002, **16**, 109

18. Q. Fang and M. A. Hanna, *Bioresour. Technol.*, 2002, **81**, 187

19. C. Chang, P. Cen and X. Ma, *Bioresour. Technol.*, 2007, **98**, 1448

20. D. W. Rackemann and W. O. Doherty, *Biofuels, Bioproducts and Biorefining,* 2011, **5**, 198

21. O. Yemiş and G. Mazza, *Bioresour. Technol.*, 2011, **102**, 7371

22. C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250

23. V. Polshettiwar and R. S. Varma, in *Aqueous Microwave Assisted Chemistry: Synthesis and Catalysis,* The Royal Society of Chemistry, 2010, 1-9

24. R. C. Richter, D. Link and H. M. Kingston, *Anal. Chem.*, 2001, **73**, 30A

25. (a) C. Kappe and D. Dallinger, *Mol. Divers.*, 2009, **13**, 71; (b) S. Caddick and R. Fitzmaurice, *Tetrahedron,* 2009, **65**, 3325; (c) C. O. Kappe, D. Dallinger and S. Murphree, *Practical Microwave Synthesis for Organic Chemists*, Wiley-VCH, Weinheim, Germany, 2009

26. J. D. Moseley and C. O. Kappe, *Green Chem.*, 2011, **13**, 794

27. S. M. Payne and F. M. Kerton, *Green Chem.*, 2010, **12**, 1648

28. (a) C. Lansalot-Matras and C. Moreau, *Catal. Commun.*, 2003, **4**, 517; (b) K. Shimizu, R. Uozumi and A. Satsuma, *Catal. Commun.*, 2009, **10**, 1849; (c) X. Tong, Y. Ma and Y. Li, *Appl. Catal. A,* 2010, **385**, 1

29. B. Capai and G. Lartigau, US Pat., 5 175 358, 1992

30. (a) N. Mizuno and M. Misono, *Chem. Rev.*, 1998, **98**, 199; (b) G. V. Smith and F. Notheisz, *Heterogeneous Catalysis in Organic Chemistry*, Academic Press, San Diego, USA, 1999

31. E. G. Leelamani, N. M. Nanje Gowda, M. Magdalene and G. K. N. Reddy, in *Recent Developments in Catalysis: Theory and Practice,* ed. B. Viswanathan and C. N. Pillai, Editions Technip, New Delhi, India, 1991, 99-102

32. Y. Roman-Leshkov, in *Synthesis of furan compounds by liquid-phase catalytic processing of biomass-derived carbohydrates,* PhD Thesis, The University of Wisconsin - Madison, 2008, 68-70

33. N. Villandier and A. Corma, *Chem. Commun,* 2010, **46**, 4408

34. D. J. Adams, P. J. Dyson and S. J. Tavener, in *Chemistry in Alternative Reaction Media,* John Wiley & Sons, Ltd, West Sussex, England, 2005, 95-129

35. (a) B. Girisuta, L. P. B. M. Janssen and H. J. Heeres, *Chem. Eng. Res. Des.*, 2006, **84**, 339; (b) H. Heeres, R. Handana, D. Chunai, C. B. Rasrendra, B. Girisuta and H. J. Heeres, *Green Chem.*, 2009, **11**, 1247; (c) X. Hu and C. Li, *Green Chem.*, 2011, **13**, 1676

Chapter 4 – Conclusions and Proposed Future Work

4.1 Conclusions

The green chemistry movement has seen extensive growth in recent years, with government, academia, industry, and even the general public striving to achieve sustainability and reduce environmental impact. As discussed in Chapter 1, the use of all twelve principles of green chemistry in concert allows for steady movement towards 'greener' and more benign processes. In particular, decreased reliance on petroleum feedstocks and increased utilization of biomass will aid in the realization of global sustainability, all the while increasing profitability.

The use of bio-sourced compounds in the preparation of polymers has already been adopted by industry, and a range of bio-sourced, renewable starting materials (polysaccharides, simple sugars, furan-derivatives, acids and alcohols) are being studied by researchers worldwide, including (but not limited to) inulins, cellulose, glucose, fructose, and glycerol.[1] These endeavours have demonstrated the viability of such reagents as new sources of valuable chemicals and precursors.[2] Chapter 2 presented several sets of data outlining the solubility of selected bio-sourced feedstocks in various green solvents, and grouped them accordingly. The ready solubility of many of the studied compounds in such solvents, water in particular, is promising for their use in more environmentally responsible processes.

