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POLYMER-BASED SOLVENTS FOR MINIMIZING POLLUTION DURING THE SYNTHESIS OF FINE CHEMICALS

by

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Submitted to the Department of Materials Science and Engineering
Program in Polymer Science and Technology
in Partial Fulfillment of the Requirements for the Degree of

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ABSTRACT

Most processes used in the pharmaceutical industry are, by necessity, carried out in organic solvents. In many cases these solvents are volatile and sufficiently water-soluble to contaminate air emission and aqueous discharge streams, adding to the environmental burden and the cost of downstream processing and recovery operations. One example is the use of tetrahydrofuran (THF) as the solvent for Grignard reactions which must be carried out under anhydrous conditions. The desired product is often obtained by aqueous precipitation. Since THF is soluble in the water phase it must be recovered by distillation which is a very energy-intensive process.

We feel that solvent replacements combined with recovery and recycling will be important in the development of benign chemical processes. For this approach to be successful it is crucial that appropriate solvation properties be attained in the replacement solvent while ensuring that the potential for environmental contaminations be minimized. Furthermore, difficult separation problems must be avoided so that more efficient recovery of solvents is facilitated.

Facile synthetic methods have been developed for both low molecular weight and polymer-bound derivatives of THF for use as replacement solvents for THF. We have identified one step in the synthesis of the orally active HIV-1 protease inhibitor L-735,524 as a suitable model reaction to use in the evaluation of these novel solvents. This reaction is known to be very sensitive to the solvent medium and therefore represents a critical test of our replacement solvents. Reaction kinetics, as well as possible separation schemes necessary for regeneration of the low molecular weight and polymer-bound solvents have been investigated. Both types of solvent replacement have been very successful in the replacement of THF. The low molecular weight derivatives can be carried through several reaction steps thereby avoiding costly solvent switches because of their minimal water solubility and volatility. The polymer-bound solvents, which are dissolved in a relatively benign continuous phase, can be recovered form the process stream by microfiltration and regenerated for re-use. Thus, it is envisioned that our replacement solvents can be part of an intelligent reaction/separation sequence that improves upon currently used sequences in terms of both environmental impact and productivity.

Thesis Supervisors:
T. Alan Hatton, Ralph Landau Professor of Chemical Engineering Practice
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to my parents,

Ernest Molnar and Cecelia Bendzsuk Molnar

and to my grandmother,

Katherine Gyula Bendzsuk
September 2, 1898 - September 12, 1991

for their love and inspiration

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Introduction

Background and economic and environmental motivation for project

There has been considerable interest lately in "benign by design chemistry," synthetic chemistry designed to use and generate fewer hazardous substances.[1] The impetus for this research is a concern for our environment. For instance, the EPA estimated that 3.6 billion pounds of toxic chemicals were released in 1990. Early environmental research focused on remediation of this type of waste, but now prophylactic chemistry, or source reduction aimed at preventing environmental pollution in the first place, is being emphasized instead of focusing on recovery. This type of work is crucial in developing alternative syntheses for important industrial chemicals, fine chemicals, and pharmaceuticals. The role of the synthetic chemist is fundamental to environmental concerns and crucial to the success of pollution prevention.

The process development phase also provides an opportunity for incorporating waste minimization strategies, requiring collaboration among chemists, engineers, and environmental professionals.

The private sector is realizing that pollution prevention makes good sense from a business standpoint. Some examples are Dow Chemical Corporation's WRAP(Waste Reduction Always Pays) and 3M's 3P Program (Pollution Prevention Pays). A specific example of directed research and development for significant environmental improvements with greater economy and product quality is improved catalytic designs. Recently, DuPont has developed innovations in catalysis to create an environmentally friendly process for making tetrahydrofuran.[2]

Another industry taking note of these developments is the pharmaceutical industry. Most processes used in the pharmaceutical industry are, by necessity, carried out in organic solvents. In many cases these solvents are volatile and sufficiently water-soluble to contaminate air emission and aqueous discharge streams, adding to the environmental burden and the cost of downstream processing and recovery operations.

New drug research and development is a complex, costly, and time-consuming process. Merck & Co., for example, has a developed waste-minimization and process development strategy that consists of an iterative process of first calculating process material balance to estimate prospective waste streams(computerized batch process simulation is an important tool in this effort), then to perform an environmental assessment of the process in order to evaluate the waste-minimization options, to incorporate waste-minimization options into process design where possible and to update the process material balance incorporating waste-minimization initiatives. These four steps are repeated as necessary and finally waste minimization residuals and nonminimized wastes are evaluated for treatment and disposal. Case studies have shown that it is possible to implement process modifications even after a process has been approved by the U. S. FDA. In this case, it is essential to demonstrate that final product quality has not been compromised.

In addition to making good business sense, interest in pollution prevention is also driven by governmental regulations. In recent years, federal and state regulations have been passed which strongly discourage use of solvents which are not environmentally benign.[3,4,5] Prior to 1985, there was only one state law dealing with pollution prevention, while as of 1991 over half of the states had passed such laws, with many more pending. Of particularly strong impact is the Pollution Prevention Act passed by Congress in October 1990 and the Resource Conservation and Recovery Act of 1988. These laws strongly encourage hazardous waste minimization via recovery and recycling of solvents, and discourage disposal of hazardous wastes or clean-up processes. Such a strategy has the advantages of being less expensive than collection, treating or disposal of hazardous wastes, and is also of much less risk to workers, the environment and the community.[6] In addition, substitution of nonvolatile organic compounds for the commonly used volatile solvents is strongly encouraged, with the most hazardous solvents, such as methylene chloride, carbon tetrachloride and benzene, being strongly discouraged or scheduled for a complete phase out in the near future.[3]

Owing to economic concerns, government regulation, and increased public awareness of the harm done by such solvents, there is considerable interest in ameliorating the deleterious environmental effects associated with solvent usage in pharmaceutical reaction processes.[7] The different approaches being considered include the following (i) a search for new synthetic procedures that utilize less hazardous solvents, (ii) the establishment and exploitation of extensive computer data bases on solvents, (iii) the use of solvent mixtures to obtain the desired solvation properties, and (iv) the intelligent design of reaction/separation trains to minimize mixing of solvents in different operations, and thereby minimize the problems associated with their recovery and recycle. However, the development of new synthetic procedures for processes already in place may be at the expense of yield and productivity, and the time-frame for such developments is probably fairly long.[8,9,10] Also, process modifications involving material substitution require complete approval (and in many cases preapproval if a drug is concerned) by the FDA before the new product can be marketed. This can be an expensive and time-consuming process, and may result in a temporary shutdown of production while necessary changes are being implemented.

For the intermediate term, we feel that solvent replacements combined with recovery and recycling will be an important development.[11,12] For this approach to be successful it is crucial that appropriate solvation properties be attained while ensuring that the potential for environmental contaminations is minimized. This is where the importance of work on solvent data bases and the use of mixed solvents can be recognized. Another idea currently being explored is the use of aqueous surfactant micellar solutions to provide the solvation of hydrophobic reactants in an aqueous medium, although here there are restrictions on the reaction schemes to those which do not require anhydrous conditions. It is important in the selection of solvent replacements that difficult separation problems be avoided, and that more efficient recovery of solvents be facilitated.

Current solvent recovery and recycling processes focus on distillation and various chromatography steps.[4,8,9,10] In order for these recycled solvents to meet the FDA requirements for drug production they must be virtually contaminant free. Estimated savings due to recycling are in most cases offset by the cost of the recovery process equipment, still bottoms disposal and makeup for non-recovered solvent.[4]

The work outlined here falls in the solvent replacement and recovery category, but is developed from a radically different premise.[13] Specifically, we have designed and synthesized a new class of solvents having properties similar to those currently in use, but which are entirely nonvolatile and can easily be recovered from process streams using simple mechanical separations such as ultrafiltration. We have implemented the use of solvents "immobilized" by attachment to polymers, which can then be dissolved in a more benign solvent continuous phase. The polymeric solvent system, composed of solvent moieties attached to a polymer backbone, and a relatively benign continuous phase may form some type of microenvironment which localizes the solvent moieties, or the pendant solvent groups may form clusters. In some cases, it may be advantageous to use the solvents immobilized on macroporous solid substrates, such as chromatographic resins, which will make the solvent-recovery processes even simpler; however, there is the risk of introducing diffusional limitations that may broaden the spectrum of reaction byproducts that are formed, thereby reducing the reaction yield and adding to the complexity of the subsequent separations and purification tasks.

We have approached the development of a polymer-based solvent by first designing and synthesizing low molecular weight derivatives of the solvent targeted for replacement. This allows for evaluation of the replacement solvent at an intermediate stage before the potential complications of a polymer-based solvent are introduced.

One specific example of a solvent which is problematic for the pharmaceutical and other industries is the use of tetrahydrofuran (THF) for reactions such as Grignard reactions, and for the reaction of acid chlorides with amines, which are normally carried out under anhydrous conditions. The desired product is often obtained by aqueous precipitation. Since THF is soluble in the water phase it must be recovered by distillation. This leads to problems not only with the recovery of solvent, but also with the loss of antioxidants such as BHT, which are added to arrest the potentially-dangerous formation of peroxides.

Other often-used, but environmentally harmful, solvents include halogenated hydrocarbons (methylene chloride, freons), aromatics (xylenes, toluene, benzene) and ketones (acetone, methyl ethyl ketone, methyl iso-butyl ketone). It is anticipated that concepts developed here for the replacement of THF will also be applicable to other solvents, such as methylene chloride.

PART I

Low Molecular Weight Replacement Solvents:

Design, Synthesis, Physical Characterization, Structural Characterization, and Use as Replacement Solvents for Tetrahydrofuran

Chapter 1

Synthesis of Low Molecular Weight Replacement Solvents for Tetrahydrofuran

1.1 Introduction

We have synthesized and characterized a range of low molecular weight THF replacement solvents having both low volatility and minimal water solubility. Information gained from a study of reactions employing these solvents was then used in the design and synthesis of polymeric solvents having the desired properties. These alternative solvents are derivatives of currently used solvents that are altered in such a way that they are both soluble in a nonpolar environment such as hexanes *and* able to alter the solvent environment of the nonpolar solvent enough so that particular pharmaceutical reactions can be carried out in this new solvent system.

Criteria to be kept in mind when developing a new solvent system for use in chemical reactions are a maximum working range between melting and boiling point, chemical and thermal stability in this temperature range, good solubility of reactants and products (or sometimes insolubility of the products), compatibility with the analytical methods employed, and a high degree of purity.[1] When a solvent is used for technical purposes, additional requirements must often be met. These may include price, flammability (ignition point, flash point), explosiveness, viscosity, miscibility (e.g. blending with extenders or diluents), toxicity, corrosive action, and feasibility of recycling.

We began this work by choosing as a model system the ethereal solvent tetrahydrofuran (THF) which is of particular practical interest in the pharmaceutical industry and a ubiquitous organic solvent used in many processes such as Grignard reactions, the reaction of acid chlorides with amines, catalytic hydrogenation, metal hydride reductions, Diels-Alder cycloadditions, Wittig reactions, and Aldol reactions. While THF only poses a moderate health hazard, the fact that it is water soluble leads to problems with the recovery of the solvent which is lost to the water phase during work-up of the reaction product. Figure 1 is a T-xy diagram[2] for THF and water which shows the minimum boiling azeotrope which forms at 337 K. At the azeotrope, THF is still only 84% pure and thus an entrainer or some other means of breaking the azeotrope is necessary to purify it further. To even reach the azeotrope requires many trays due to the very shallow slope of the phase diagram. Thus, separation of THF from water is a costly, energy intensive process. Developing a replacement solvent for THF is of both economic and environmental concern. Thus, in the design of replacement solvents, we should consider the ultimate fate of the solvent in the entire process scheme. It is desirable to design a solvent which is not lost to air emissions or water discharge streams and can be easily separated from the process streams and regenerated for re-use.

Other problems associated with THF include its extreme flammability (flash point is -14 °C) and also the potential for formation of peroxides. It would be desirable if possible, to also rid THF of these unwanted characteristics. Currently, BHT is added to arrest the formation of peroxides in THF and other ethereal solvents and could be added to our replacement solvents as well if an ether-containing solvent is used. Ideally, we would be able to incorporate a peroxide-preventing moiety into the replacement solvent itself so that it would not be lost and have to be added again for re-use of the solvent, but this has not been investigated here.

In particular we studied n-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers, shown in Figure 2, as model replacement solvents for THF.

n-alkyl tetrahydrofurfuryl ether n-alkyl tetrahydro-3-furan methanol ether

Figure 2. N-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers, R=butyl, hexyl, or octyl.

The ether linkage is chosen because it is highly flexible which allows for freedom of movement of the THF moiety. This is crucial because while ether-containing solvents such as diethyl ether and THF work well in these types of reactions, methyl t-butyl ether (MTBE) which has an ether linkage sterically hindered by a t-butyl group does not work well. This is discussed further in Chapter 2 where the preformance of MTBE is compared to our THF replacement solvents. By comparing the relative success of the n-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers as THF replacement solvents we can also determine if the position of attachment of the alkyl chain is crucial to solvent performance. The length of the alkyl chain was not significant in the solvent performance, but is significant in terms of water solubility and volatility and therefore separation of the product and solvent regeneration.

1.2 Materials and Methods for Synthesis

All chemicals were received from Aldrich unless otherwise noted. When synthetic procedures required the use of a dry solvent it was taken either from the stills (dried over sodium benzophenone) or from an Aldrich sure-seal® bottle.

1.2.1 Synthesis of n-alkyl tetrahydrofurfuryl ethers

Several different methods for the synthesis of alkyl tetrahydrofurfuryl ethers have been cited in the literature[3] and in U.S. patents. They have been patented for a variety of uses including absorption refrigeration,[4] crease-proofing of cellulosic fabrics,[5] various detergent compositions,[6] and as modifiers in the polymerization of conjugated dienes.[7]

N-butyl tetrahydrofurfuryl ether was synthesized according to the reaction scheme given in Figure 3. The tetrahydrofurfuryl alcohol (THFA) was activated with NaOH pellets by refluxing at 150 °C. The mixture was cooled to 90-110 °C before dropwise addition of 1-chlorobutane. After addition was complete, the mixture was allowed to reflux an additional 2-3 hours until completion of the reaction; it was then filtered to remove the NaCl which was formed as a byproduct. The filtrate was washed with 100 mL of diethyl ether and water was added for separation of the product in a separatory funnel. Several small volume washings with water and then brine produced a light yellow product which became clear after removal of the diethyl ether. The ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) NMR spectra are consistent with the literature values for this compound. This synthetic procedure yielded the desired product in high yield (85-95%) as well as high purity with an easy work-up of washing twice with water and then with brine. It is an important method in light of possible industrial application because it has been scaled up to kilogram quantities.[8] The largest scale that this solvent was made on in the lab was tetrahydrofurfuryl alcohol (4.0 mole, 388 mL), sodium hydroxide (1.5 mole, 60 g), and chlorobutane (1.0 mole, 104.4 mL).

A similar procedure was followed to synthesize n-octyl tetrahydrofurfuryl ether on the same scale. In this case, however, it was crucial that sufficient NaOH be added to ensure that excess THFA was activated relative to the amount of 1-chlorooctane added, to drive the reaction to completion as it was difficult to remove any unreacted 1-chlorooctane from the product. N-hexyl tetrahydrofurfuryl ether has been synthesized by the same method. The general synthetic scheme is shown in Figure 3. The ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) NMR spectra are consistent with the literature values for this compound.

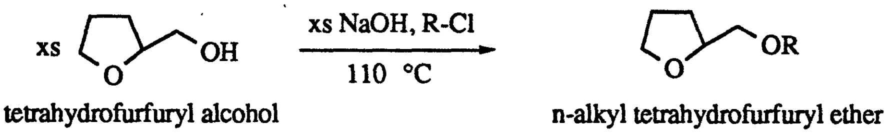

Figure 3. Synthesis of n-alkyl tetrahydrofurfuryl ethers, R=butyl, hexyl, or octyl.

Significant amounts of n-butyl and n-hexyl tetrahydrofurfuryl ethers are lost to the water phase during work-up resulting in lower yields for these ethers (closer to 85%). The yield for the n-octyl tetrahydrofurfuryl ether was generally 95%.

1.2.2 Synthesis of n-alkyl tetrahydro-3-furan methanol ethers

The n-alkyl tetrahydro-3-furan methanol ethers are not as widely mentioned in the literature as the n-alkyl tetrahydrofurfuryl ethers. This is probably due to the much greater expense of the 3-position alcohol starting material. Whereas the 2-position alcohol is made from commonly available furfural, the three-position alcohol is made from β-furfural which is very difficult and expensive to synthesize. Furthermore, it was not possible to synthesize the n-alkyl tetrahydro-3-furan methanol ethers using sodium hydroxide. The difference in location of the ether linkage on the THF moiety necessitated the use of a stronger base than NaOH. Owing to the greater expense of the alcohol starting material, THF was used as the solvent in this case instead of the excess alcohol used for the two-position ethers. In addition, a more reactive (and expensive) alkyl bromide was also required to form the ether linkage with this alcohol starting material. Once the alcohol was activated with the base, the alkyl bromide was added dropwise and the resulting solution was allowed to reflux at 70 °C until the reaction was complete (several hours). The product was washed and separated using diethyl ether and water after quenching with saturated ammonium chloride. It was then washed twice with water and then brine and produced a light yellow product which became clear after removal of the diethyl ether. The n-butyl, n-hexyl and n-octyl tetrahydro-3-furan methane ethers were synthesized by the same method, shown in Figure 4. The ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) NMR spectra are consistent with the literature values for this compound. A typical scale for their synthesis was the following, tetrahydro-3-furan methane ether (0.69 mole, 66.4 mL), sodium hydride (0.76 mole, 18.22 g), 1-bromooctane (0.69 mole, 119.45 mL).

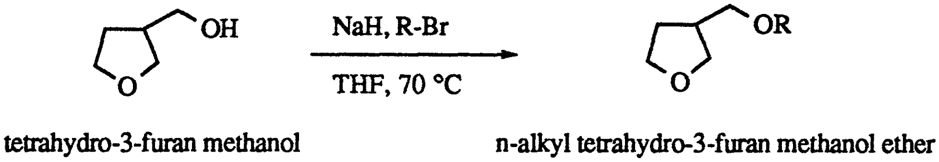

Figure 4. Synthesis of n-alkyl tetrahydro-3-furan methane ethers, R=butyl, hexyl, or octyl.

1.2.3 Purification of n-alkyl tetrahydrofurfuryl ethers and n-alkyl tetrahydro-3-furan methane ethers for use under anhydrous reaction conditions

Both the two and three position ethers needed to be distilled from sodium benzophenone ketyl in order to render them anhydrous for use in model reactions. This procedure is used routinely to dry THF when used on a lab scale, but required several modifications for our replacement solvents. It did not seem safe or practical to distill the octyl solvents from sodium benzophenone continuously because of their significantly higher boiling points. Instead, the solvent was dried over sodium by adding a 60% dispersion of sodium in paraffin available from Aldrich and warming it gently to 50 °C which was just sufficient to melt the paraffin and release the sodium. After several hours or overnight, benzophenone was added to test for the presence of water. Once the dark purple sodium benzophenone ketyl complex was formed indicating that there was no water present, the solvent was distilled under vacuum at about 70 °C into a Schlenk flask and taken from this flask for use in model reactions. In some cases, the solvent was transferred to Aldrich sure-seal® bottles in a glove box so that it could be handled more easily.

1.3 Summary

Facile synthetic methods have been developed for the n-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers. While the cost of their synthesis is high relative to THF, it is not so high that their potential benefit may not outweigh the additional cost to synthesize them. Since sodium hydroxide may be used to the synthesize the n-alkyl tetrahydrofurfuryl ethers, they are more attractive for industrial use. In addition, the n-alkyl tetrahydrofurfuryl ethers were fairly simple to purify and dry as compared to conventional solvents.