Water is a popular 'green' solvent because it is both abundant and harmless[3] and is one of the few solvents in which sugar alcohols are highly soluble.[4] Microwave heating is known for being more efficient than conventional heating. It affords time and energy

savings, particularly when multi-modal instruments are used.[5] These factors were combined, as described in Chapter 3, with a heterogeneous, and therefore easily separable, catalyst (Amberlyst-15) and a renewable, bio-sourced feedstock (xylitol) to afford a relatively green method of levulinic acid production. Additionally, there is the potential to further reduce waste while conserving time and energy by coupling this process with other reactions.

4.2 Future Work

While the trends in solubility presented in Chapter 2 are useful in predicting which reaction mediums might prove useful for a given compound, there is certainly room for improvement. By expanding this study to include a greater variety of bio-sourced feedstocks, these trends could be extended and applied with a greater degree of confidence. Furthermore, obtaining specific solubilities for all of the studied compounds in each green solvent (where data does not already exist) would be of value in some specific applications, and would be especially useful in cases where biphasic systems are employed.

The dehydration of xylitol to levulinic acid reported in Chapter 3 is certainly exciting and novel, but finding ways to improve the yield would help to further its impact. Given the catalyst leaching reported, investigations into catalyst resins with greater thermal stability (such as Amberlyst 35, 36, or 70) are warranted. Also, studies to determine the minimum catalyst requirements have yet to be undertaken, and there is the potential that a reduction in acid concentration could reduce the amount of xylitol over-dehydration that occurs. Finally, one-pot reactions with earlier feedstocks such as xylose,

xylan, hemicellulose, and/or even pure biomass should be explored as they have the potential to improve economics and reduce environmental impact by reducing time, energy, and waste, thus increasing overall reaction efficiency. Likewise, simultaneous dehydration of both glucose and xylitol to levulinic acid in a single reactor may be possible, given that hexose conversion to levulinic acid is typically carried out via mild acid treatment at elevated temperatures.[6]

4.3 References

1. (a) G. Kharchafi, F. Jerome, J. Douliez and J. Barrault, *Green Chem.*, 2006, **8**, 710; (b) S. Hu, Z. Zhang, Y. Zhou, J. Song, H. Fan, and B. Han, *Green Chem.*, 2009, **11**, 873; (c) G. Epane, J. C. Laguerre, A. Wadouachi and D. Marek, *Green Chem.*, 2010, **12**, 502; (d) X. Qi, M. Watanabe, T. M. Aida and R. L. Smith Jr., *ChemSusChem*, 2009, **2**, 944

2. (a) M. Schlaf, *Dalton Trans.*, 2006, 4645; (b) R. M. Deshpande, V. V. Buwa, C. V. Rode, R. V. Chaudhari and P. L. Mills, *Catal. Commun.*, 2002, **3**, 269; (c) M. Pagliaro, R. Ciriminna, H. Kimura, M. Rossi and C. D. Pina, *Angew. Chem. Int. Ed.*, 2007, **46**, 4434

3. F. M. Kerton, *Alternative Solvents for Green Chemistry*, The Royal Society of Chemistry, Cambridge, UK, 2009

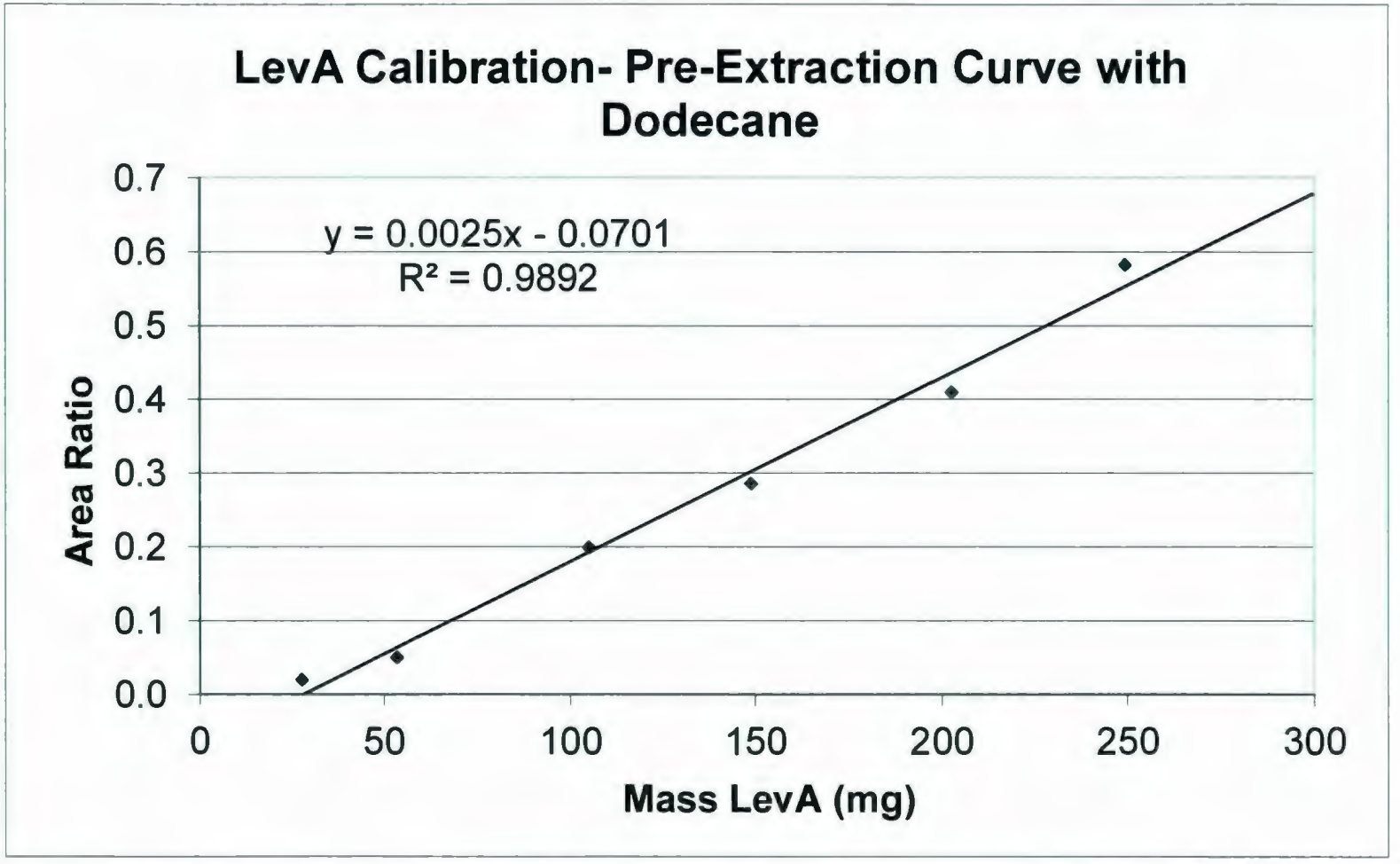
4. S. M. Payne and F. M. Kerton, *Green Chem.*, 2010, **12**, 1648-1653

5. J. D. Moseley and C. O. Kappe, *Green Chem.*, 2011, **13**, 794-806

6. J. Y. Cha and M. A. Hanna, *Industrial Crops and Products*, 2002, **16**, 109

Appendices

Extended Data Pertinent To Chapter 3



Appendix 1: Calibration curve for determination of levulinic acid yield, using dodecane as an internal standard.