Chapter 1: List of Figures

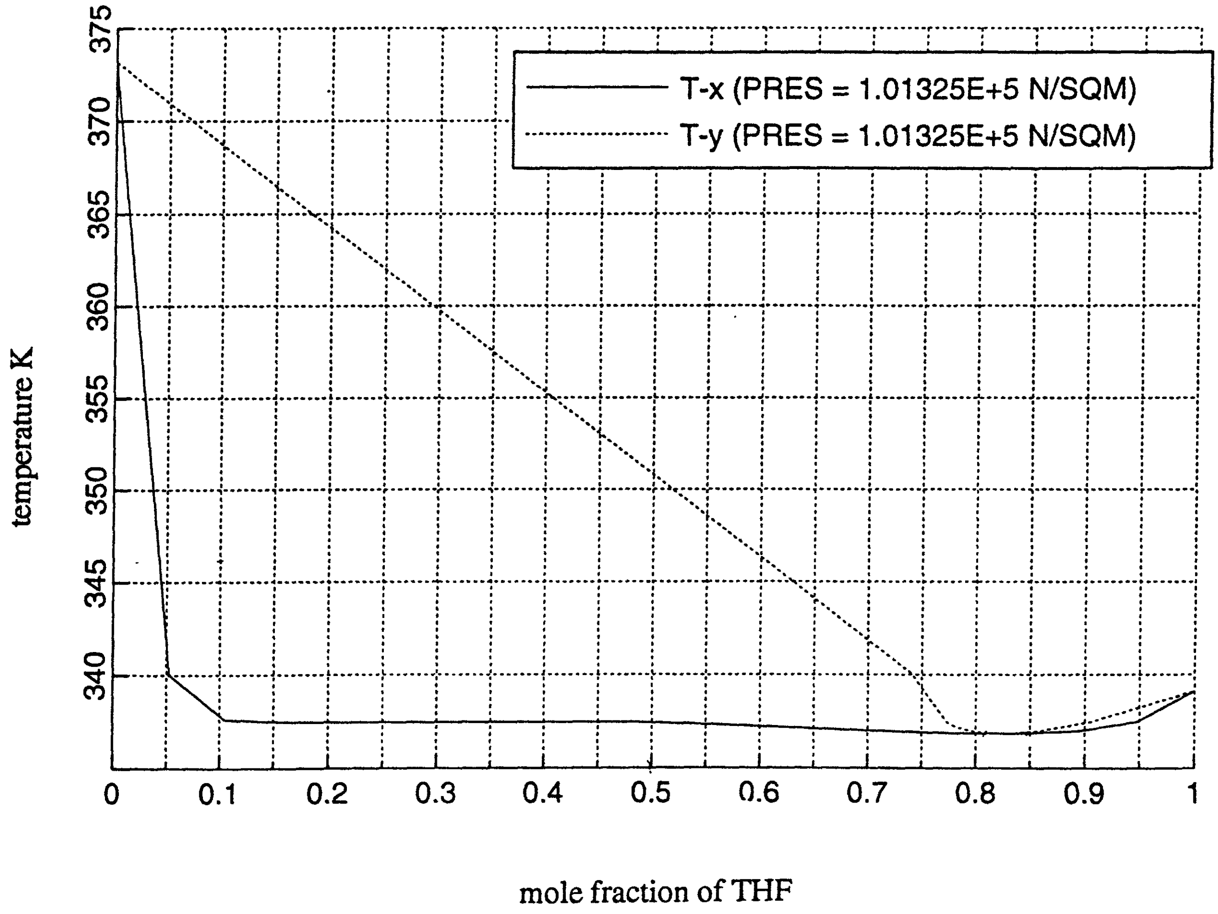

Figure 1. T-xy diagram for THF and water calculated on ASPEN using Non-Random Two Liquid (NRTL) phase theory.

Chapter 2

Testing of Tetrahydrofuran Replacement Solvents in Model Reactions Pertinent to the Pharmaceutical Industry

2.1 Introduction

The most important test for replacement solvents is their use in reactions which are normally run in conventional solvents. In the case of THF, which is a ubiquitous organic solvent, we are interested in studying Grignard reactions. This chapter shows the results of substituting the replacement solvent for THF in several types of organic reactions and the development of experiments and analyses used to test the success of the replacement solvents as compared to THF.

A suitable model pharmaceutical reaction has been identified for use in the evaluation of these novel solvent systems. This model reaction has been studied in detail because it was amenable to experimental evaluation and it is currently of interest to the scientific community.[1] Furthermore, researchers at Merck have been unable to replace THF with other solvents for this reaction whereas they have been able to do this for other reactions in which THF was routinely used.[2] In other words, the reaction has been shown to have some degree of specificity for THF.

Several other examples of THF replacement are also given to demonstrate the potential widespread applicability of the replacement solvents developed in this thesis. The last example illustrates the use of the replacement solvents n-octyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers in a sequence of acyl transfer reactions including a step which is normally run in methylene chloride and then finally the allylation step which we have focused on for kinetics studies of the replacement solvents as compared to THF. It has been shown that the n-octyl tetrahydrofurfuryl ether can be re-used in each step where THF is used because unlike THF, it is not lost in any of the aqueous work-up steps. Thus, less solvent is used to begin with, and, in addition, solvent recovery from the water phase is minimized.

2.2 Grignard reaction

Organomagnesium halides, which were discovered by chemist Victor Grignard in 1900 and are now called Grignard reagents, are very useful in organic chemistry. Grignard reagents are made in ether solvents and then used in the ether solution in which they were made without first isolating them. It is known that the Grignard reagents exist in solution in an equilibrium between the alkylmagnesium halide and dialkylmagnesium. In addition, the Grignard reagents form complexes with ether solvents as shown in Figure 1.

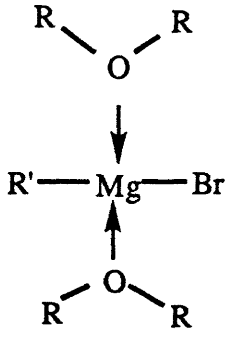

Figure 1. Complex formation of molecules of ether with a Grignard reagent.

Complex formation with molecules of ether is important for the formation and stability of Grignard reagents. Thus, the ether moiety of solvents such as THF and diethyl ether is crucial both for reactions used to form the Grignard reagents themselves and for the use of the Grignard reagents in other reactions. This is due to the ability of the oxygen atom to interact with the magnesium metal in the Grignard reagent.

Grignard reagents are very strong bases and powerful nucleophiles. Reactions of Grignard reagents with carbonyl compounds are used to form primary, secondary and tertiary alcohols by nucleophilic addition to a carbon-oxygen double bond. The specific reaction that was tested is shown in Figure 2.

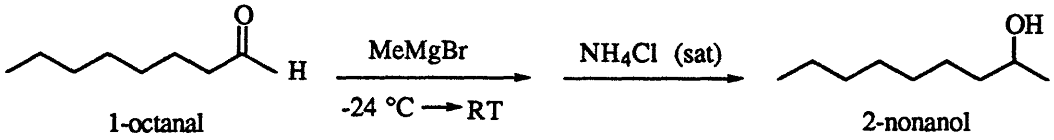

Figure 2. Synthesis of 2-nonanol from 1-octanal using methylmagnesium bromide.

Here, methyl magnesium bromide and octanal are used to form 2-nonanol. The octanal (10 mmole, 1.56 mL) is purified first by passing it through an alumina plug to remove residual water, ICN alumina of activity grade I was used, and then distilling to purify. 3.0 M methylmagnesium bromide (11 mmole, 3.70 mL) was added dropwise to a solution of anhydrous THF (10 mL) at -24 °C. A precipitate formed immediately and after several minutes the slurry was allowed to warm to room temperature. The reaction was quenched with saturated ammonium chloride. The organic layer was extracted with ether in a separatory funnel, washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*.

N-octyl tetrahydrofurfuryl ether was tested in this model reaction using the same procedure as for THF. It was interesting to note that the n-octyl tetrahydrofurfuryl ether solubilized the salt by-product better than did the THF. The ether reaction mixture in which n-octyl tetrahydrofurfuryl was employed was noticeably more viscous, but this did not appear to have an effect on the reaction rate. Salt by-product was formed immediately, and after several minutes the reaction was allowed to warm to room temperature and then quenched with saturated ammonium chloride. As before, the organic layer was extracted with ether, separated in a separatory funnel, washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. In this case, however, because the n-octyl tetrahydrofurfuryl ether was not lost to the water phase during extraction or evaporated off, the 2-nonanol product was isolated as a mixture with the n-octyl tetrahydrofurfuryl ether. For illustrative purposes, the 2-nonanol was removed by distillation using a variable pressure pump (3 mm Hg, 110 °C) and its structure verified by NMR. In this case, separation of the 2-nonanol by distillation was easy because it is not miscible with the n-octyl tetrahydrofurfuryl ether and has a considerably lower boiling point. This would not always be the case.

While it was encouraging that the n-octyl tetrahydrofurfuryl ether could be directly replaced for THF in a Grignard reaction, it was necessary to find a more rigorous test of the replacement solvent for a number of reasons. First, the chemical similarity between the octanal staring material and the n-octyl tetrahydrofurfuryl ether solvent does not provide proof that our solvents would work on a more complicated starting material such as a heterocyclic molecule. Also, it was not possible to determine any difference in the reaction kinetics because the reaction occurred so quickly. It would be preferable to have a slower reaction rate so any differences in reaction rate could be detailed.

2.3 Allylation of an Acetonide

To demonstrate the efficacy and utility of the replacement solvents, several reactions relevant to the pharmaceutical industry were tested. It is known that hydroxy ethylene dipeptide isosteres which contain the 1S,2R-1-amino-2-hydroxy-indanamide (AHI) moiety can be potent inhibitors of HIV-1 protease.[3] Thus, a series of reactions toward the synthesis of the Merck HIV-1 protease inhibitor L-723,524, were investigated. Its structure is shown in Figure 3.

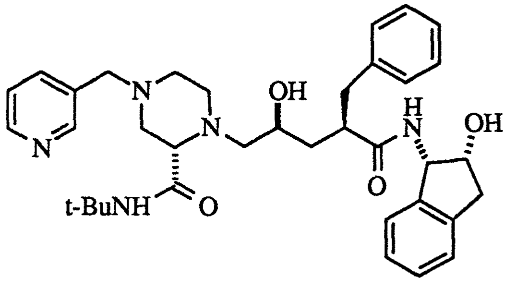

Figure 3. The orally-active HIV-1 protease inhibitor, Merck's L-723,524, now called Indinavir®.

The replacement of THF with n-octyl tetrahydrofurfuryl ether and n-octyl tetrahydro-3-furan methanol ether in a series of reactions is discussed in section 2.4. This section focuses on one specific reaction in the series in order to compare the kinetics of the reaction in THF and the replacement solvents. The reaction is given in figure 4. The acetonide starting material was made from (1S, 2R)-amino alcohol (Sepracor, Marlborough, MA) according to supplemental material in an article that was published by Merck researchers.[3] Currently, economical production of this compound is being investigated by Merck. Because therapeutic doses of this drug are in gram quantities and the synthesis itself is very difficult due to the many chiral centers in the molecule, it has been a huge challenge for drug companies to efficiently synthesize up to one million kilograms per year.[1]

Furthermore, Merck researchers have found that THF is the only solvent in which this specific step of the reaction can be run.[2] Thus, because the reaction is very sensitive to the reaction medium, it was chosen as a model reaction in which to test our replacement solvents. Reaction kinetics using different solvents and reaction conditions were evaluated by conventional methods, primarily high pressure liquid chromatography (HPLC).

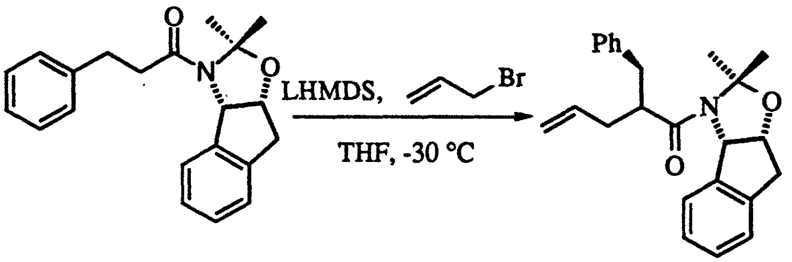

Figure 4. Allylation reaction used to study reaction kinetics of THF replacement solvents.

2.3.1 Materials and Methods: Allylation reaction and HPLC analysis with THF and modification for replacement solvents

The allylation reaction was run using the following ratio of reactants unless noted otherwise, 1.0 acetonide:1.03 allyl bromide:1.1 lithium hexamethyldisilazide(LHMDS). In a dry, three-neck, 50 mL round bottom flask, was placed 5.0 mL of solvent. To this was added the hexamethyldisilazane (HMDS) and the solution was cooled to 0 °C using an ice bath before slowly adding the n-butyl lithium (1.6M in hexanes) to the reaction vessel. The reaction mixture was allowed to stir for one-half hour and then used in the allylation step. For the allylation step, the acetonide starting material was placed in a dry, 50 mL round bottom flask. 5.0 mL of solvent and the allyl bromide were added and the reaction vessel was cooled to and maintained at -10 °C using a NESLAB cryocool 65II. The LHMDS was added over five minutes (later for the kinetics experiments it was added all at once) and an aliquot taken as soon as the addition was complete. Reaction aliquots were quenched with a solution of citric acid in THF at a concentration of 4.74 g/ 24 mL. In the case of the replacement solvents, the citric acid quench was prepared in methanol in order to totally eliminate THF from the process and to ensure that the reaction was never exposed to another ethereal solvent. The reaction was monitored using a Hewlett Packard 1090 LC equipped with a UV/Vis detector and interfaced with a Hewlett Packard 3396 Series II Integrator. The aliquots were diluted to a concentration of about 250 ppm in a 40:60 mixture of 0.01 ammonium phosphate: acetonitrile. This sample diluent was not compatible with the low molecular replacement solvents, especially the n-octyl tetrahydrofurfuryl and tetrahydro-3-furan methane ethers, with which it formed two distinct phases because they are not miscible with water. For these samples methanol was used as a diluent. A C-8, 3 micron(120 Å), 150x4.6 mm column was obtained from YMC (Wilmington, NC) for the separation of the major and minor products formed in the allylation reaction. The mobile phase consisted of 0.01M ammonium phosphate, monobasic (A) and methanol (B) run on a gradient as follows:

(1) For the first fifteen minutes, 35:65, A:B, (2) Switch to 25:75 A:B over five minutes, (3) Hold for fifteen minutes, (4) Switch back to 35:65 A:B over five minutes.

Additional HPLC parameters included the following: flow rate = 1 ml/minute, wavelength=254 nm, temperature = ambient, and injection volume = 10 μl.

2.3.2 Reaction monitoring of allylation reaction for THF and replacement solvents

Reaction kinetics and product profiles were monitored by HPLC to measure the success of the replacement solvents as reaction media. Initial studies showed that the reactions employing n-octyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers gave similar reaction kinetics and product profiles as THF when replaced one to one by volume. These results were obtained on a visit to Merck in Rahway, NJ. Because neat LHMDS was not available at Merck, a solution of LHMDS in THF was used in these reactions. Thus, the final reaction mixture contained 10% THF. In all future testing, LHMDS was made from n-butyl lithium and HMDS in the replacement solvent so that no THF was used and there was complete solvent replacement. In this manner, all of the n-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers were tested in the allylation reaction. The n-octyl tetrahydrofurfuryl ether consistently performed better than the other solvents in these experiments. When it was used the reaction always went to completion whereas with the other solvents 5-10% of the starting material was left unreacted. We feel that some minor impurity present in the n-butyl and n-hexyl tetrahydrofurfuryl ethers and the n-octyl tetrahydro-3-furan methane ether caused these reactions to not go to completion. Thus, future studies were conducted with the n-octyl tetrahydrofurfuryl ether which not only gave the best results, but is relatively simple and inexpensive to make in large quantities. Studies using the n-octyl tetrahydrofurfuryl ether showed completion of the allylation reaction when the replacement solvent was diluted 1:1 by volume with heptane. Figure 5 shows completion of the reaction with as little as 10% (v/v) of replacement solvent in heptane. These experiments were conducted at -15 °C. 100% heptane (or 0% replacement solvent) is shown as a reference. Little or no reaction occurs in pure heptane. Results for methyl t-butyl ether (MTBE), one of the potential THF replacement solvents that Merck investigated, is shown in figure 6 compared to THF, n-octyl tetrahydrofurfuryl ether, and heptane. Like heptane, it shows the desired reaction only proceeds to a minor extent. This is probably because the ether linkage is sterically hindered by the bulky t-butyl group.

THF can also be diluted with heptane, but it is not as effective as the n-octyl tetrahydrofurfuryl ether when diluted to concentrations below 50% by volume of THF in heptane. Figure 7 shows results of the allylation reaction using THF diluted to 50% and 10% by volume with heptane as compared to solutions of 50% and 10% n-octyl tetrahydrofurfuryl ether diluted with heptane. Density, surface tension, and polarity measurements of the solvent mixtures indicate a different mixing behavior for THF and heptane and n-octyl tetrahydrofurfuryl ether and heptane which may account for this. The mixing behavior of these solvents is discussed in Chapter 3.

2.3.3 Kinetics of allylation reaction for THF and n-octyl tetrahydrofurfuryl ether

The allylation reaction was run under pseudo-first order conditions to see if the kinetics, and therefore the mechanism, are any different with the replacement solvents. In a classic article by Bergman and Wax[4] which reported on alkyl migration processes involving cyclopentadienyltricarbonyl(alkyl)molybdenum in various methyl-substituted THF derivatives, it was observed that the kinetic order of the reaction was highly dependent on the reaction medium. Changes in kinetic order were not observed, however, for the allylation reaction in our THF replacement solvents. Initial kinetics studies were run in the following manner.

The overall reaction is A + B + C --------> P, where A=acetonide, B=allyl bromide, C=LHMDS, and P=allylated acetonide. LHMDS is made separately and then added to the reaction mixture containing acetonide and an excess of allyl bromide. It was assumed that the deprotonation of the acetonide would be fast relative to the allylation step, so the reaction was not run with a large excess of base. Figure 8 shows a comparison of the solvent effects on the kinetics of the allylation reaction run at -30 °C in THF and n-octyl tetrahydrofurfuryl ether with an excess of allyl bromide(10 eq). Both reactions show similar kinetic behavior, although it can be inferred that the assumption that the deprotonation step is fast relative to the allylation step was not valid. There are clearly two rates present in the graphs of percent starting material (log scale) vs. time. A comparison of the allylation reaction run with different excesses of allyl bromide is shown in Figure 9. These experiments show the dependence of the reaction on the concentration of the allyl bromide. Since it would not be feasible experimentally to run with a large excess of the LHMDS (decomposition of the starting material occurs), the experiment was altered as follows. Instead of having the allyl bromide already present in the reaction mixture when the LHMDS is added, the LHMDS was added first in an attempt to allow for the deprotonation of the acetonide to occur before adding the allyl bromide and monitoring the kinetics. Thus, we have the following rate law:

$$-d[A]/dt=k[A]^n[B] \qquad (1)$$

where, [A] is the deprotonated acetonide concentration, [B] the allyl bromide concentration. Since we used a large excess of B (i.e. 10 fold), [B] is essentially constant giving the following rate law from which we can determine n:

$$d[A]/dt=k_{obs}[A]^n, \text{ where } k_{obs}=k[B] \qquad (2)$$

The latter portion (after deprotonation) of the log-linear of [A] vs. time for the allylation reaction, run in THF at -30 °C and collected over three half-lives, yields a straight line implying that the reaction is first order in A (n=1). Results for THF at -15 °C, -30 °C and -45 °C are shown in Figure 10. By running the reaction at different temperatures, the activation energy (E_a) of the reaction can be obtained from an Arrhenius plot where,

$$k=Ae^{-E_a/RT} \tag{3}$$

and the slope of a plot of lnk vs. 1/T yields the activation energy. These experiments were also completed for 100%, 50%, 25% and 10% n-octyl tetrahydrofurfuryl ether diluted with heptane, shown in figure 11. The activation energy is defined as the minimum energy that reactants must have in order to form products. As expected, figure 11 shows that the activation energy is the same, within experimental error, regardless of the solvent or solvent mixture that the reaction is run in. Thus, the exponential factor in equation 3 represents the fraction of collisions that have enough energy to lead to reaction. The pre-exponential factor, A, is a measure of the rate at which collisions occur irrespective of their energy. In a gas phase reaction, for instance, it is proportional to the collision density in the gas. In our experiments, A is found to be directly proportional to the solvent dilution at the experimental temperatures investigated. Interpretation of the Arrhenius parameters E_a, and A is, however, much more difficult in solution than in a gas because the encounter pair is surrounded by solvent and thus the encounters between reactants in solution occur in a very different way from those in gases. We have found the E_a to be approximately the same in each case for the solvents tested. The average value of E_a obtained was 6.3 kJ/mole.