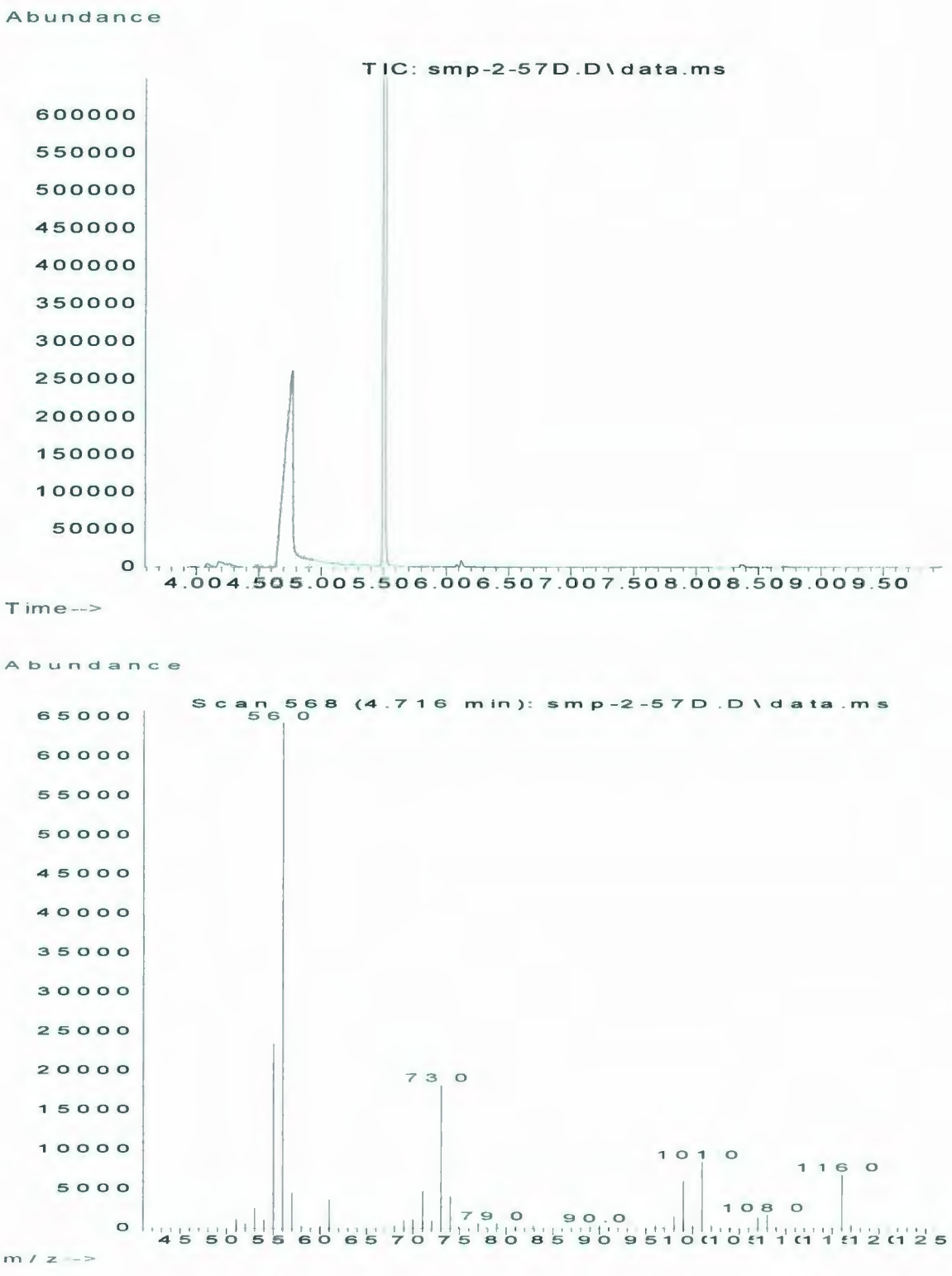
Entry	A(LA)	A(std)	A(LA)/A(std)	Mass LA (mg)
1	1599299	80801545	0.019793	27.6
2	4812947	96105570	0.050080	53.5
3	16194975	81437628	0.198864	105.1
4	27210276	95328975	0.285436	148.9
5	37996440	92744713	0.409688	202.6
6	48255680	82820934	0.582651	249.4

100.6 mg of standard per sample (134 μL)

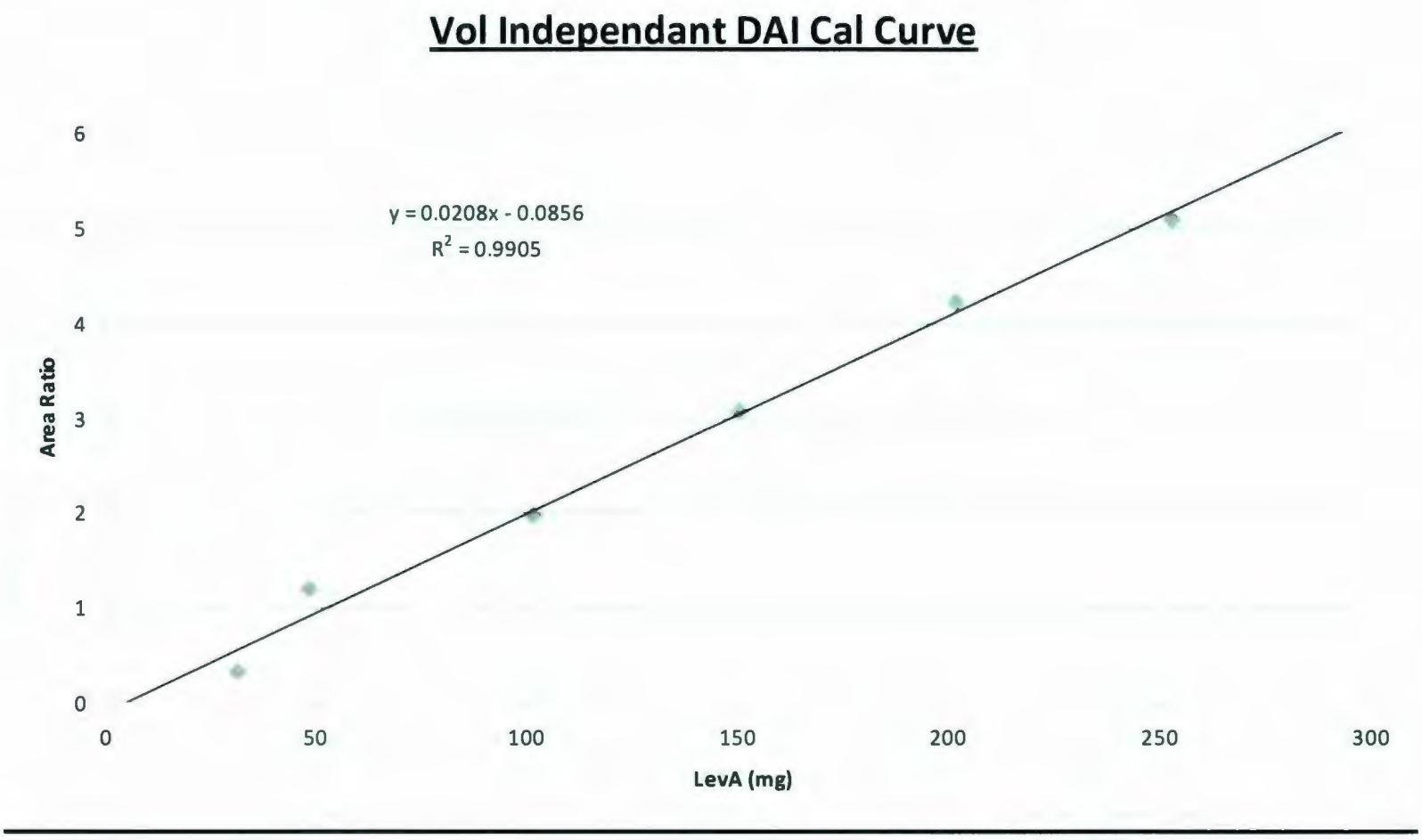
Calibration Method

Six vials were prepared with 20 mL of DI water, saturated with NaCl. To each vial was added 134 μL of dodecane (as internal standard), and a known amount of levulinic acid (LA – see table above). Each of these 6 samples was then extracted into 3 × 10 mL of EtOAc, and a 1 mL aliquot taken for GC-MS analysis. From the GC spectrum of each sample, the areas (A) of the peaks corresponding to dodecane and levulinic acid were determined. The ratio of these areas was calculated and plotted against LevA mass (Appendix 1), then fit with a line of formula $y = 0.0025x - 0.0701$. This formula could then be used to determine the mass of levulinic acid in unknown samples of the same volume (20 mL) treated in the same manner: 'y' = area ratio, as determined from GC spectrum; solve for 'x' = mass of LevA (in a 20 mL solution).

Appendix 2: Pre-extraction calibration curve data and preparation.



Appendix 3: GC-MS spectra of a post-reaction sample in EtOAc, showing levulinic acid (retention time ~ 4.7 min) produced. Peak at 5.5 min = dodecane (internal standard).



Appendix 4: Calibration curve for determination of levulinic acid yield, using HBL as an internal standard.