Determination of further kinetic information would require a detailed analysis of the exact mechanism of this particular reaction.[5,6] It appears to be a case of two consecutive first order reactions, namely enolate formation followed be allylation. Originally, we assumed the enolation step to be fast relative to the allylation step, but this was not the case. In fact, even after allowing the LHMDS to react with the acetonide for at least thirty minutes before addition of the allyl bromide, we still see evidence of a very fast initial rate, followed by the relatively slower rate of the allylation step. This was a surprise because in most cases the deprotonation step is relatively very fast to other types of reactions and by using an excess of one of the reagents it is easy to access pseudo-first order kinetics. Because we have been unable to eliminate evidence of the enolate formation from the allylation step, it may in fact exist in an equilibrium. In this case, the reaction would follow Michaelis-Menton type kinetics and analysis of the kinetics would be very labor intensive using the experimental methods that are available to us for this particular reaction sequence. Varying the concentration of the LHMDS used, for instance, is not viable experimentally because it leads to decomposition of the starting materials.

2.4 Synthesis of Acetonide Starting Material with Replacement Solvents (acyl transfer reactions) Directly Followed by Allylation Step

The reaction sequence that was investigated is shown in Figure 12. First, hydrocinnamic acid is dissolved in dry THF and cooled to 0 °C. Triethylamine is then added followed by slow addition of pivaloyl chloride. The mixture is then stirred for one hour at 0 °C. The amino-alcohol is slurried in THF and added to the 0 °C reaction mixture over a one hour period and the entire mixture is warmed to 25 °C and allowed to stir for 2.5 hours. According to the published synthesis of this compound,[3,7] THF is used in the first step of this particular sequence and the reaction is partitioned with water and ethyl acetate. After re-extraction of the aqueous phase with ethyl acetate, the combined organic layers were washed with water, aqueous sodium bicarbonate, saturated sodium sulfate, and then dried over magnesium sulfate. Then the intermediate is concentrated *in vacuo*. In the usual case then, all solvent is removed before proceeding to the next step. Any THF not lost to the water phase has thus been removed under vacuum before addition of the next solvent. In the case of the n-octyl tetrahydrofurfuryl ether replacement solvent, loss to the water phase during separation, work-up, or vacuum concentration is very minor. The n-octyl tetrahydrofurfuryl ether can also serve as the extraction solvent instead of ethyl acetate for separation of the intermediate product. In addition, the amino-alcohol starting material was more soluble in the replacement solvent than in the THF.

It has been found that the n-octyl tetrahydrofurfuryl ether solvent also yields successful completion of the next step in the reaction which is normally run in methylene chloride. In addition to avoiding the use of a chlorinated solvent it avoids a costly solvent switch. According to the published synthesis, the crude amide obtained in step one is slurried in methylene chloride at 25 °C. To this suspension is added the 2-methoxy propene followed by the pyridinium *p*-toluene sulfonate. Almost instantly, a pale yellow solution is formed which is stirred for 5 hours at 25 °C. This solution is then poured into saturated aqueous sodium bicarbonate for partitioning and the aqueous phase is extracted with methylene chloride. The combined organic phase is then washed with saturated sodium bicarbonate followed by water and dried over magnesium sulfate. The volatiles are removed *in vacuo* to afford the crude product which is dissolved in THF at 50 °C and cooled to 25 °C. Hexane is added and the stirred slurry is cooled to 0 °C and filtered. The product is washed with cold hexane and dried *in vacuo*. The yields for these reactions are generally somewhat low, about 60-65%. In the case of the replacement solvent, instead of distillation of the methylene chloride and addition of fresh THF to recrystallize the product, the product is already in the n-octyl tetrahydrofurfuryl ether in which it is soluble and can be recrystallized by the addition of hexane. The identity of the recrystallized acetonide was confirmed by elemental analysis (calculated for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36, found: C, 78.71; H, 7.34). This reaction sequence can also be run in n-octyl tetrahydro-3-furan methanol ether with the same results (calculated for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36, found: C, 78.63; H, 7.38). In each case, at least 98.5% of the solvent could be recovered when this reaction scheme was run on a laboratory scale. It is important to note that both reactions can be run in THF, but the THF does not have the advantage of being carried through each step because of its high water solubility.

Also, in the case of the replacement solvent it is not necessary to crystallize and isolate the amide acetonide product. Instead of recrystallization after the second step, LHMDS made in replacement solvent can be added to the reaction mixture after drying it over magnesium sulfate. When the reaction is complete, the reaction mixture is partitioned with saturated aqueous sodium bicarbonate, the aqueous layer is extracted with replacement solvent, and the combined organic layers are washed with saturated aqueous sodium bicarbonate followed by water and drying over magnesium sulfate. Hexane is then added slowly to the reaction mixture and it is placed in a 0 °C freezer for recrystallization of the allylated acetonide product. The product is washed with cold hexane to remove any replacement solvent and then concentrated *in vacuo*. The overall yield of the allylated acetonide product for this three-step process is the same as obtained for THF, about 60-65%. However, the replacement solvent is also recovered. After crystallization of the product and filtration from the solvent and any excess reagents, the solvent is re-distilled in order to retrieve pure solvent. In this manner, approximately 95% of re-usable replacement solvent can be recovered.

2.5 Summary

N-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers were tested as replacement solvents for THF in a model reaction of pertinence to the pharmaceutical industry. No significant differences in performance of the solvents were found with regard to the position of attachment of the alkyl chain or the length of the alkyl chain itself. Thus, because the n-octyl tetrahydrofurfuryl ether was less expensive to synthesize and purify than any of the three position solvents, and it has the added feature of very minimal water solubility, it was used for most of the future solvent replacement testing. It has been shown that n-octyl tetrahydrofurfuryl ether can be used to synthesize the allylated acetonide in a time frame similar to that of THF and also that the allylation reaction goes to completion when a mixture of n-octyl tetrahydrofurfuryl ether:heptane, 10:90, is used. This is a considerable reduction of ethereal solvent. Furthermore, both the n-octyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers can be used instead of THF in the reaction sequence to produce the allylated acetonide from the (1S, 2R)- amino alcohol starting material. In this particular case, it is possible to add hexanes to the reaction mixture and crystallize out the product. It has been demonstrated by elemental analysis and proton NMR that the allylated acetonide product is cleanly separated from the replacement solvent to an acceptable level of purity. It may not always be this simple to separate the solvent from the product because our derivatized solvents have a higher molecular weight than conventionally used solvents. Their higher molecular weight could make separation, by distillation for instance, problematic. Indeed, ease of separation of solvent from product is one of the biggest challenges in developing replacement solvents and is one of the main reasons for investigating a polymer-based solvent.

Thus, in some cases, the low molecular weight replacement solvents, originally intended as only as an intermediate step towards the development of a polymer-based replacement solvent, have themselves proven to be very useful in the replacement of THF.

Chapter 2. List of Figures.

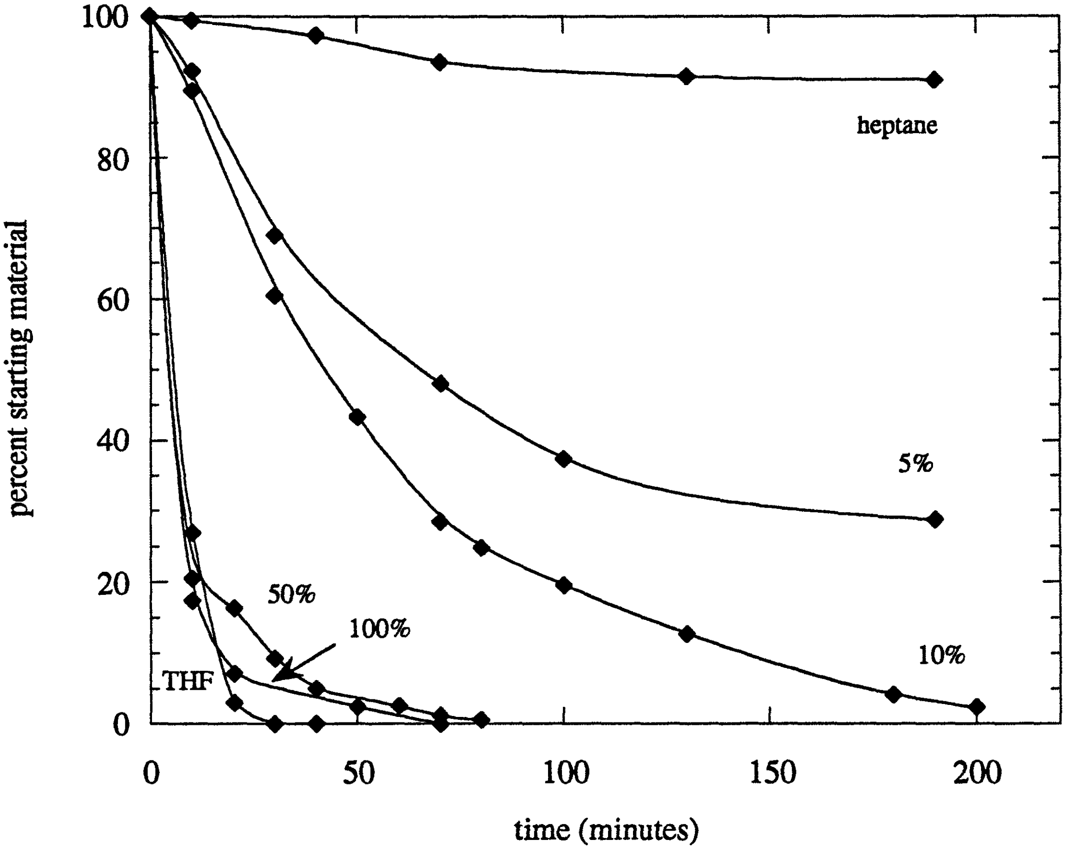

Figure 5. Percent starting material vs. time (minutes) for THF, 100%, 50%, 10%, and 5% n-octyl tetrahydrofurfuryl ether and heptane.

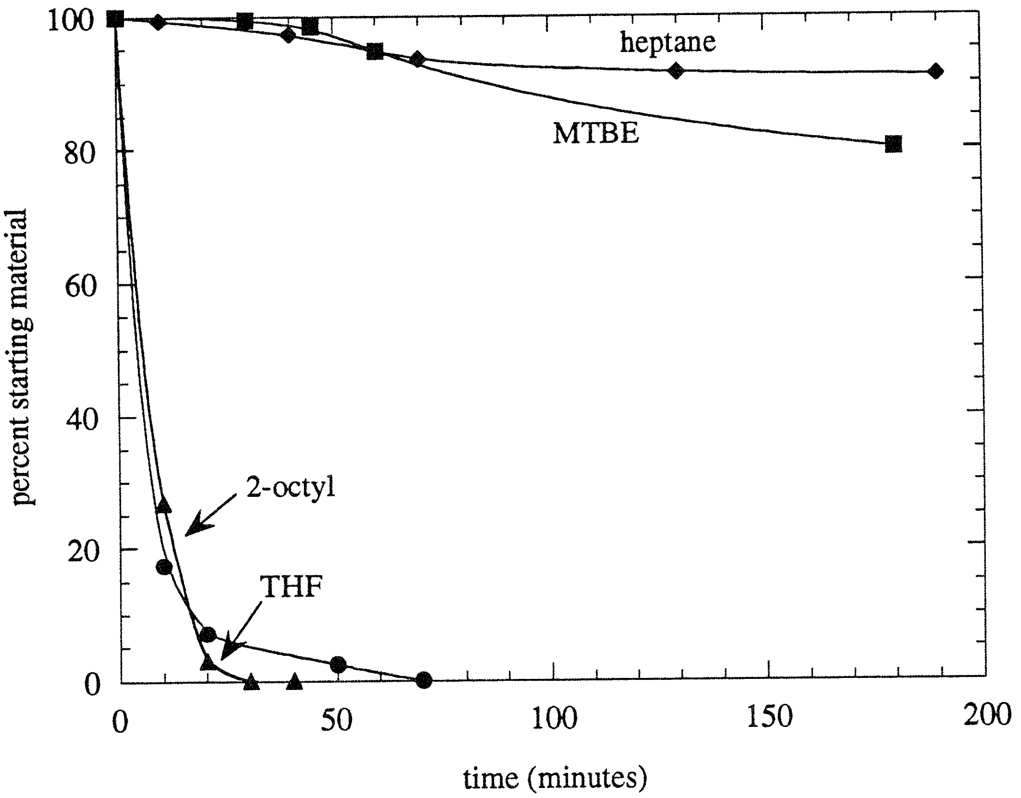

Figure 6. Percent starting material vs. time for THF, n-octyl tetrahydrofurfuryl ether, MTBE, and heptane.

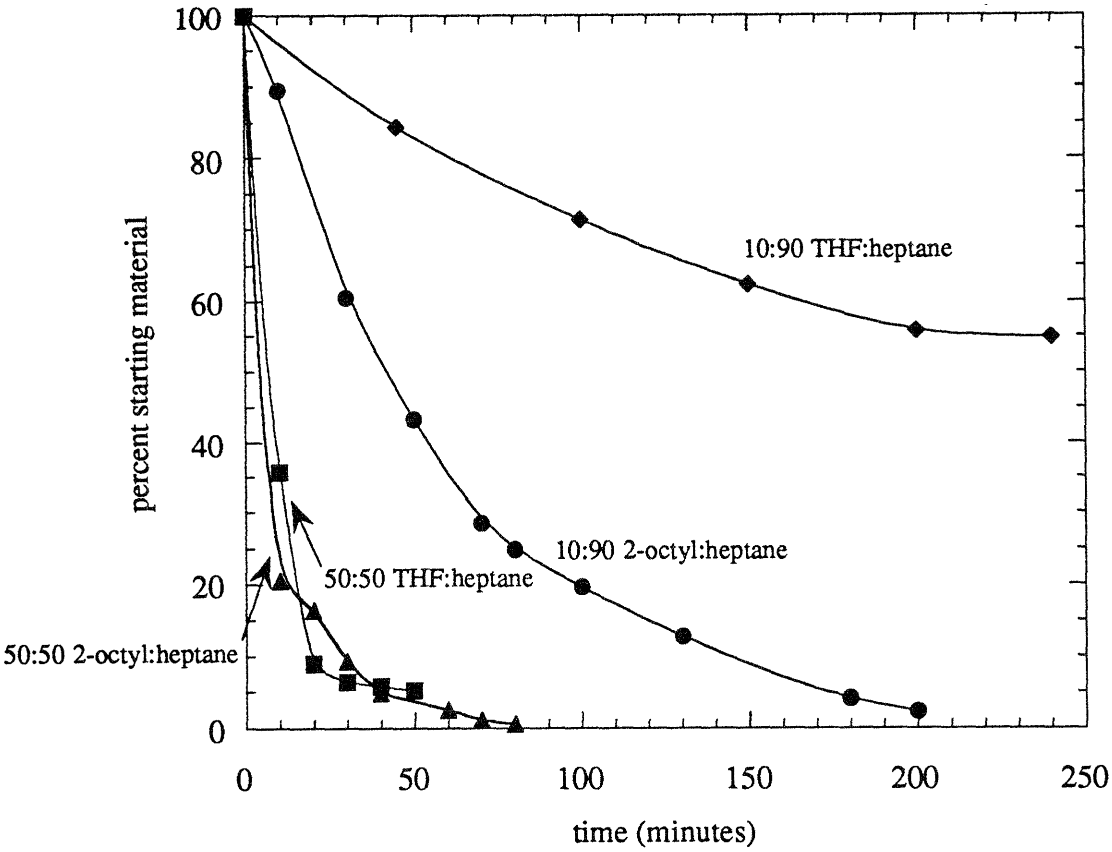

Figure 7. Model reaction results for THF/heptane and n-octyl tetrahydrofurfuryl ether/heptane mixtures.

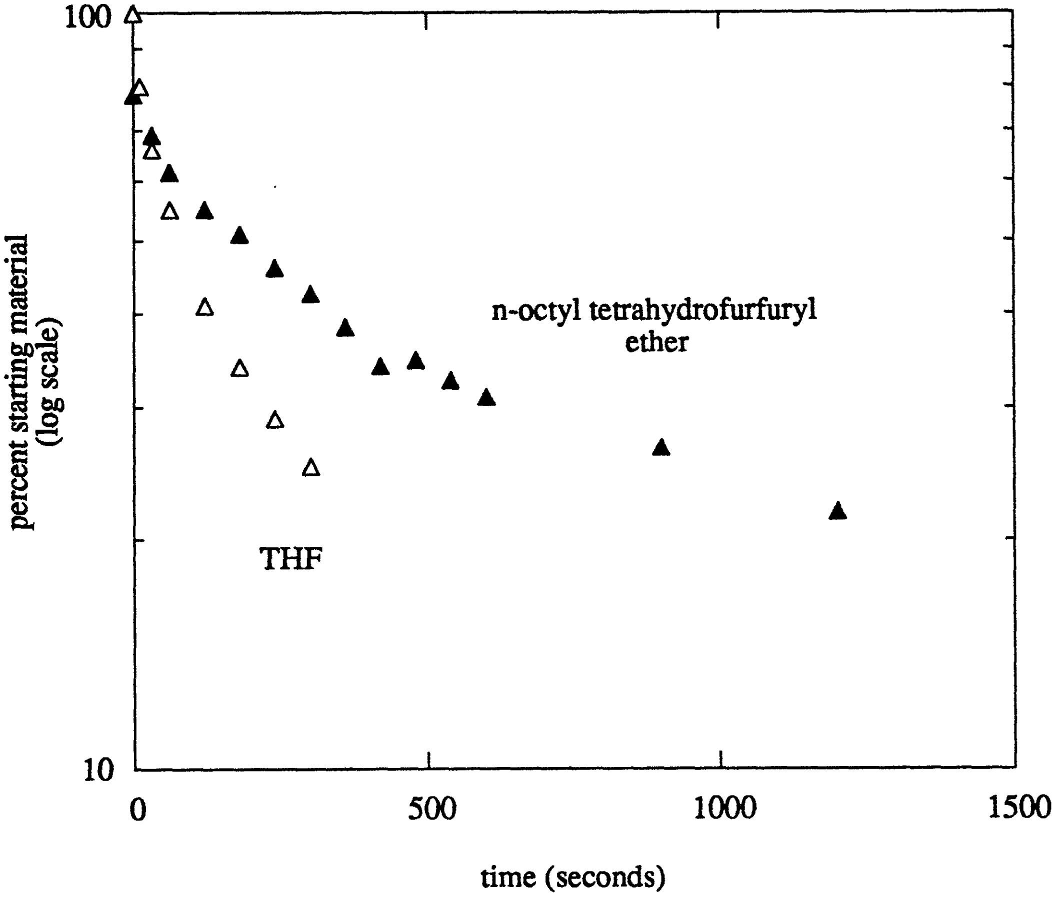

Figure 8. Comparison of model reaction results for THF and n-octyl tetrahydrofurfuryl ether at T=-30 °C and with an excess of allyl bromide (10 eq).

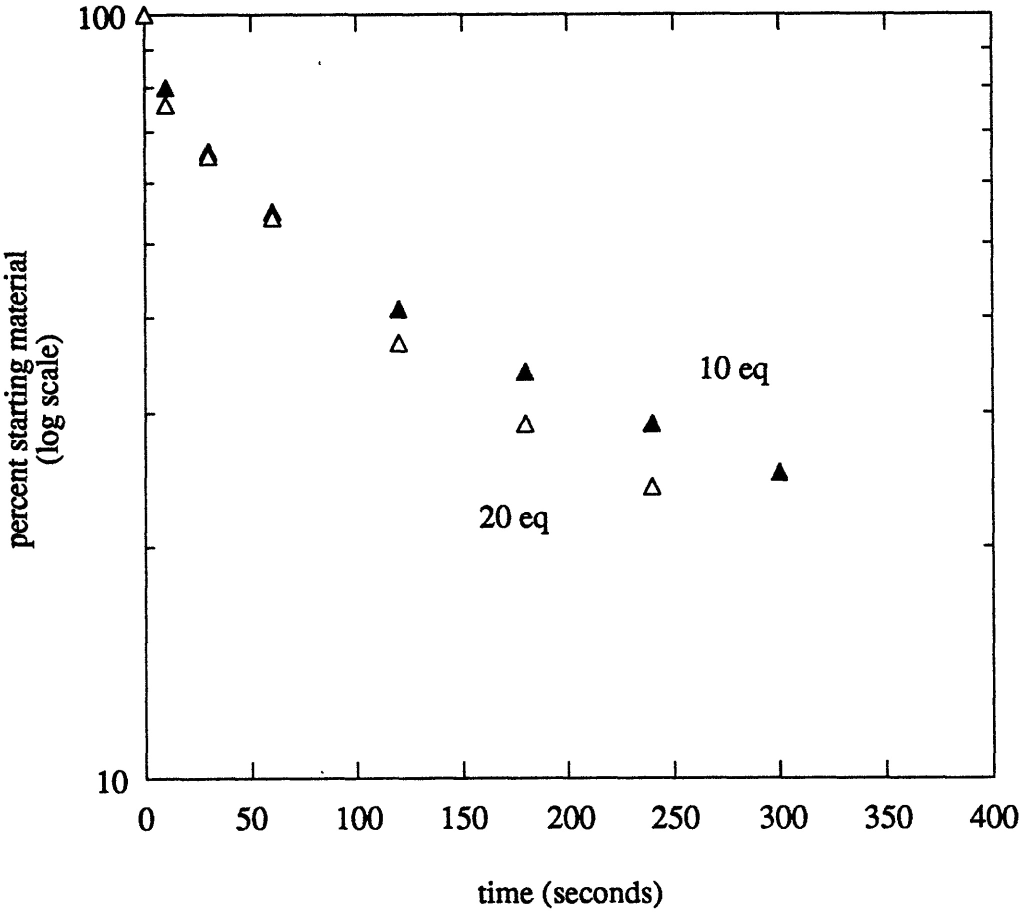

Figure 9. Model reaction results for THF with 10 and 20 equivalent excesses of allyl bromide.

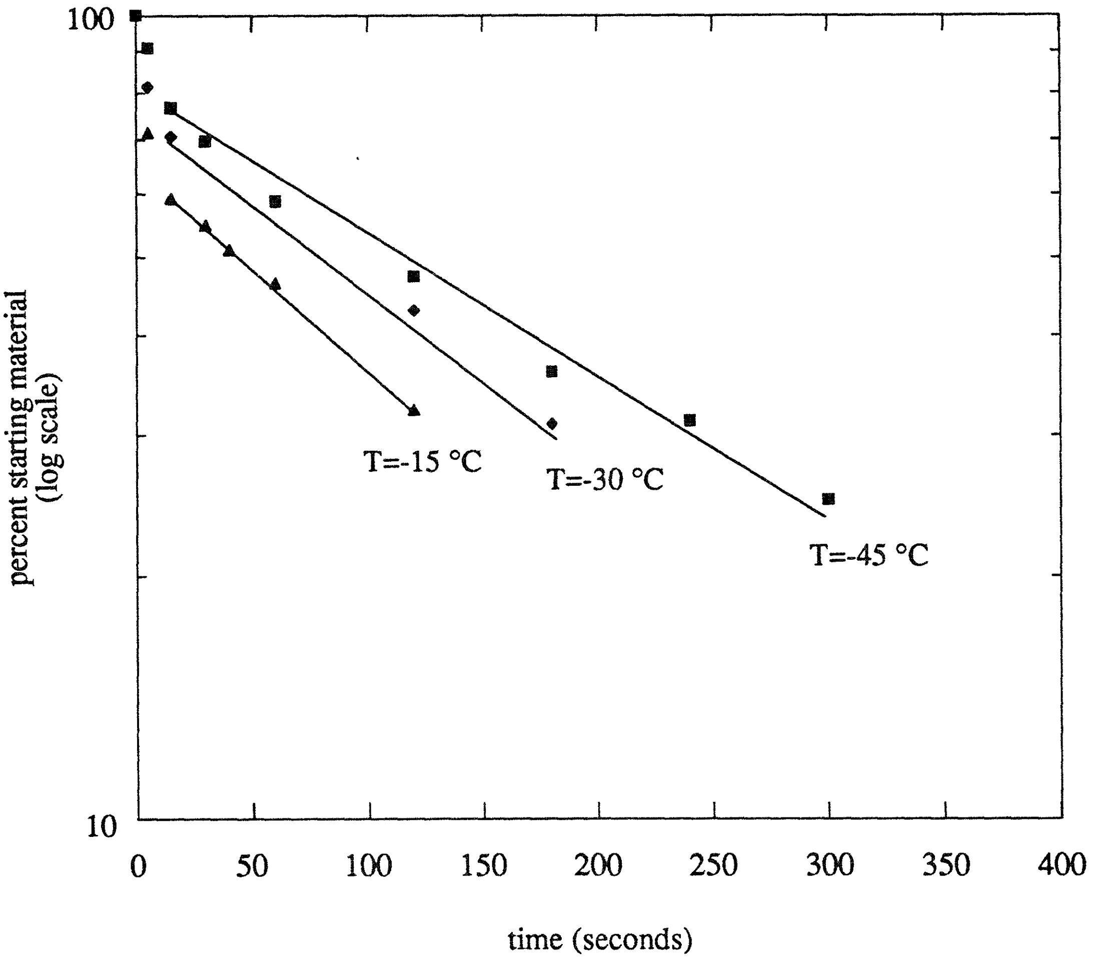

Figure 10. Influence of temperature on model reaction run in THF, percent starting material (log scale) vs. time (seconds).

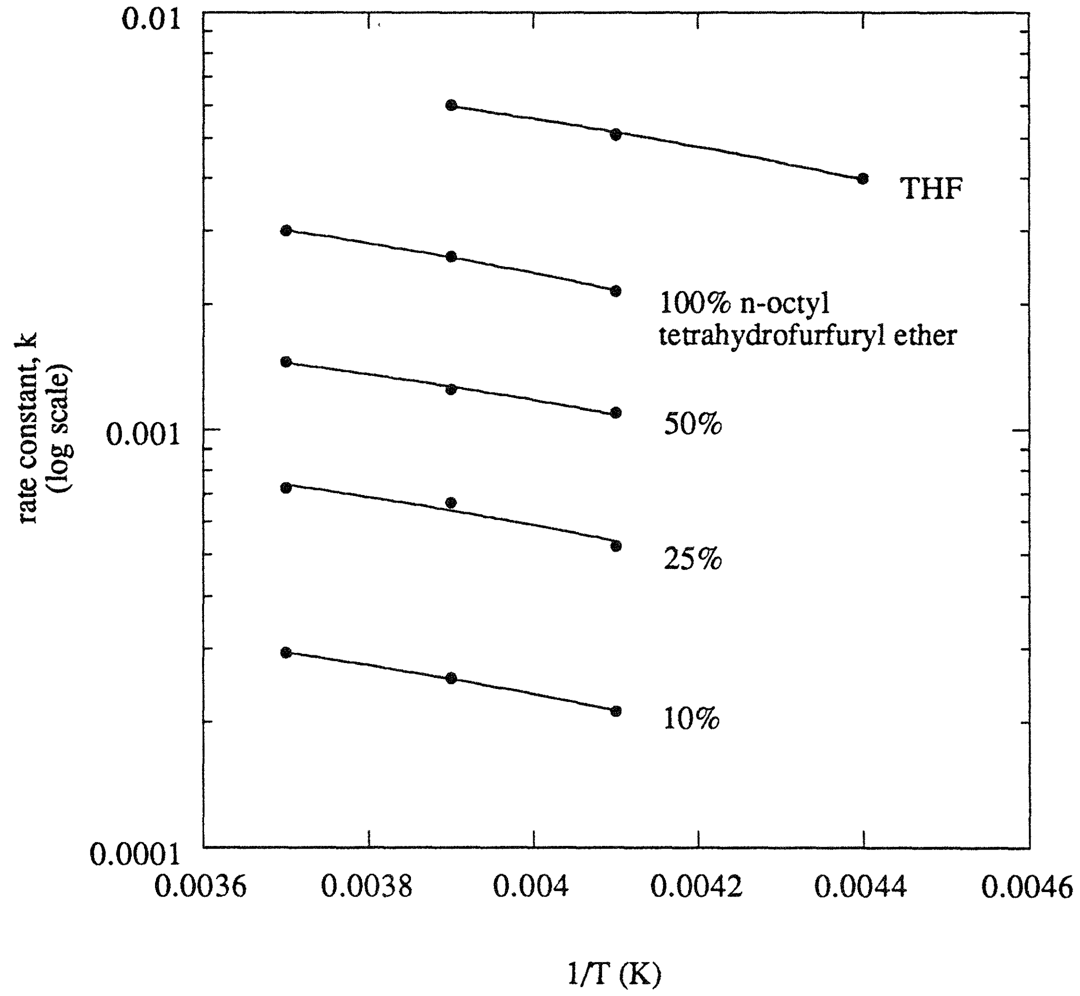

Figure 11. Arrhenius plots of THF from model reactions run at T=-15, -30, and -45 °C, and n-octyl tetrahydrofurfuryl ether diluted with heptane run at T= 0, -15, and -30 °C.

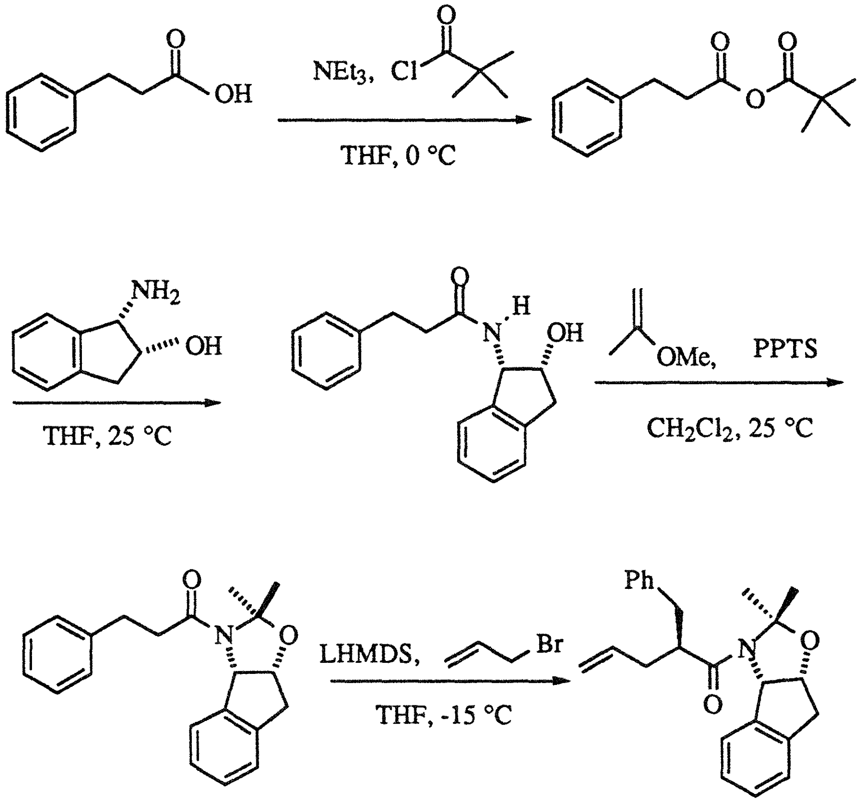

Figure 12. Reaction sequence leading to the synthesis of the Merck HIV-1 protease inhibitor Indinavir that is currently in clinical trials. The THF replacement solvents, n-octyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ether were used instead of THF and methylene chloride. PPTS=pyridinium-*p*-toluene sulfonate.

Chapter 3

Physical Characterization of Low Molecular Weight Replacement Solvents: Neat Solvents and Solvent Mixtures

3.1 Introduction

Physical parameters of the neat solvent and solvent mixtures were determined in order to compare their physical properties to that of THF and to provide an indication of their applicability as replacement solvents for THF. Basic physical characterization included the measurement of boiling and melting points, viscosity, density, polarity and surface tension. The temperature range between the boiling and melting points defines the range of potential use of the replacement solvents. Viscosity measurements are relevant on both a laboratory and industrial scale. Density and surface tension measurements are indicative of solvent interactions. Similar experiments were used to explore the physical characteristics of mixtures of replacement solvents with a relatively benign diluent such as heptane.

The solution structure of the replacement solvents diluted in a relatively benign continuous phase was also probed by small-angle neutron scattering (SANS). First, evidence of any type of structure in the solvent mixtures was investigated using a density meter. A linear relationship between density and concentration which demonstrates a break is a good indication that there is micelle formation. In the simplest case, micelles are structures in which the hydrophobic portions of the surfactant molecule associate together to form regions from which the solvent, water, is excluded. In this case, our alkyl ethers have a hydrophobic portion, the alkyl chain, and a polar moiety, the THF molecule attached via the ether linkage. Thus, when placed in a nonpolar solvent such as hexanes, they have the potential to form what is called a reverse micelle. Here, the polar THF groups would associate together and exclude the nonpolar solvent, hexanes. The concentration at which micelles first form in solution is called the critical micelle concentration (cmc). It is marked by drastic changes in slope when transport and equilibrium properties are plotted versus concentration. It can be determined by measurements of conductance, density, surface tension, UV/Vis or fluorescence spectroscopy, and less commonly, titration calorimetry.[1] Although our replacement solvents cannot form true reverse micelles, these experimental techniques can be utilized to determine if there are any deviations from non-ideality in the solvent mixtures and also how these solvent mixtures compare with mixtures of THF and hexanes or some other nonpolar solvent such as heptane or cyclohexane. It is not known whether deviations from ideality or the formation of aggregates would be favorable or unfavorable from the standpoint of using these solvent mixtures for chemical reactions. Formation of some sort of local microenvironment where there exists a higher concentration of ether linkages than in the bulk mixture would, however, be one way in which less solvent could be used. Formation of this type of local microenvironment would probably have more meaning when developing a polymer-based solvent.

3.2 Materials and Methods

3.2.1 Density measurements

A Calculating Digital Density Meter DMA 45 (Anton Paar, Graz, Austria, Mettler Corp.) was employed to measure the densities of the replacement solvent and THF as well as mixtures with hexanes in the full concentration range. The density is determined by placing the sample in a U-shaped tube and measuring the change in the resonant frequency of a hollow, vibrating tube when it is filled with fluids of varying density.[2,3] The technique is simple to perform and accurate to four decimal places. The rapidity of the measurement (10-100 seconds) is limited only by the sensitivity of the electronic detection circuitry. Temperature of the sample was maintained within 0.05 °C of 25 °C by the use of a NESLAB RTE-110 refrigerated bath-circulator.

3.2.2 Viscosity measurements

Cannon-Fenske viscometer tubes (Cannon Instrument Co., State College, PA), were used to measure the viscosity of the neat replacement solvents. The temperature of the sample was maintained by the use of a NESLAB RTE-110 refrigerated bath circulator. The viscometer tube was mounted vertically in a water bath and the solvent was allowed to pass freely between two marks on the tube. The time for the meniscus to pass between these two points was measured. Samples were run in triplicate and average times were then used to determine viscosity using constants specific to each tube size.

3.2.3 Surface tension measurements

The Wilhelmy plate method[4] was employed for measuring the surface tension of the solvent mixtures. In this method changes in interfacial tension are measured by the vertical pull on a rectangular plate which is dipped into the solution interface at zero contact angle. Changes in force are measured by a torsion wire. A Kruss K10T tensiometer (Kruss USA, Charlotte, NC) was used. Temperature control within 0.05 °C was achieved using a NESLAB RTE-110 refrigerated bath/circulator. All glassware was washed in a 1N NaOH-ethanol bath, then in a nitric acid bath, and then thoroughly rinsed with Milli-Q water before use. The platinum Wilhelmy plate was washed using acetone, rinsed in Milli-Q water, and flamed until red-hot before each measurement.[5]

3.2.4 Polarity measurements

3.2.4.1 Indigo dye measurements

A Perkin Elmer Lambda 3B UV/Vis Spectrophotometer was used to measure the maximum absorbance of Indigo dye in the various replacement solvents. The UV/Vis absorbance spectra of Indigo was recorded from 500-900 nm.

3.2.4.2 Fluorescence measurements

All fluorescence spectra were recorded on a SPEX FluoroMax spectrofluorometer using a 1 nm bandpass in the "s" mode (sample counts); sample PM counts were always smaller than 2×10^5 counts/sec to ensure linear response of the detector. Wavelengths of excitation were chosen according to the maximum intensity obtained in the emission spectra of pyrene; in this case, 335 nm. Step increments and integration times were set at 0.5 nm and 0.5 seconds respectively. All samples were aerated, magnetically stirred, temperature controlled using a thermostatted cuvette holder connected to a circulating water bath, and examined at right-angle geometry. For the low temperature studies, the sample chamber was purged with nitrogen as needed to prevent condensation on the cuvettes. Each spectrum was obtained by averaging three scans, corrected for scatter using an equivalent blank solution. In all cases the I_1/I_3 values were averaged over four different experiments. The reproducibility of the results was better than 3% and the standard deviation of the I_1/I_3 values was less than 0.01. The pyrene concentration was 3×10^{-7} M in all samples. Pyrene in 99% purity was obtained from Aldrich Chemical Co. (Milwaukee, WI) and was recrystallized four times from ethanol. A stock solution of 1 mM pyrene in acetone was prepared, from which 1 µl was added to 3 ml of sample.

3.2.5 Small-angle neutron scattering

Experiments were performed at the cold neutron research facility at NIST in Gaithersburg, MD. Scattering data was corrected for background and empty cell scattering and converted to absolute intensity using water as a standard. The data was then masked and radially averaged to obtain absolute average intensity versus scattering vector as outlined in the NIST guide for data rectification.

3.3 Basic physical characterization, neat solvents, results and discussion

3.3.1 Boiling and melting point measurements

Standard techniques were used for the measurement of the boiling and melting points. Results are shown in Table 1, where the effects associated with the length of the alkyl chain, and with the positioning of the alkyl ether linkage can be seen. In particular, it is noteworthy that attaching an octyl chain in the two position on the THF moiety raises its boiling point by 170 °C over THF, thereby decreasing its volatility considerably. The melting point of the octyl ether is -62 °C, however, which means that the useful temperature range for the solvent is decreased. Where on a laboratory scale reactions run in THF can be run at -78 °C, this cannot be done with the octyl ether. This decrease in the useful temperature range of the octyl ether solvent may not be an issue on an industrial scale.

3.3.2 Viscosity measurements

Viscosities of the n-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers were measured at 15 °C, 20 °C, and 35 °C and are shown in Table 2. There are modest increases in the solvent viscosity as the length of the alkyl chain is increased and as the temperature is decreased. The differences are not a concern from a processing point of view, especially in cases where a lower molecular weight diluent, such as heptane, may be used.

3.3.3 Density measurements

The densities of the neat solvents were measured in the range of 15-45 °C. Density measurements give an indication of how the solvent molecules interact with each other in solution. As expected, density decreases with increasing temperature in all cases. The n-butyl, n-hexyl, and n-octyl tetrahydrofurfuryl ethers were measured at varying temperatures. At each of the temperatures measured, the same trend was seen. The density decreases as the length of the alkyl chain increases. This implies that the shorter the alkyl chain, the closer the association of the solvent molecules in solution. These trends can be seen in Figure 1. Density data is shown in Table 3. As a comparison, the density of THF at 25 °C is 0.8830 g/ml.