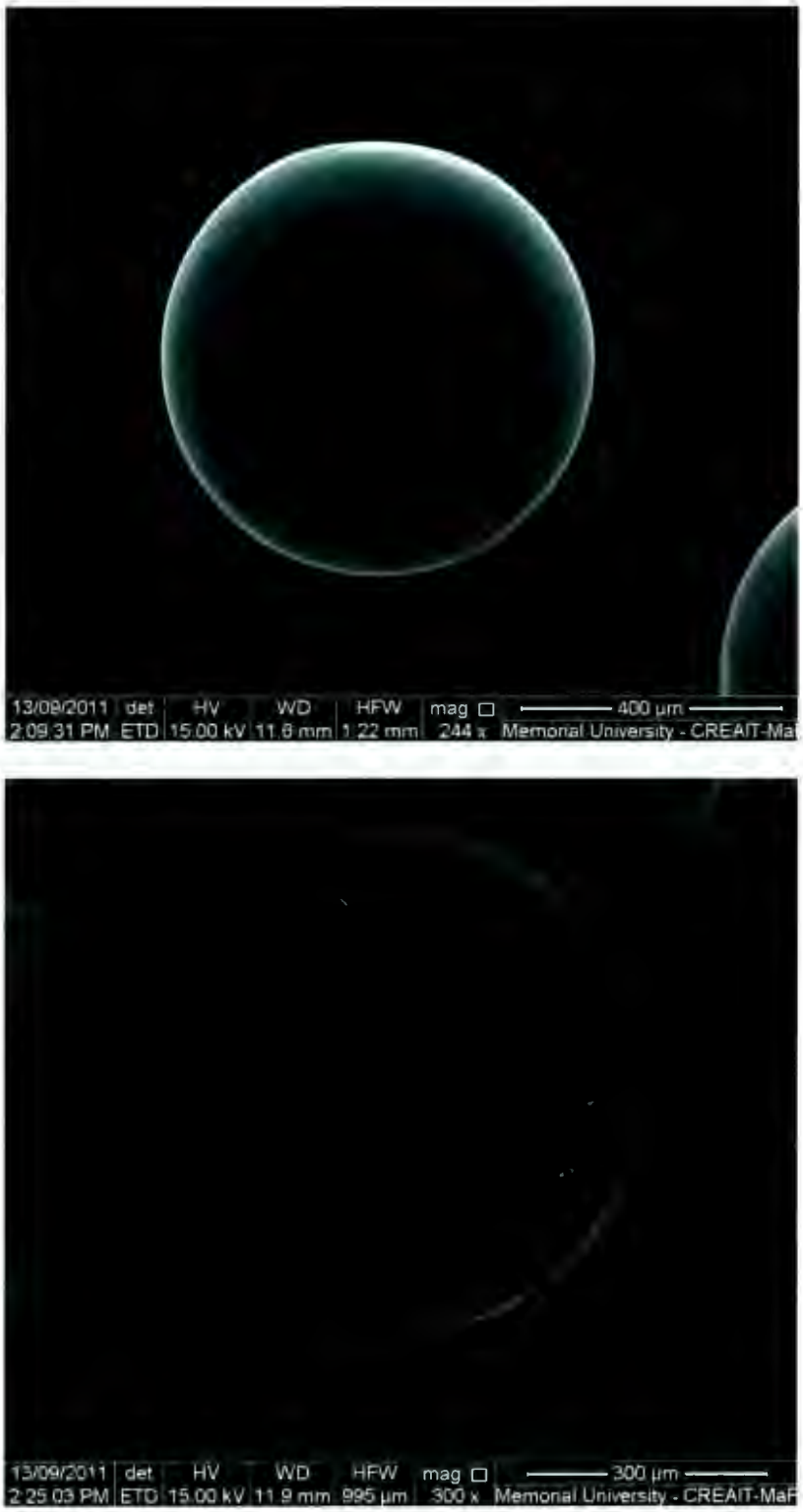
Entry	A(LA)	A(std)	A(LA)/A(std)	Mass LA (mg)
1	1533211	4770410	0.321400	31.5
2	6898553	5783257	1.192849	48.3
3	14056186	7117187	1.974964	101.7
4	27943375	9134746	3.059020	150.8
5	37057003	8790324	4.215658	202.3
6	36827511	7237257	5.088601	253.3