3.3.4 Surface tension measurements

The surface tension values for n-butyl, n-hexyl, and n-octyl tetrahydrofurfuryl ethers and THF, measured at ambient temperature, are 24.4, 24.7, 25.9 and 26.5 dynes/cm, respectively. Because measuring surface tension as a function of mole fraction is a common technique for investigating micelle formation, it was hoped that it could also give an indication of solvent interaction of the solvent mixtures. As in the case of the density measurements, the surface tension increases as the length of the alkyl chain increases.

3.3.5 Polarity measurements

3.3.5.1 Indigo dye measurements

The UV/Vis absorbance maximum of indigo is influenced by solvent polarity. In THF for instance, the UV/Vis absorbance maximum of indigo dye is 602nm. As a basis of comparison, carbon tetrachloride, a nonpolar solvent, shifts the absorbance maximum of Indigo to 588nm, and dimethyl sulfoxide, a very polar solvent, shifts it to 620nm. Bergman and Wax[6] measured the UV/Vis absorbance maximum of various methyl and dimethyl substituted THF solvents to determine whether or not the polarity of these THF derivatives was significantly different from THF itself. In their study, they found that the polarities of their THF derivatives were not different from THF because the absorbance maximum of Indigo in the THF derivatives did not change significantly from the maximum in THF. Thus, they were able to conclude that steric hindrance, not polarity, played a role in changing the kinetic order of the reactions they were investigating. In our studies, we also found that the absorbance maximum of Indigo dye did not vary with the THF replacements. These results are shown in Figure 2. We did notice, however, a shape change in the UV/Vis absorbance at higher wavelengths which was investigated by looking at n-octyl tetrahydrofurfuryl ether diluted with heptane at various concentrations. These results are discussed in section 3.4.3.1

3.3.5.2 Fluorescence measurements

Pyrene is a well characterized spectroscopic probe which is sensitive to the polarity of the medium in which it is dissolved.[7,8] Pyrene exhibits a characteristic fluorescence emission spectrum, consisting mainly of five bands that are referred to as, I_1, I_2, ...I_5 (from shorter to longer wavelengths). The I_1/I_3 intensity ratio of this vibrational fine structure, often referred to as the "Py scale" depends strongly on the polarity of the medium; the larger the ratio, the more polar the medium. Electronically excited pyrene is a reporter of the average micropolarity of the environment it visits during its lifetime (about 300 ns). Pyrene can therefore provide a sensitive measure of polarity. Comparison of the I_1/I_3 ratios of the neat solvents and THF is shown in Figure 3. The I_1/I_3 value for hexane is also shown for perspective. The 3-position solvents show a slightly lower polarity than the 2-position solvents due to the greater distance between the ether linkages. In the 2-position solvents there exists the potential for a chelation effect because the oxygen atoms are close enough to associate together. Thus, these molecules would have a higher dipole moment and therefore polarity.

3.3.6 Solubility testing

It was also found that both THF and the alkyl ethers are soluble in hexanes, but pure THFA is not. The THFA is, however, soluble in our alkyl ethers. When these alkyl ethers were added to hexanes in limited amounts they were able to solubilize the THFA. To demonstrate this, THFA was added to 5.0 mL of hexanes in 0.1 mL increments until it turned cloudy. This mixture was then titrated with 0.1 mL droplets of n-octyl ether until it became clear again. It is evident that at small concentrations of the ether, approximately stoichiometric amounts of THFA were solubilized. However, above about 7.0 percent ether (THFA-free) the solubility of THFA increased dramatically, and appeared to be infinitely miscible with the hexanes/ether mixture. Thus, it has been shown that small amounts (in this case, 7.0%) of alkyl ether solvent in an inert solvent phase (hexanes) can enhance the solubility of the otherwise insoluble solutes. This is encouraging for the application of polymeric solvents, which will need to be dispersed in such inert solvents to be effective, as it is unlikely that they will be low viscosity liquids in their pure form.

3.4 Physical characterization of solvent mixtures: results and discussion

Several conventionally used physical characterization studies were done to determine whether or not the low molecular weight solvents are forming any type of clusters or other microenvironments. Typical methods to investigate micelle formation for example, include measuring density, surface tension and fluorescence properties as a function of composition. In this case, these techniques were used to study the solution characteristics of the replacement solvents mixed with hexanes or heptane. These studies all show a positive deviation from ideality that increases as the length of alkyl chain increases. Mixtures of THF and heptane or hexane show either ideal mixing behavior or a slight negative deviation from ideality when these methods are employed.

3.4.1 Density measurements

Results spanning the full concentration range for mixtures of the n-butyl, n-hexyl, and n-octyl tetrahydrofurfuryl ethers with hexanes are shown in figure 4 along with density measurements for THF-hexane mixtures. This figure shows the raw density data plotted versus mole fraction of replacement solvent in hexanes and gives a direct comparison of the different mixing behavior of the replacement solvents and hexane as compared to THF and hexane and also shows the increasing positive deviation from ideal mixing as the length of the alkyl chain is increased from 4 to 8 carbons. A similar graph is shown in Figure 5 for mixtures of the n-alkyl tetrahydro-3-furan methanol ethers and hexane as compared to THF and hexane. The same trends are seen for the 3-position solvents. This indicates that as the length of the alkyl chain is increased and the replacement solvent becomes more like the hexanes, there is an increase in their interaction as evidenced by the increase in density. The THF/hexane mixtures show a slight negative deviation from ideality- the opposite behavior form the replacement solvents because the nonpolar hexanes and polar THF do not interact when they are mixed together.

3.4.2 Surface tension measurements

The surface tension measurements of mixtures on n-butyl, n-hexyl, and n-octyl tetrahydrofurfuryl ethers and THF with hexanes are shown in Figure 6. As in the case of the density measurements, the n-alkyl tetrahydrofurfuryl ethers display different mixing behavior with hexanes than does THF. The positive deviation from ideality increases as the length of the alkyl chain increases.

3.4.3 Polarity measurements

3.4.3.1 Indigo dye measurements

The results of the polarity measurements of solvent mixtures are inconclusive for both the replacement solvent mixtures (figure 7) and THF and heptane mixtures (figure 8). The position on the absorption maximum is approximately the same in all cases demonstrating that the use of Indigo dye to measure the polarity of solvent mixtures is not valid. It can also be seen that the replacement solvent creates a new absorption maximum at a higher wavelength, but this change is not consistent with dilution. In the case of the THF/heptane mixtures, changes in the absorption spectrum of Indigo are seen at lower wavelengths, but again there is no clear trend.

3.4.3.2 Fluorescence measurements

Fluorescence spectroscopy can be used to determine the local microviscosity and polarity of solutions by use of a single molecule species, usually a dye. Since most dyes have different charge distributions in their ground and excited states, their absorption and emission spectra are often sensitive to solvent polarity. This is especially true if differences in charge distribution are significant.[9] Pyrene was used to investigate the polarity of the n-alkyl tetrahydrofurfuryl ethers when they are mixed with hexanes. Bulk dielectric polarity of mixtures of THF and hexanes follows the simple rule of additivity according to the solvent's mole fractions.[10] We obtained the same results using pyrene as a probe. Since it was possible to explore a wider range of temperatures with the pyrene probe, a study of the temperature dependence of the I_1/I_3 ratios was completed at temperatures relevant to the use of the solvents in organic reactions. Figure 9 shows that the polarity (as evidenced by the I_1/I_3 ratio) increases as the temperature is decreased as expected, and that the linear relationship between the intensity ratio and mole fraction is maintained at lower temperatures.

The I_1/I_3 ratios of mixtures of n-butyl tetrahydrofurfuryl ether and hexanes and THF and hexanes plotted vs. mole fraction of solvent at 25 °C are shown in Figure 10. While the THF/hexanes mixtures show linear behavior as predicted by theory, a positive deviation from ideality is seen for the n-butyl tetrahydrofurfuryl ether/hexanes mixtures at mole fractions less than 0.8. This behavior was also seen at lower temperatures as shown in Figure 11. Figures 12 and 13 show comparisons of the n-butyl tetrahydrofurfuryl ether and hexanes mixtures and THF and hexanes mixtures at 10 and -10 °C. The alkyl ether shows the same positive deviation from ideality at lower temperatures.

3.4.4 Scattering techniques

Initially it was attempted to discern what is happening with the mixtures of the n-alkyl tetrahydrofurfuryl ethers and hexanes by using conventional light scattering techniques. The results of these experiments indicated that either there was no structure to the solutions or that any structure that did exist was too small to be detected by light scattering.

Thus, we explored the solution structure of n-alkyl tetrahydrofurfuryl ethers and n-alkyl tetrahydro-3-furan methanol ethers when they are mixed with hexane by using small-angle neutron scattering.[11] The solution structure is of interest to us because of the success we have had with the model reaction even at very low concentrations of ethereal solvent. We expected to see some small scale structure based on aggregation of the ether linkages. This may or may not be affected by the presence of the acetonide which preferentially dissolves in ethereal solvents as opposed to hydrocarbons. SANS is necessary for these experiments because of the very small length scales (less than 20 Å) we are trying to investigate. Other physical characterization methods have not indicated the presence of micelles, so we hoped to pick up smaller structural evidence, such as clustering or even only dimers, that may be present.

While we would have liked to investigate the entire concentration range, there were some experimental limitations inherent in the use of neutrons. Mainly, we were using the scattering from the deuterated hexane to determine structure so we needed large amounts of hexane present. This limited us to lower concentrations of replacement solvent, but perhaps this was more interesting because this is also where the largest deviations from ideality occur in the n-octyl tetrahydrofurfuryl ether/hexane solvent mixtures.

The experiments were analogous to the investigation of microemulsions. Normally water is added to systems which form reverse micelles such as AOT/water/octane system. The water "induces" the formation of reverse micelles. In our case, we are not forming a reverse micelle, but some type of clustering where the alkyl chains of the octyl ether prefer to associate with the hexanes and the ether linkages cluster together. Initially, it was thought that perhaps the ether and hexanes system did not have the appropriate energetics to form this type of clustering, so water was added to try and form a microemulsion. However, not even the smallest amount of water could be mixed with the n-octyl tetrahydrofurfuryl ether and hexanes in any proportion. While this was not advantageous for our SANS experiments, it was encouraging with regard to other aspects of the project. Namely, that n-octyl tetrahydrofurfuryl ether solvents are not lost to the water phase during processing, and it may be easier to render them anhydrous for their use and re-use. In any case, since water could not be used, the amide acetonide material was used to help induce aggregation of the ether moieties since it is soluble in THF , but not hydrocarbon solvents such as hexanes.

The experiment was set up in the following manner. Solutions of n-octyl tetrahydrofurfuryl ether and hexanes were made with a fixed concentration of acetonide starting material, 1.25%. The concentration range of the n-octyl tetrahydrofurfuryl ether was determined by putting a known amount of the acetonide in the hexanes which is was not soluble in, even with strong vortexing, as expected. Then, n-octyl tetrahydrofurfuryl ether solvent was added very slowly to determine the exact amount necessary to dissolve the acetonide in the hexanes. The n-octyl tetrahydrofurfuryl ether was added in 50 ul aliquots and vortexed in between each addition until the acetonide was completely dissolved. The concentration range of the n-octyl tetrahydrofurfuryl ether was from

W_o=20-40, where Wo is equal to the molar concentration of the n-octyl tetrahydrofurfuryl ether divided by the molar concentration of the acetonide. W_o was increased in increments of 4. In this way, the mole percent of n-octyl tetrahydrofurfuryl ether in hexanes ranged from 8.2% to 28.6% corresponding to W_o=20-40. The volume/volume percent ranged from 17.3% to 60% 2-octyl in deuterated hexanes. The same samples were made without the addition of the acetonide so the size of the acetonide particles could be determined. Since we are exploring the lower limit of the acetonide solubility in this solvent mixture, by adding more n-octyl tetrahydrofurfuryl ether than is necessary to dissolve the acetonide, we can see if smaller acetonide particles are formed when more n-octyl tetrahydrofurfuryl ether is added, or if the "extra" n-octyl tetrahydrofurfuryl ether goes into the bulk. This can be determined by seeing if the incoherent scattering at high Q increases with increasing n-octyl tetrahydrofurfuryl concentration. This indicates that n-octyl tetrahydrofurfuryl is going into the bulk and interfering with the scattering of the deuterated hexanes.

Thus, the samples were explored in two configurations so that we could explore both low and high Q. Samples cells with a 1mm path length were used because the samples were weakly scattering. As a control, THF/hexane-d_{14} (from Aldrich, 99%) solvent mixtures were investigated to see if they formed any structure. As expected, they did not show any structure. Surprisingly, the scattering pattern of the n-octyl tetrahydrofurfuryl ether/hexane-d_{14} solvent mixtures was very similar to the scattering patterns of the THF/hexane-d_{14} solvent mixtures.

To determine if there was solvent cluster formation, a Guinier analysis was performed. Guinier's Law is as follows,

$$\ln I(Q) = \ln I(Q) + R_g^2/3*Q^2 \qquad (1)$$

where I(Q) is the intensity, R_g is the radius of gyration and Q is the scattering angle. A plot of the natural logarithm of the intensity versus the square of the scattering angle should yield a straight line whose slope is related to the radius of gyration of the scattering object. Then, by assuming a geometric cluster model the characteristic dimensions of the scattering object may be calculated.

Determination of the range of feasible scattering angles to include in the analysis was done as follows. First, the minimum scattering angle was determined. This is the Q value where scattering intensity is first detected. Then, a sample of neat deuterated hexane was examined. Because the solution is isotropic, its scattering curve should appear flat and uniform over the range of scattering angles. However, some curvature was detected in the deuterated hexane samples. This curvature may be due to leaking at the beam stop in the center of the neutron detector that is unaccounted for during the data correction. Thus, the minimum scattering angle was taken to be the angle where the deuterated hexane began to exhibit a flat isotropic section. The maximum scattering angle was obtained by an iterative approach. Because Guinier's Law is only valid for scattering at small angles, the following constraint ensures that this is true:

$$R_g * Q < 1 \qquad (2)$$

Molecular size was estimated using a space filling molecular model. A spherical cluster shape was assumed and the radius of gyration was calculated. The maximum Q value was then determined by equation 2. The data was examined in this scattering vector range and a new value of R_g was determined. This process was continued until the small angle criteria was met. The sizes determined by neutron scattering appear to be on the order of the size of one molecule. Values for R_g ranged from 3.5-4.0Å. In addition, the aggregation number calculated from the SANS data was on the order of 1. Thus, we can conclude that compared to THF/hexanes is shown in Figure 14. The slopes of the lines are very flat and show no evidence of structure.

3.5 Summary

Density, surface tension, and polarity measurements of mixtures of the replacement solvents and a nonpolar solvent (hexanes or heptane) all show that there exists a positive deviation from ideality for these mixtures. There do not exist, however, any abrupt changes or discontinuities in these measurements that would indicate formation of micelles or some other definite structure. This was confirmed by SANS measurements. The THF mixtures show ideal behavior (or slightly negative deviation from ideality) as expected. This is seen explicitly in the most sensitive measurement we used which was the pyrene fluorescent probe. Thus, non-idealities present in the replacement solvent mixtures do not result in an aggregate structure.

List of tables and figures for Chapter 3

Figure 10. Comparison of I_1/I_3 ratios for mixtures of 2-butyl tetrahydrofurfuryl ether and hexanes and THF and hexanes at 25 °C.

Figure 11. Temperature dependence of I_1/I_3 ratios of mixtures of 2-butyl tetrahydrofurfuryl ether and hexanes.

Figure 12. Comparison of I_1/I_3 ratios for mixtures of 2-butyl tetrahydrofurfuryl ether and hexanes and THF and hexanes at 10 °C.

Figure 13. Comparison of I_1/I_3 ratios for mixtures of 2-butyl tetrahydrofurfuryl ether and hexanes and THF and hexanes at -10 °C.

Figure 14. SANS results, Guinier plot for 5Å, 1M configuration.

Table 1. Boiling and Melting Points of n-Alkyl Tetrahydrofurfuryl and Tetrahydro-3-furan Methanol Ethers as Compared to THF

Solvent	Molecular Weight (g/mole)	Boiling Point (°C)	Melting Point (°C)
Tetrahydrofuran	72.1	65.4	-108*
2-butyl ether	158	168	< -78
2-hexyl ether	186	225	< -78
2-octyl ether	214	239	-62
3-butyl ether	158	168	< -78
3-octyl ether	214	229	-60

*from CRC of Chemistry and Physics

Table 2. Viscosity (cp) Measurements of n-Alkyl Tetrahydrofurfuryl and Tetrahydro-3-furan Methanol Ethers as a Function of Temperature

Solvent	15 °C	20 °C	35 °C
Tetrahydrofuran	0.572	0.556	------
2-butyl ether	1.883	1.728	1.375
2-hexyl ether	2.857	2.695	1.876
2-octyl ether	4.173	3.760	2.649
3-butyl ether	2.100	1.906	1.553
3-octyl ether	4.646	4.117	3.027

Table 3. Density Measurements of n-Butyl, n-Hexyl and n-Octyl Tetrahydrofurfuryl Ethers and n-Octyl Tetrahydro-3-Furan Methanol Ether as a Function of Temperature.

Temperature (°C)	Density (g/ml) 2-butyl ether	Density (g/ml) 2-hexyl ether	Density (g/ml) 2-octyl ether	Density (g/ml) 3-octyl ether
15	0.9155 (g/ml)	0.9032 (g/ml)	0.8925 (g/ml)	0.8978 (g/ml)
17.5	0.9134	0.9012	0.8906	0.8959
20	0.9113	0.8993	0.8887	0.8940
22.5	0.9092	0.8973	0.8868	0.8921
25	0.9070	0.8952	0.8849	0.8902
27.5	0.9049	0.8934	0.8832	0.8883
30	0.9029	0.8913	0.8813	0.8864
32.5	0.9008	0.8894	0.8794	0.8844
35	0.8987	0.8873	0.8775	0.8824
37.5	0.8966	0.8853	0.8757	0.8804
40	0.8945	0.8833	0.8738	0.8786
42.5	0.8924	0.8813	0.8719	0.8766
45	0.8902	0.8793	0.8700	0.8746

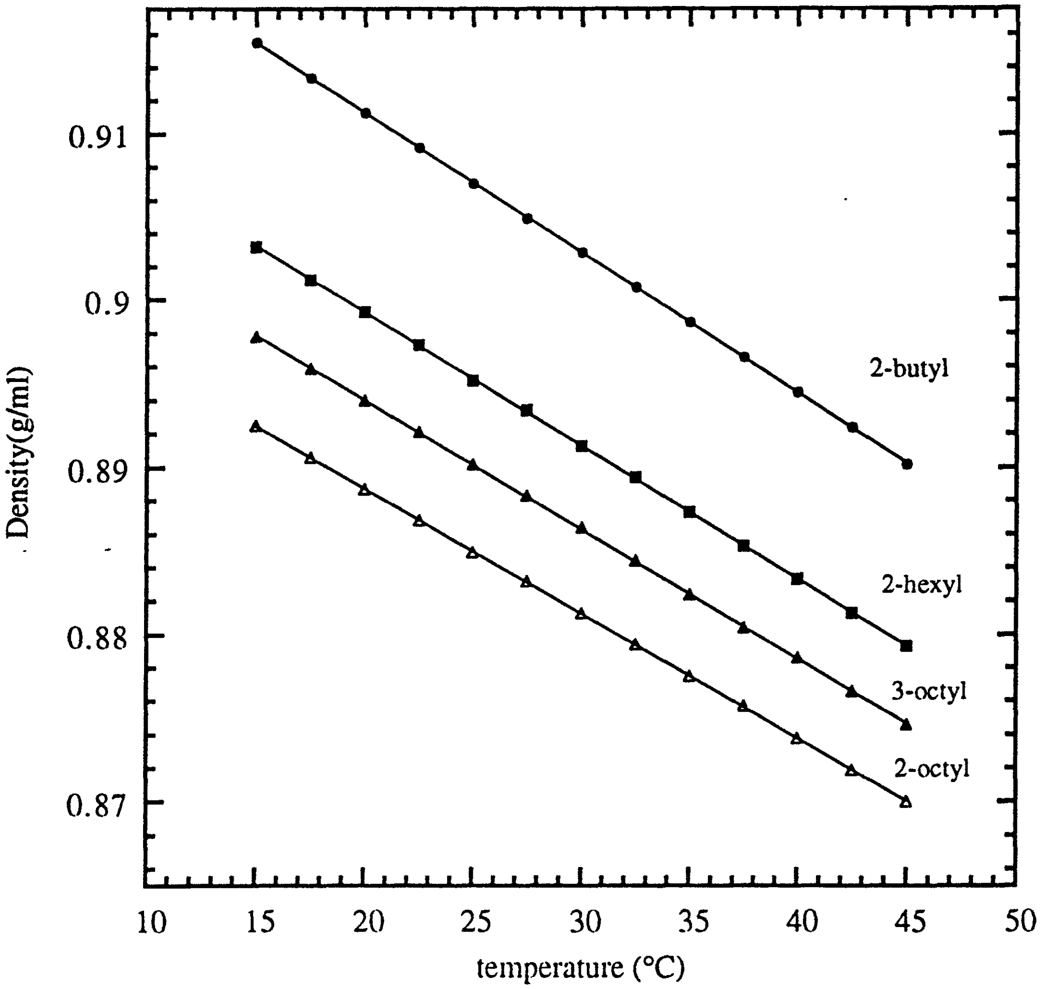

Figure 1. Density (g/ml) vs. temperature for n-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers

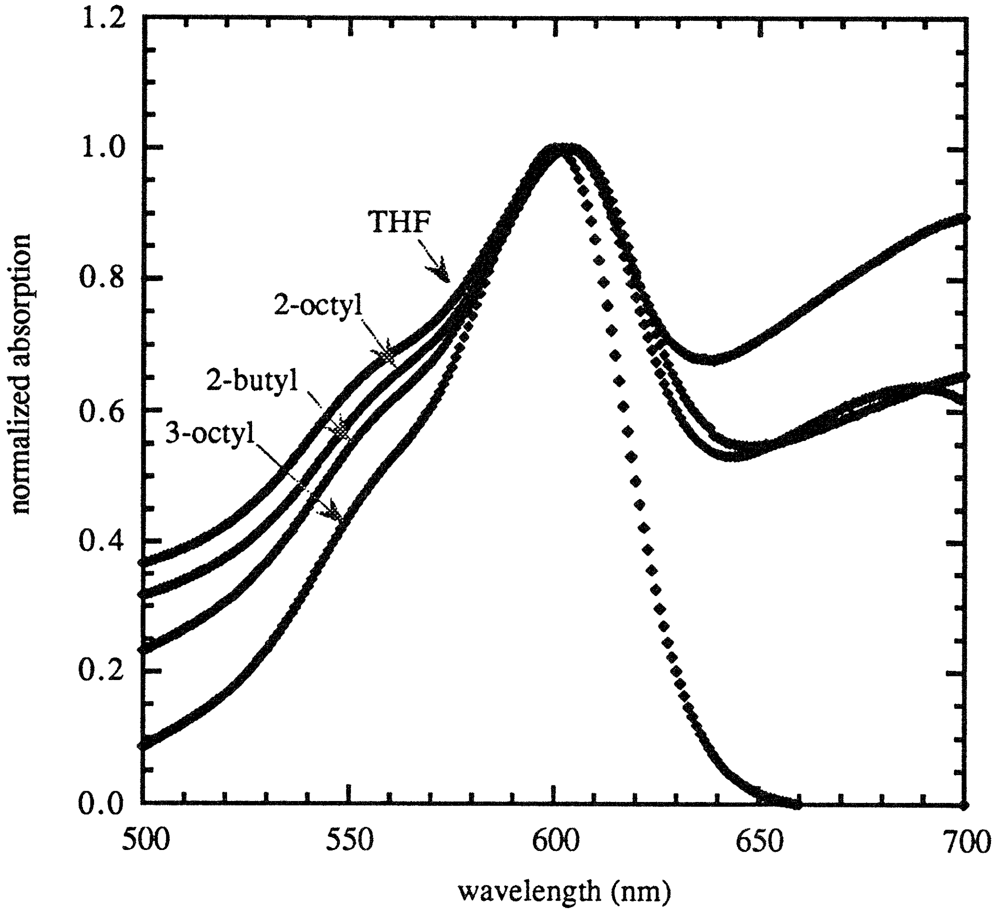

Figure 2. Indigo absorption vs. wavelength for n-alkyl tetrahydrofurfuryl and tetrahydro-3-furan methanol ethers.

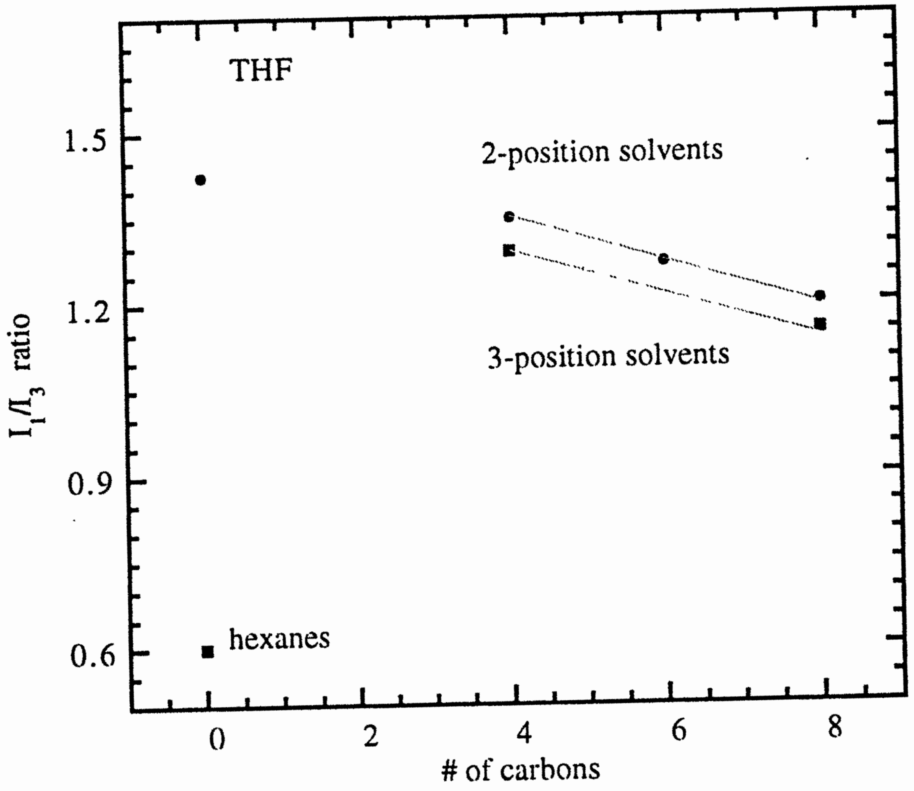

Figure 3. I_1/I_3 ratios from fluorescence spectra of pyrene in neat solvents.

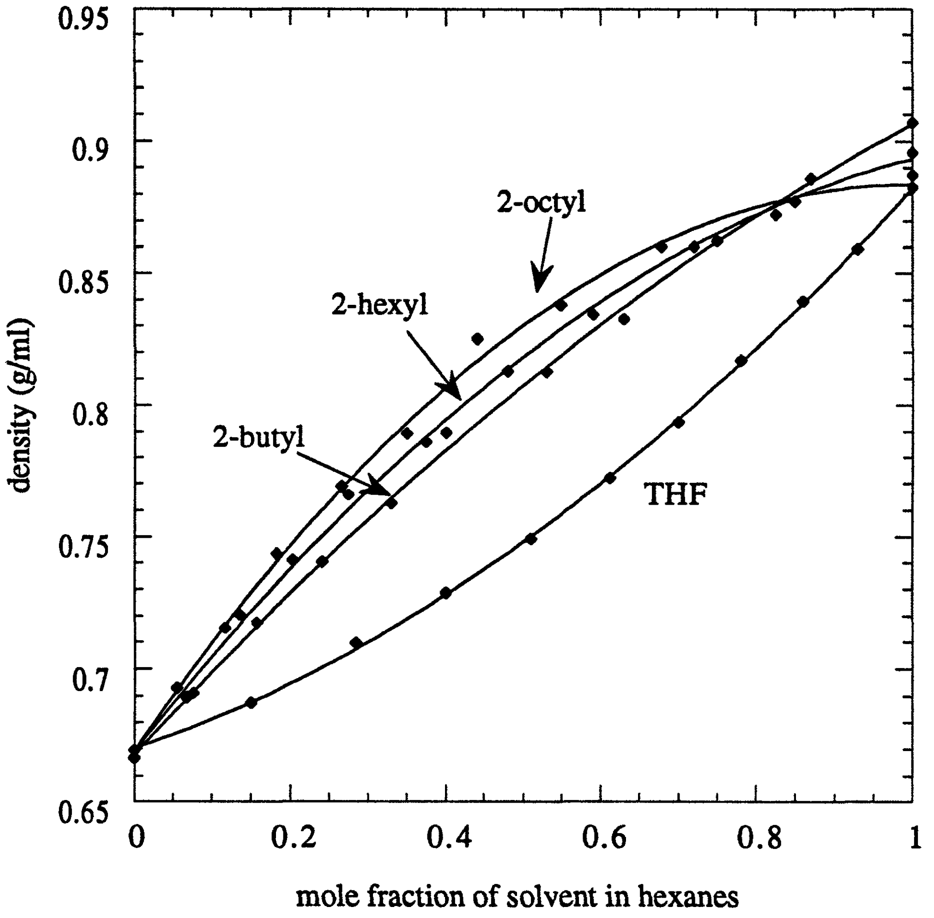

Figure 4. Densities of n-alkyl tetrahdyrodfurfuyrl ethers in hexanes as compared to THF in hexanes (T=25 °C)

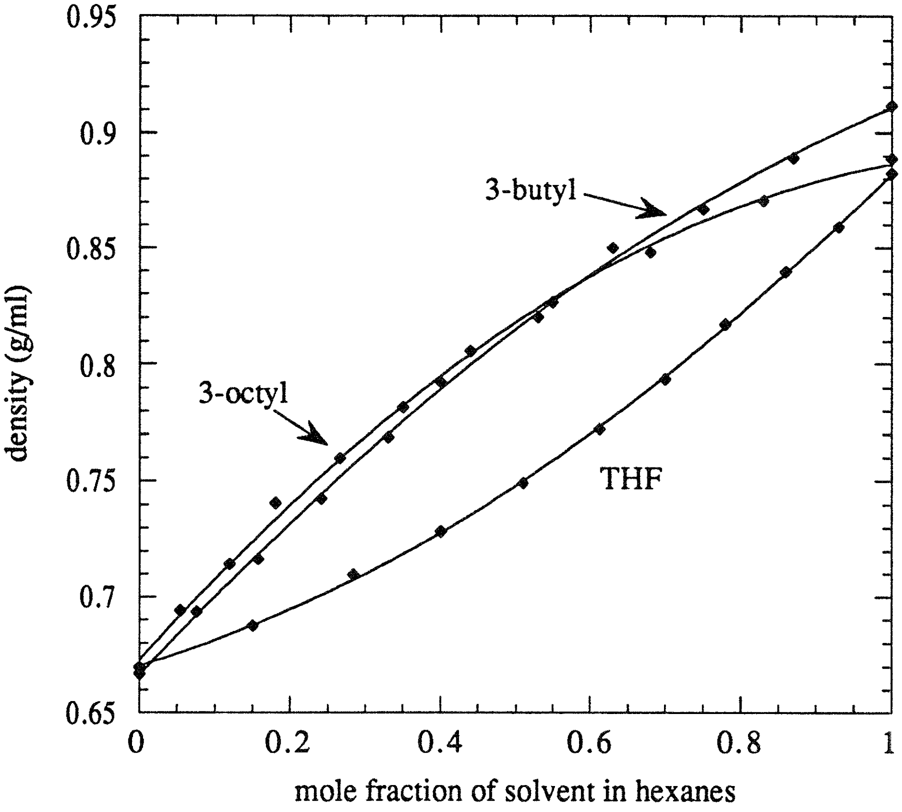

Figure 5. Densities of n-alkyl tetrahydro-3-furan methanol ethers in hexanes as compared to THF in hexanes (T=25 °C).

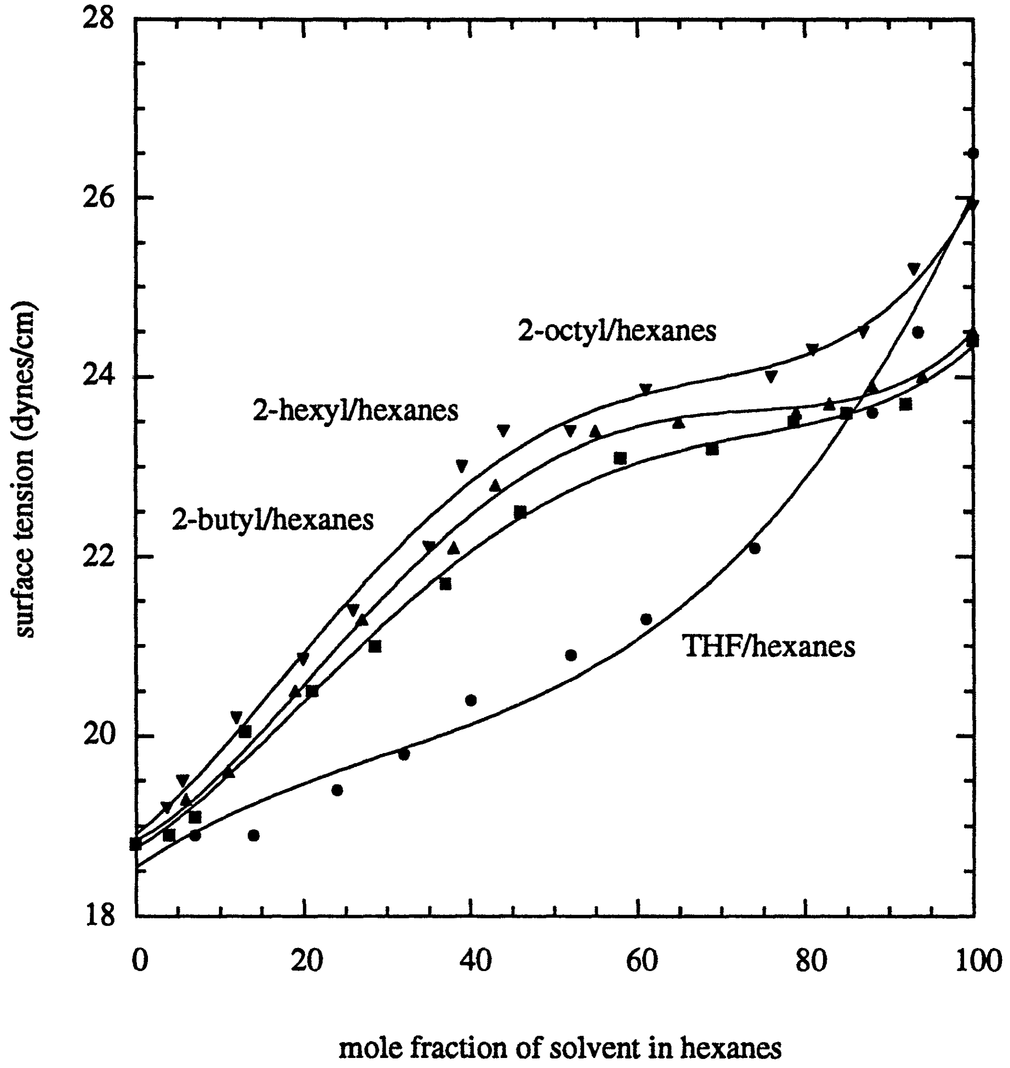

Figure 6. Surface tension (dynes/cm) vs. mole fraction of solvent in hexanes for mixtures of n-alkyl tetrahydrofurfuryl ethers and THF with hexanes.

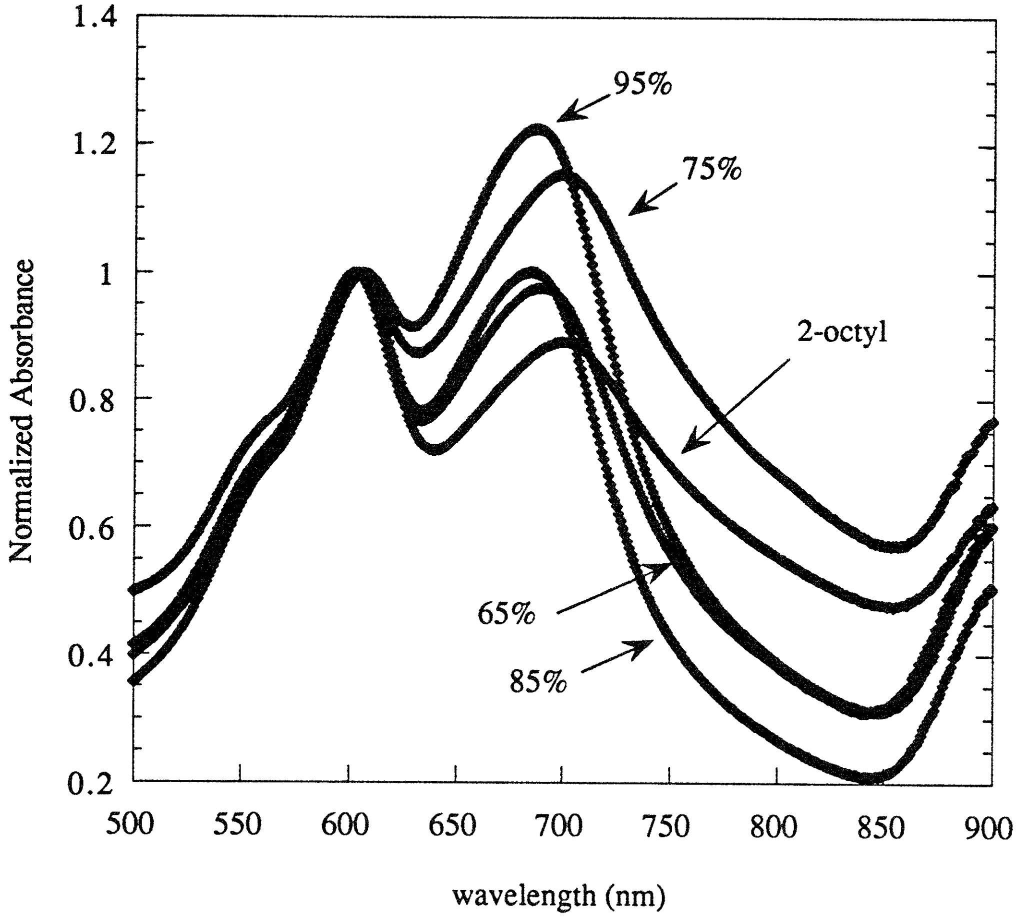

Figure 7. Indigo absorbance of n-octyl tetrahydrofurfuryl ether diluted with heptane to various concentrations.