400 μL of standard per sample

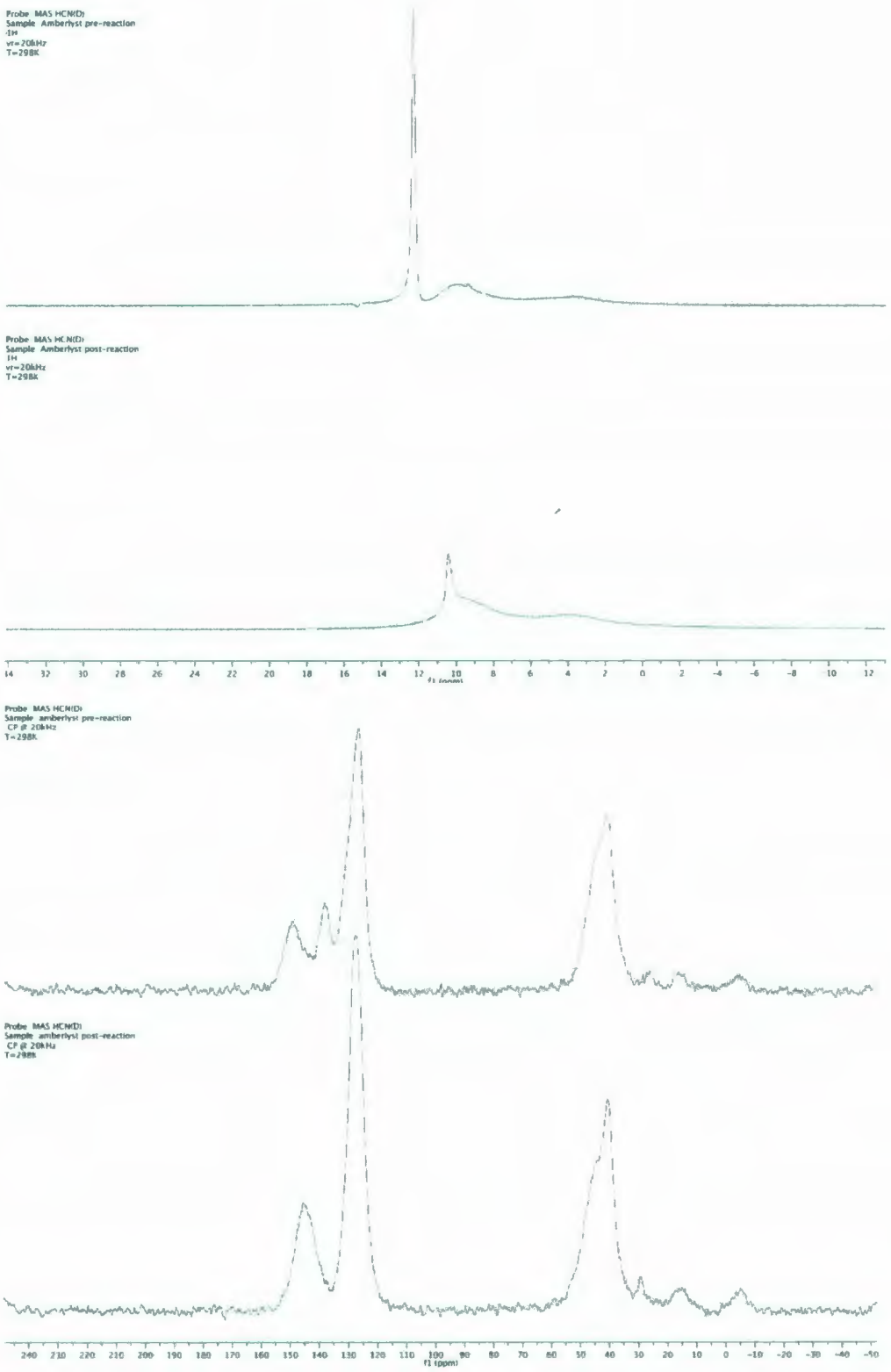
Calibration Method

A standard solution was prepared with 2.8922 g of β-hydroxy-γ-butyrolactone (HBL) made up to 10 mL with DI water (in a volumetric flask). Six vials were then prepared with 20 mL of DI water, and to each vial 400 μL of HBL solution (as internal standard) and a known amount of levulinic acid (LA – see table above) was added. A 1 mL aliquot of each sample was taken for DAI GC-MS analysis. From the GC spectrum of each sample, the areas (A) of the peaks corresponding to HBL and levulinic acid were determined. The ratio of these areas was calculated and plotted against LevA mass (Appendix 4), then fit with a line of formula $y = 0.0208x - 0.0856$. This formula could then be used to determine the mass of levulinic acid in unknown samples of initial volume range 15-40 mL: 'y' = area ratio, as determined from GC spectrum; solve for 'x' = mass of LevA.

Appendix 5: Volume-independent DAI calibration curve data and preparation.



Appendix 6: SEM of Amberlyst-15 resin before (top) and after (bottom) reaction.



Appendix 7: Proton (top) and carbon (bottom) solid-state NMR of pre- (upper) and post-reaction (lower) Amberlyst-15.