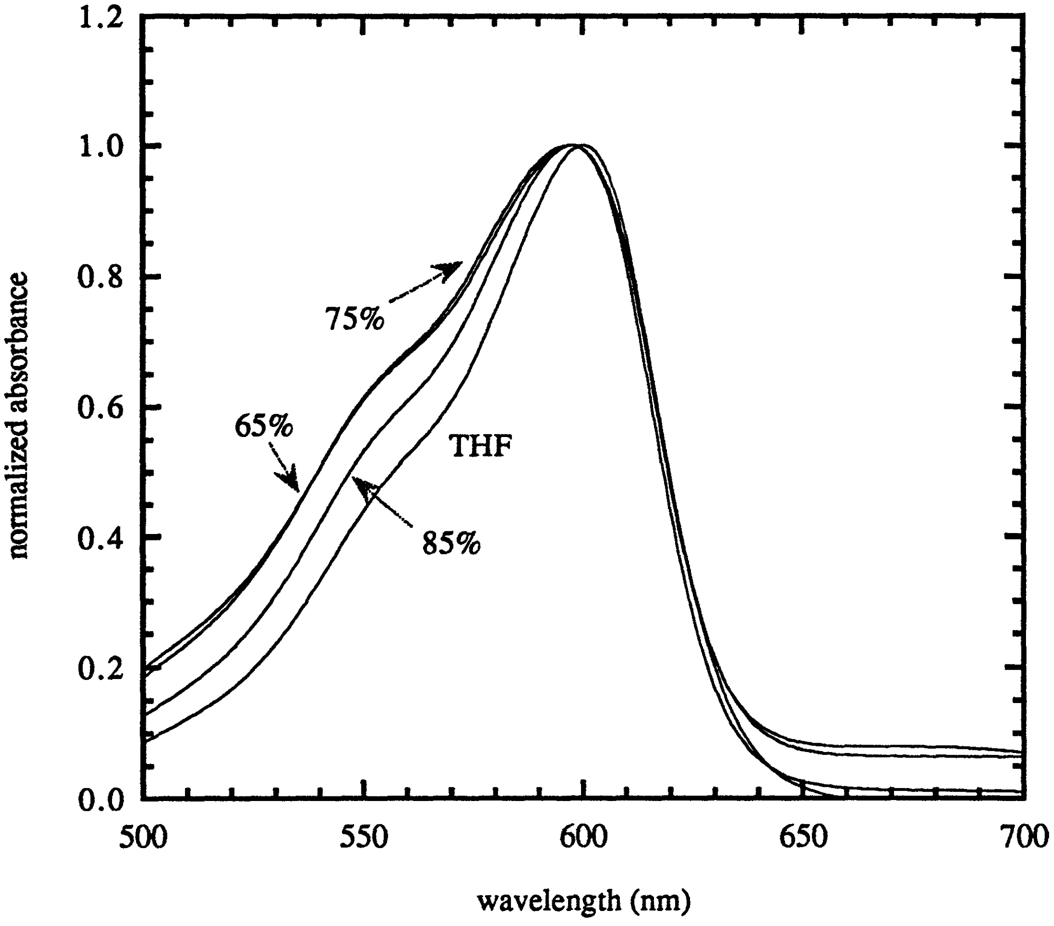

Figure 8. Indigo absorption vs. wavelength for THF and THF diluted with heptane.

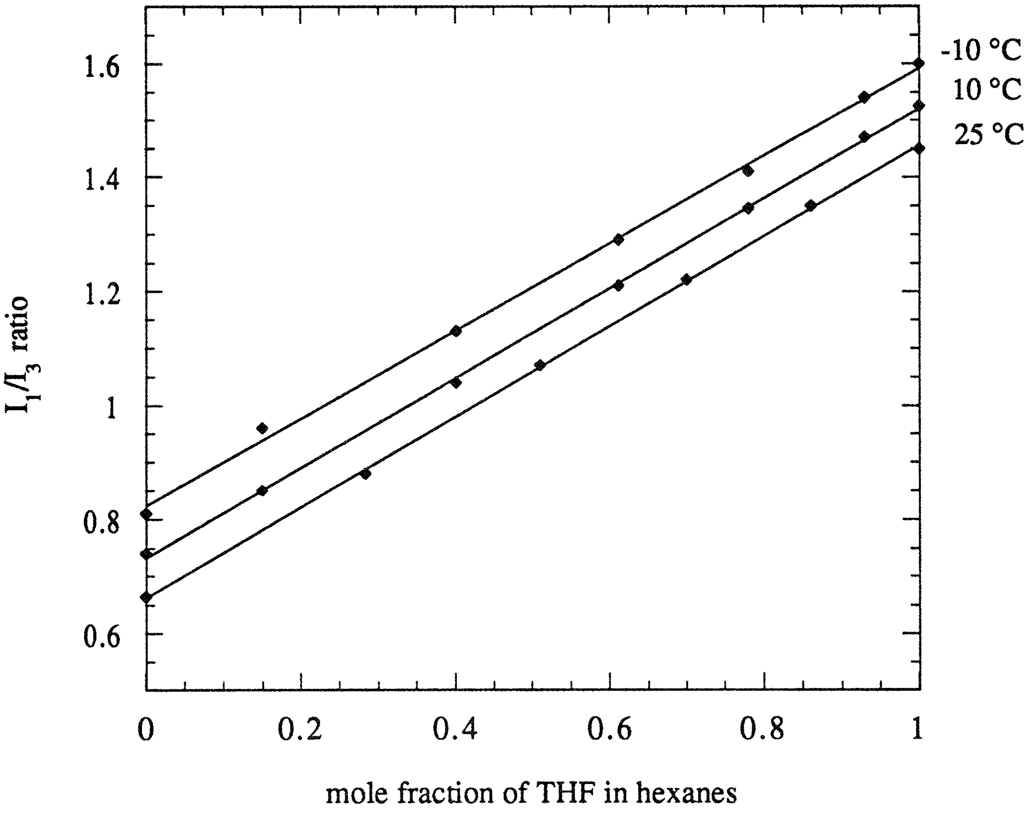

Figure 9. Temperature dependence of I_1/I_3 ratios of mixtures of THF and hexanes.

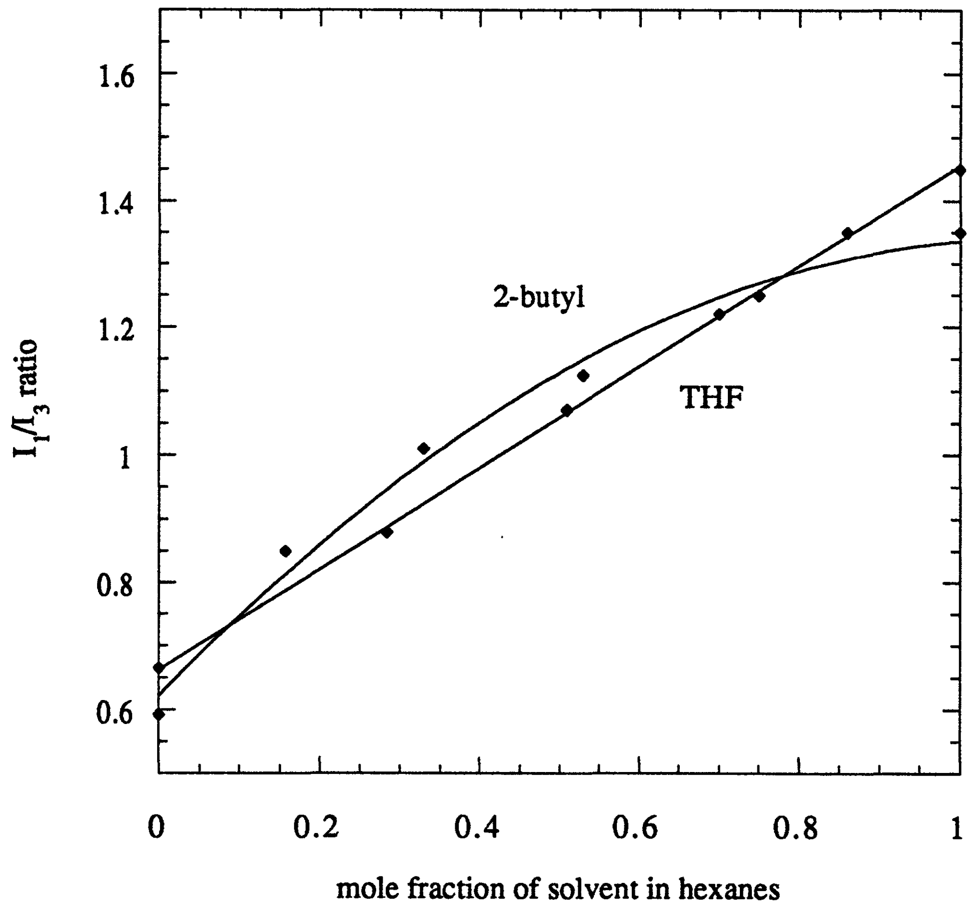

Figure 10. Comparison of I_1/I_3 ratios for mixtures of 2-butyl tetrahydrofurfuryl ether and hexanes and THF and hexanes at 25 °C

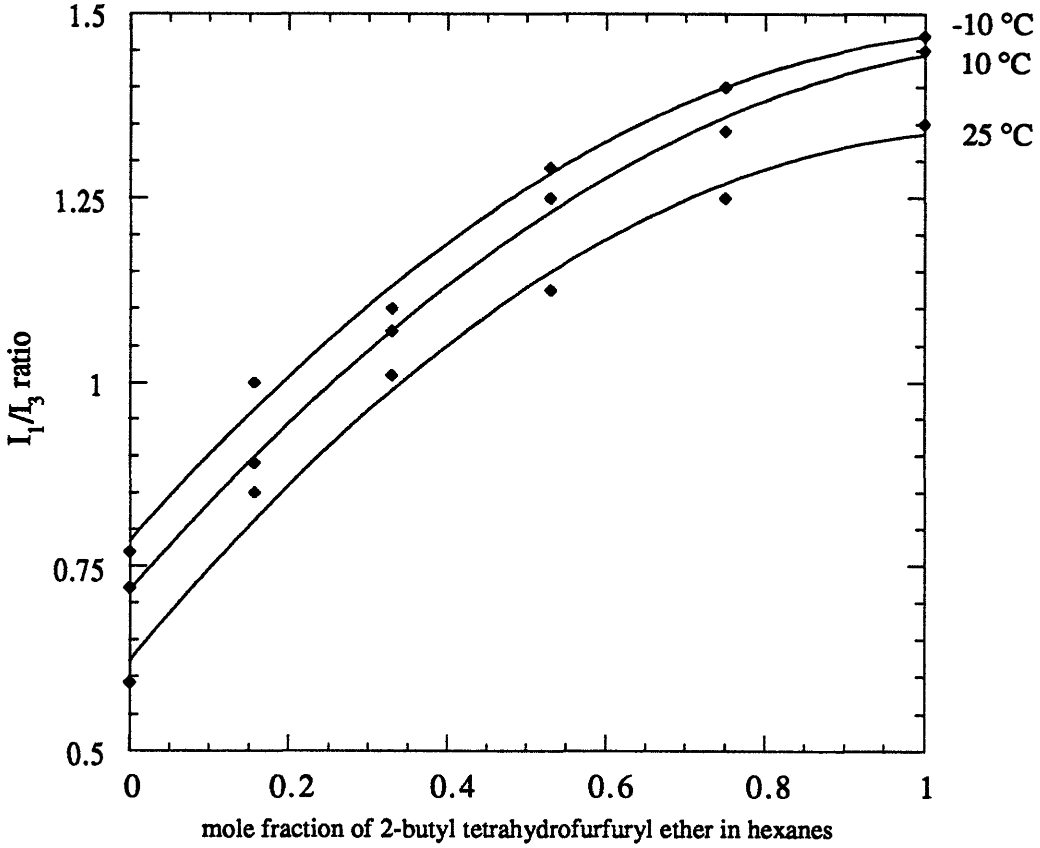

Figure 11. Temperature dependence of I_1/I_3 ratio of mixtures of 2-butyl tetrahdyrofurfuryl ether and hexanes

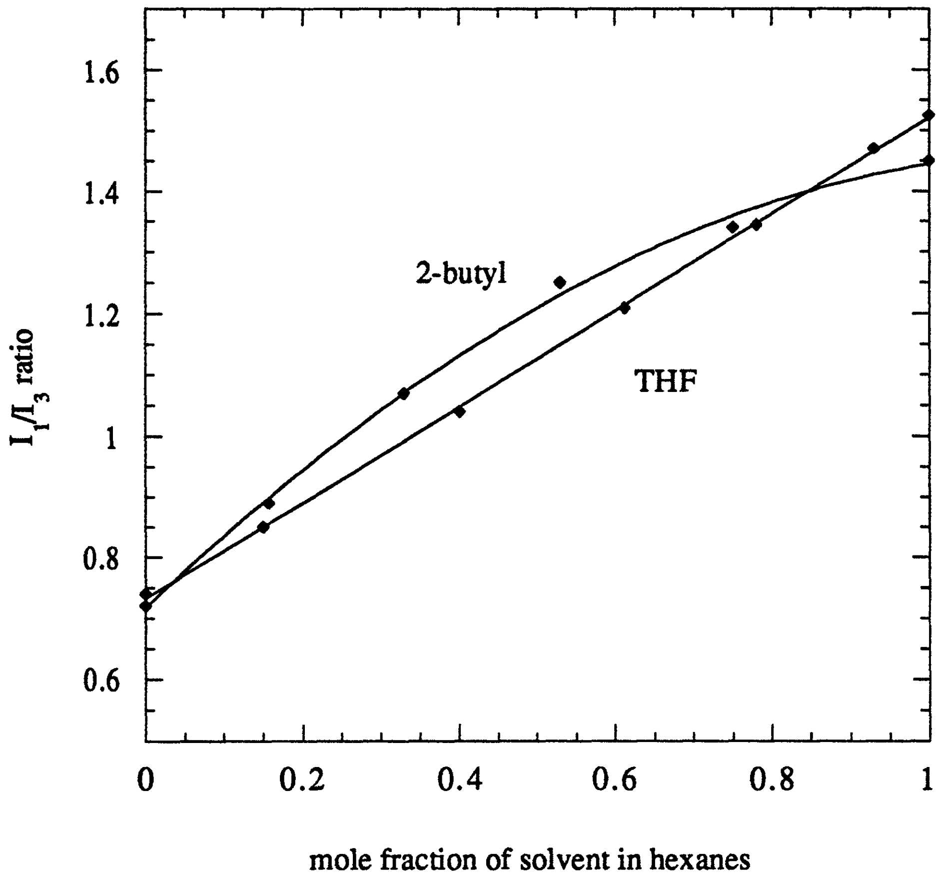

Figure 12. Comparison of I_1/I_3 ratios of mixtures of 2-butyl tetrahydrofurfuryl ether and hexanes and THF and hexanes at 10 °C

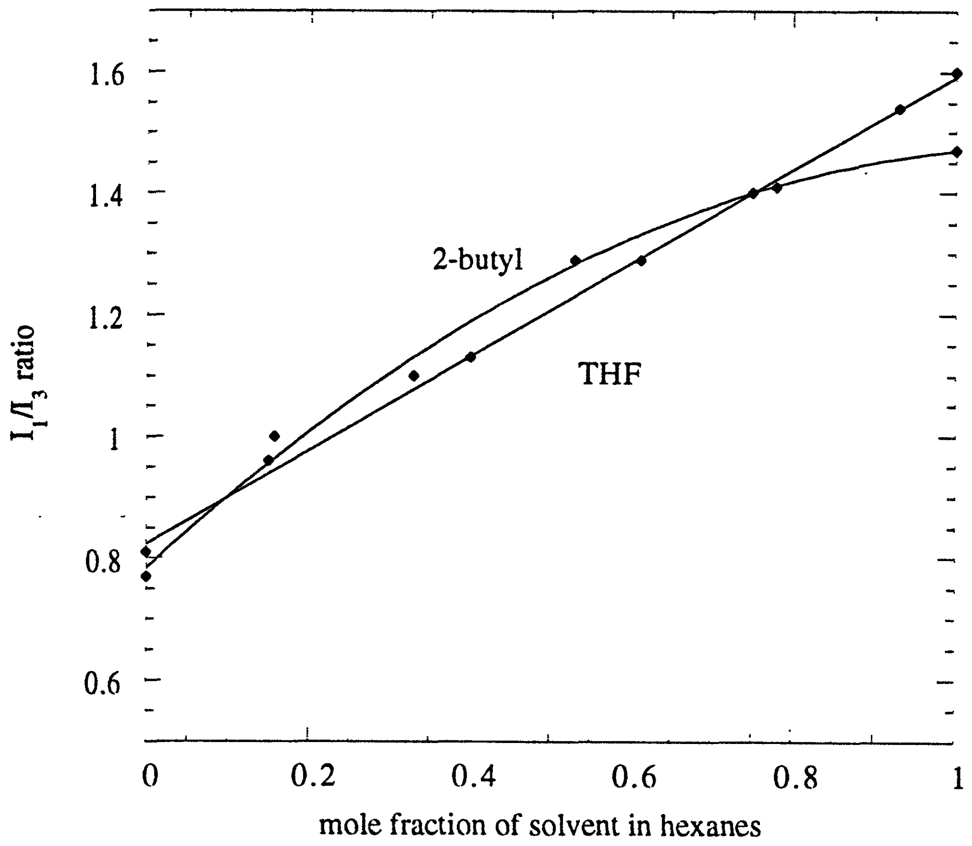

Figure 13. Comparison of I_1/I_3 ratios of mixtures of 2-butyl tetrahdyrofurfuryl ether and hexanes and THF and hexanes at -10 °C.

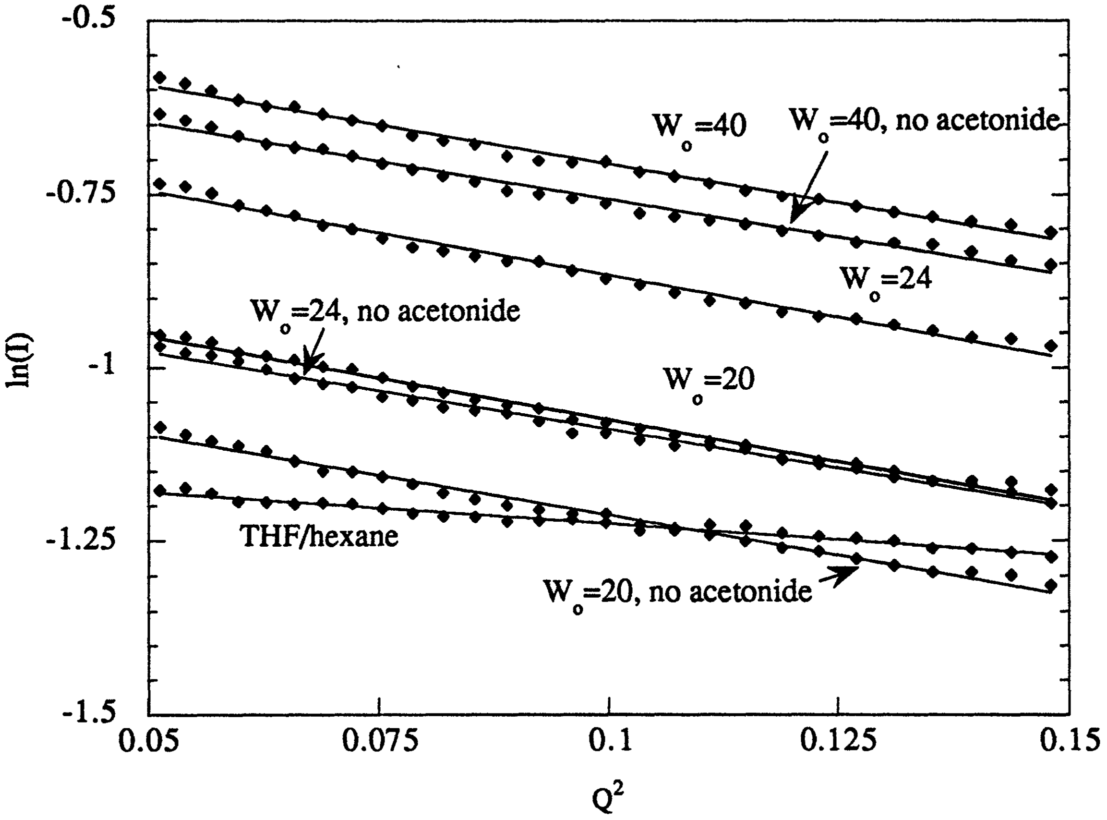

Figure 14. SANS results. Guinier plot for 5A, 1M configuration showing three different ratios of replacement solvent and hexanes with and without acetonide as compared to THF/hexanes.

PART II

Polymer-Based Replacement Solvents:

Design, Synthesis, and Use as Replacement Solvents for Tetrahydrofuran

Chapter 4

Design and Synthesis of Polymer-Based Replacement Solvents for Tetrahydrofuran

4.1 Introduction

A polymer-based solvent has the advantage of being nonvolatile, non-water soluble, and easily removed from process streams. The motivation for investigating a polymer-based solvent, as opposed to the replacement solvents discussed in the first part of this thesis, is the potential for facile separations and regeneration for re-use. We have established several criterion for a suitable polymeric replacement solvent. The polymeric solvent must be (1) soluble in a relatively benign continuous phase, preferably a solvent used in the separation of the product such as the recrystallization solvent or the next solvent used in the synthetic scheme (2) provide the requisite solvation environment for the reaction either by micellization or clustering (3) be chemically inert to reactions of interest for the solvent it is to replace (4) non-volatile and non-water soluble (5) readily separated from the process scheme using mechanical separations such as ultrafiltration instead of energy-intensive distillation processes (6) reasonably inexpensive to synthesize.

Polymers can derivatized with solvent groups such as tetrahydrofuran using several different approaches. Appropriately-functionalized monomers can be synthesized to produce new "macromonomers" which will then be polymerized via free radical polymerization to produce polymers having the desired solvation properties.[1] A suitable monomer for this purpose would be 3-vinylbenzyl chloride, which is shown in Figure 1 along with the reaction scheme for attachment of the THF moiety to form a macromonomer.

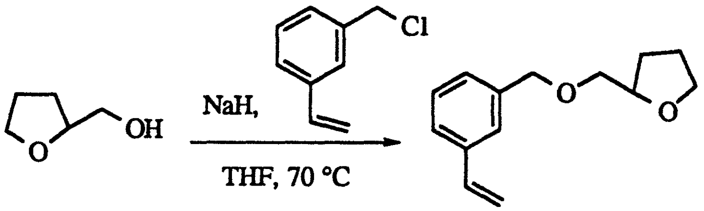

Figure 1. Synthesis of 3-vinyl benzyl tetrahydrofurfuryl ether from 3-vinyl benzyl chloride and tetrahydrofurfuryl alcohol.

This particular monomer is desirable because it can be easily polymerized by free radical polymerization, and may also be polymerized anionically. This may be important if a monodisperse polymer is required. It will be discussed in more detail in section 5.2. It is also possible to functionalize a readily available polymer such as poly(vinyl alcohol). This is not as efficient because it is difficult to achieve complete functionalization which would be necessary for use as a solvent. Other possibilities would be attachment of the solvent molecules or their derivatives to dendrimers[2,3] or other highly branched polymers with appropriate functionalized end groups, such as star polymers.[4] These options can, however, be very expensive. In some cases, it may be advantageous to use the solvents immobilized on macroporous solid substrates, such as chromatographic resins, which will make the solvent-recovery processes even simpler; however, there is the risk of introducing diffusional limitations that may broaden the spectrum of reaction byproducts that are formed, thereby reducing the reaction yield and adding to the complexity of the subsequent separations and purification tasks. Another option would be to attach the solvent moiety to a magnetic particle so that separation could be achieved by application of a magnetic field. This approach is currently being used for the separation of proteins. When studying these approaches it is important to remember that there should not be any linkages in our solvent replacement molecule that would be chemically incompatible with the pharmaceutical reactions to be tested.

4.2 Monomer synthesis

4.2.1 3-Vinyl benzyl tetrahydrofurfuryl ether

This THF-derivatized monomer is made from commercially available 3-vinylbenzyl chloride (3-(chloromethyl)styrene) monomer purchased from Aldrich. Because of its moisture sensitivity, sodium hydroxide could not be used as the base because it results in the formation of water. Tetrahydrofurfuryl alcohol was used instead of the tetrahydro-3-furan methane alcohol because it is less expensive.

Glassware was dried for at least four hours in a 150 °C oven, followed by cooling under vacuum, and refilling with Argon gas three times. Dry THF (from stills or Aldrich sure-seal bottles) is used as a solvent. The tetrahydrofurfuryl alcohol is deprotonated with sodium hydride (either dry and transferred in a glove box or a 60% dispersion in mineral oil that is washed three times with hexanes) in a 1.1 excess. After about one hour of refluxing the reaction mixture, the 3-vinylbenzyl chloride is added dropwise and the reaction mixture is allowed to reflux for two hours at 70 °C. As the chloride is added, the reaction mixture turns from dark purple, to blue, to green. After refluxing overnight, the mixture becomes creamy white indicating the formation of the sodium chloride salt byproduct. The reaction mixture is cooled to room temperature and then saturated ammonium chloride is used to quench any unreacted sodium hydride. Ether is added in order to extract the product phase in a separatory funnel and the water phase is re-extracted with ether. The organic layers are then combined and washed with water and brine and dried over magnesium sulfate. The ether and any tetrahydrofuran solvent that is left is removed on a rotary evaporator. A dark orange product is obtained. Purification was attempted using the method described for the low molecular weight solvent replacements, but the 3-vinyl benzyl tetrahydrofurfuryl ether was not amenable to this procedure. The monomer is so reactive that it is impossible to keep it from polymerizing uncontrollably even when distilled under vacuum at 70 °C. The addition of hydroquinone as an inhibitor to the polymerization did not help because it distilled over first and the monomer would then polymerize. Since it should be easier to remove any low molecular weight impurities once a high molecular weight polymer is formed, it was decided to carry through the free radical polymerization without further purification. Also, any impurities do not seem to be interfering with the reactivity of the monomer.

4.2.2 Allyl tetrahydrofurfuryl ether

Allyl chloride may also be derivatized with the tetrahydrofurfuryl alcohol to form an allylic ether monomer, as shown in Figure 2. It was found that it could also be made using sodium hydroxide, but this may lead to impurity problems. It was purified by distillation and dried with calcium hydride. This monomer is not soluble in hexanes and shows a high degree of water solubility. It was felt that having a longer alkyl chain between the double bond and the THF moiety might produce a monomer which has less water solubility and is soluble in hexanes. Because this monomer would not be allylic, it may also be more reactive to free radical polymerization.

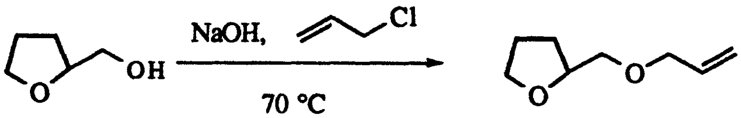

Figure 2. Synthesis of allyl tetrahydrofurfuryl ether from tetrahydrofurfuryl alcohol and allyl chloride.

4.2.3 8-octene tetrahydrofurfuryl ether

1-bromo-8-octene was derivatized with tetrahydrofurfuryl alcohol to form 8-octene tetrahydrofurfuryl ether as shown in Figure 3. This monomer, like the n-octyl tetrahydrofurfuryl ether, is soluble in hexanes and has negligible water solubility. It was purified by distillation under reduced pressure (3mm, 70 °C) and dried with calcium hydride.

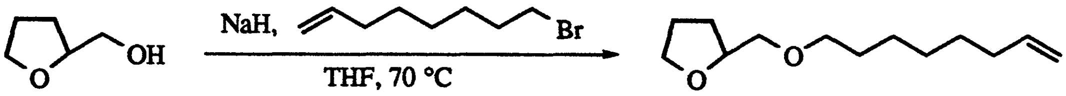

Figure 3. Synthesis of 8-octene tetrahydrofurfuryl ether from 1-bromo-8-octene and tetrahydrofurfuryl alcohol.

4.3 Polymerization Methods

4.3.1 Poly[3-vinylbenzyl tetrahydrofurfuryl ether]

The 3-vinylbenzyl tetrahydrofurfuryl ether monomer was first distilled under reduced pressure (3mm, 80 °C) to remove any low molecular weight impurities and then dried over calcium hydride. The monomer was then distilled under vacuum (3mm, 80 °C) before the polymerization. This leads to considerable loss of monomer because it polymerizes uncontrollably before the distillation is complete and forms an insoluble gel.

First attempts at polymerization of this monomer were free-radical methods using benzoyl peroxide (99% Aldrich Chemical Co.) recrystallized from acetone as an initiator as shown in Figure 4.

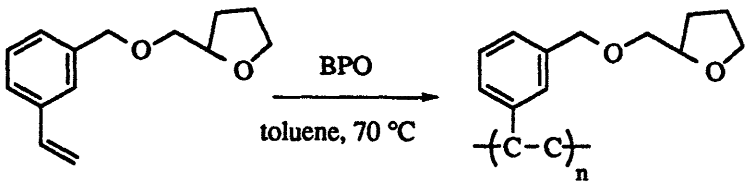

Figure 4. Polymerization of Poly[3-vinylbenzyl tetrahydrofurfuryl ether] using BPO.

The polymerization of the neat monomer at 85 °C resulted in an insoluble gel that was unusable. In order to control the molecular weight, toluene distilled from sodium benzophenone ketyl was used as a solvent. This still led to an unusable gel when 0.1% BPO was used as an initiator. When a chain transfer agent such as methanol is used, reasonable molecular weights are achieved, but the molecular weight distribution is very broad. Size Exclusion Chromatography(SEC) in THF shows a polydispersity index of 4, the molecular weight ranging from 4-50,000 g/mole. There are several problems with this polymer sample. First, it is necessary to have a molecular weight above 10,000 g/mole so ultrafiltration methods can be used for separation of the polymer from process streams. A polymer with a low molecular weight (<10,000 g/mole) fraction is therefore not desirable. Secondly, the resulting polymer is soluble in a 1:1 mixture of toluene:heptane. It was hoped that if a molecular weight fraction between 10-20,000 could be isolated it could be separated by ultrafiltration and without the higher molecular weight fraction it would be soluble in heptane only. The toluene/heptane mixture is suitable to demonstrate proof of principle for polymer-based solvents. This first polymer sample was used to get preliminary results.

Anionic polymerization was attempted in order to get a polymer sample which had a narrow molecular weight distribution above 10,000 g/mole, however it was impossible to initiate an anionic polymerization because the monomer could not be rendered pure enough or dry enough due to its high reactivity to auto-initiate its own polymerization free radically. Polymer Sources, Inc. of Dorval, Quebec, CANADA determined the conditions necessary for a controlled free radical polymerization of the monomer that would result in a polymer of low polydispersity and within the molecular weight range of 10-20,000 g/mole.

Benzene was distilled from sodium benzophenone ketyl. 2,2'-azobisisobutyronitrile (AIBN) (98% from Aldrich Chemical Co.) was recrystallized in ethanol and used as the initiator. Monomer, benzene, and initiator were placed in a 500 mL round-bottom flask which was sealed under vacuum. The polymerization was allowed to proceed under vacuum at 60-65 °C for 48 h with stirring. After the reaction was cooled to room temperature, the polymer was precipitated in hexane. The hexane was decanted and the polymer washed several times with more hexane. It was then dried in a vacuum oven at 60-70 °C overnight. The polymerization is shown in Figure 5.

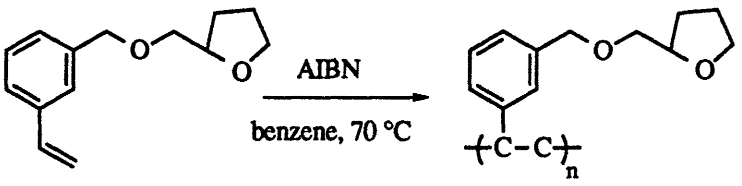

Figure 5. Polymerization of Poly[3-vinylbenzyl tetrahydrofurfuryl ether] using AIBN.

SEC was carried out on a Varian liquid chromatograph equipped with a UV detector and a refractive index detector. Three GPC columns from Supelco (G6000-4000-2000 HXL) were used with THF as eluent. 2% triethyl amine was added to the eluent in order to avoid polymer absorption onto the columns. The columns were calibrated with monodisperse polystyrene standards. The molecular weights and polydispersity index were calculated from the SEC data: M_n=11,600, M_w=21,400, PI=1.84. Fourier transform infrared spectroscopy was performed on a Nicolet Impact 400D. Polymer films were cast on a KBr window from chloroform solution and 16 scans were taken at a resolution of 2 cm^{-1}. A strong ether peak at 1090 cm^{-1} confirms the identity of the polymer.

4.3.2 Polymerization of allyl tetrahydrofurfuryl ether

The self-terminating polymerization undergone by allylic monomers when polymerized free-radically limits the polymer to low molecular weights, e.g. 5-10 monomer units.[1] It was hoped, however, that an oligomer could be made by free radical polymerization, but this particular monomer showed no reactivity towards free radical polymerization. Polymerization using BPO, AIBN, and redox initiators was attempted.

4.3.3 Polymerization of 8-octene tetrahydrofurfuryl ether

This monomer was also found to be unreactive to polymerization by free radical methods. BPO, AIBN, and redox initiators were tried.

4.4 Summary

Poly[3-vinylbenzyl tetrahydrofurfuryl ether] has been investigated as a model polymer-based solvent. Model reaction testing results can be used to determine what characteristics are desired for the THF polymer-based solvent. Solubility characteristics, for instance, can be altered by changing the structure of the polymer. It may desirable to not have a phenyl group present in the polymer, or it may be necessary to change the solution characteristics. It is known that monomers which are themselves unreactive to free radical polymerization can sometimes be copolymerized with very reactive monomers.[1] Thus, it may be possible to copolymerize the unreactive allyl and 8-octene tetrahydrofurfuryl ether monomers with the very reactive benzylic monomer. This would help to alter the solubility characteristics of the resulting polymer and lessen the amount of phenyl groups in the polymer Other options would be to make a copolymer of the benzylic monomer and butadiene.

Chapter 4. List of Figures.

Chapter 5

Testing of a model reaction in polymer-based solvent system and separation and work-up using microfiltration

5.1 Introduction

When developing a polymer-based THF replacement solvent, one must also consider that due to its high viscosity it will require dilution with a relatively benign continuous phase. Ideally, this diluent will be another solvent used in the reaction scheme. To develop a polymeric solvent to replace THF we first had to design a THF-derivatized monomer that would be simple to polymerize and that could be made from commercially available and fairly inexpensive materials. 3-Vinyl benzyl chloride was used to make 3-vinylbenzyl tetrahydrofurfuryl ether and the corresponding polymer as shown in Chapter 4. The use of the toluene is not ideal for the overall environmental goals of this work, but this specific example demonstrates the potential utility of a polymer-based solvent.

5.2 Materials and methods

5.2.1 Materials

10.0 g of poly[3-vinylbenzyl tetrahydrofurfuryl ether] was purchased from Polymer Sources, Inc., Dorval, Quebec, Canada. A known weight (4.25 g) of the polymer was transferred to an Aldrich sure-seal bottle in a glove box. The polymer was then diluted with dry toluene to make a 20 w/w% stock solution to use in the testing of the model reaction.

5.2.2 HPLC methods

HPLC methods used were the same as described in Chapter 2 for the low molecular weight replacement solvents.

5.2.3 Microfiltration

0.1 µm Durapore filters made for use in a centrifuge were obtained from Millipore. Aliquots taken from model reaction kinetic studies were microfiltered at 4500 rpm for one hour. The residue was washed with methanol twice and re-filtered. The filtrate from each washing was combined and used to make HPLC samples for kinetic analysis. Regenerated polymer was also microfiltered in this manner. Hexanes, which is a nonsolvent for the polymer, was used for final collection of the polymer and preparation for re-use.

5.3 Model reaction testing: Allylation of an acetonide

The model reaction used to investigate the polymer-bound solvents was the same as discussed in Chapter 2 for the low molecular weight solvents. Initial kinetics studies were done using poly[3-vinylbenzyl tetrahydrofurfuryl ether] made with the BPO initiator.

The progress of the allylation reaction in a 5.0 w/w% polymer in toluene[1] has been monitored using HPLC and compared to that of the n-octyl tetrahydrofurfuryl ether in heptane also at a concentration of 5.0%. Results are shown in Figure 1. While we knew that the 5% low molecular weight solvent is not going to completion because there is simply not enough ethereal solvent present, we were not sure why the reaction did not go to completion for the polymer-bound solvent. Was it because of the polymer, or was it simply that a higher concentration was needed? It was decided to make a more well-defined polymer with a molecular weight high enough so that it could be filtered, but not so high that we have viscosity problems or diffusional limitations. A monodisperse polymer with a molecular weight of 10,000 g/mole would help rule out these concerns. Unfortunately, due to problems with purifying this monomer, it was not possible to polymerize it anionically. So, the polymer was polymerized free radically using AIBN and fractionated to obtain as low a polydispersity as possible. Kinetics experiments were done using this polymer. Several different conditions were tried to improve the rate and progress of the reaction from the preliminary experiments. The main variables to manipulate were the concentration of the polymer and also the temperature of the reaction because these factors affect the viscosity[2] of the solution. Results for a 20% polymer solution at -30 °C are shown in Figures 2 and 3. Figure 2 shows that for the model reaction under these conditions, only about 40% of the acetonide starting material gets converted to product in the course of three hours. It was felt that this was due to the higher concentration of the polymer solution, or the low temperature. When the results are plotted on a log scale, as in Figure 3, it is seen that although the reaction does not go to completion, the polymer-based solvent shows similar kinetic behavior to THF and n-octyl tetrahydrofurfuryl ether. The model reaction was then attempted using a 10% polymer solution at -10 °C. These results are shown in Figures 4 and 5. The reaction still does not go to completion, but there is some improvement.

It was found that the allylation reaction did not go to completion in the polymer-bound solvent because the reaction to produce LHMDS (form n-butyl lithium and HMDS) did not go to completion. The benzylic proton of the polymer competes with the HMDS for deprotonation by the n-butyl lithium. This was tested by reacting the 3-vinyl benzyl tetrahydrofurfuryl ether monomer with n-butyl lithium in the presence of 1,10-phenanthroline as an indicator to titrate the n-butyl lithium to see if any was still active. The mixture of monomer and n-butyl lithium turned a dark brown indicating that a reaction had occurred.

However, even though the allylation reaction did not go to completion because there was not enough LHMDS present, the concept of using a polymer solution as a solvent did not appear to be a problem. To circumvent the problem of the polymer reacting with the n-butyl lithium, the LHMDS can be made in as small a volume of THF as possible. In this way, the polymer is not exposed to n-butyl lithium, only to LHMDS. However, it was found that the LHMDS is also able to deprotonate the polymer. As a result, the allylation reaction did not go to completion. Future work should, therefore, include the design and synthesis of a polymeric THF solvent that is completely inert to either or both of these bases.

5.4 Separation of polymer from reaction by microfiltration

As in the case of the n-octyl tetrahydrofurfuryl ether, the polymer is not lost to the water phase during workup. On a lab scale, the polymer is removed from the reaction mixture by ultrafiltration. In the specific case of the allylation reaction, for instance, quenching of the reaction with a solution of citric acid in methanol causes the polymer to form a suspension in solution and this mixture can then be microfiltered using a centrifuge. This process is repeated several times to ensure that all of the product and excess reagents are removed from the polymer. The reaction product and any excess reagents are thereby separated from the polymer and remain in the toluene diluent. The product can then be separated by recrystallization or carried on to the next step in the reaction scheme. The polymer may be washed with a nonsolvent, in this case hexane, and recovered by microfiltration for re-use. 95%+ of the polymer can be recovered in this way. It is anticipated that micorfiltration or ultrafiltration techniques can be used on an industrial scale for facile separation of the polymer from the process stream.[3]

5.5 Polymer re-use experiments

Polymer-based solvent that has been recovered as described in section 5.4 can be re-used in the model reaction with the same results. Since any polymer that has been deprotonated during the reaction is exposed to methanol when the reaction is quenched, the original polymer is recovered.

5.6 Summary

The polymer-bound solvents developed here will provide many opportunities for minimizing pollution, as they can be easily recovered and prevented from entering waste streams. Thus, these applications fall directly under the category of "source reduction" which is a primary goal of current pollution control practices. The high molecular weight solvents will not be volatile, and therefore the risk of polymer loss with air emissions will be negligible. Recovery of the polymers from the process streams by membrane microfiltration processes is anticipated to be more energy efficient than, say, distillation for the recovery of small amounts of solvents dissolved in effluent water streams. Moreover, risk of degradation of the solvents, as often occurs at the elevated temperatures required for distillation, will be greatly reduced. In addition, it is also possible that the solvents may be reused *in situ*, in membrane reactors, for instance, without the need for downstream recovery from effluent streams. Thus, these solvents will be intrinsically less-polluting than those traditionally used in the pharmaceutical and fine chemical industries.

Chapter 5. List of Figures.

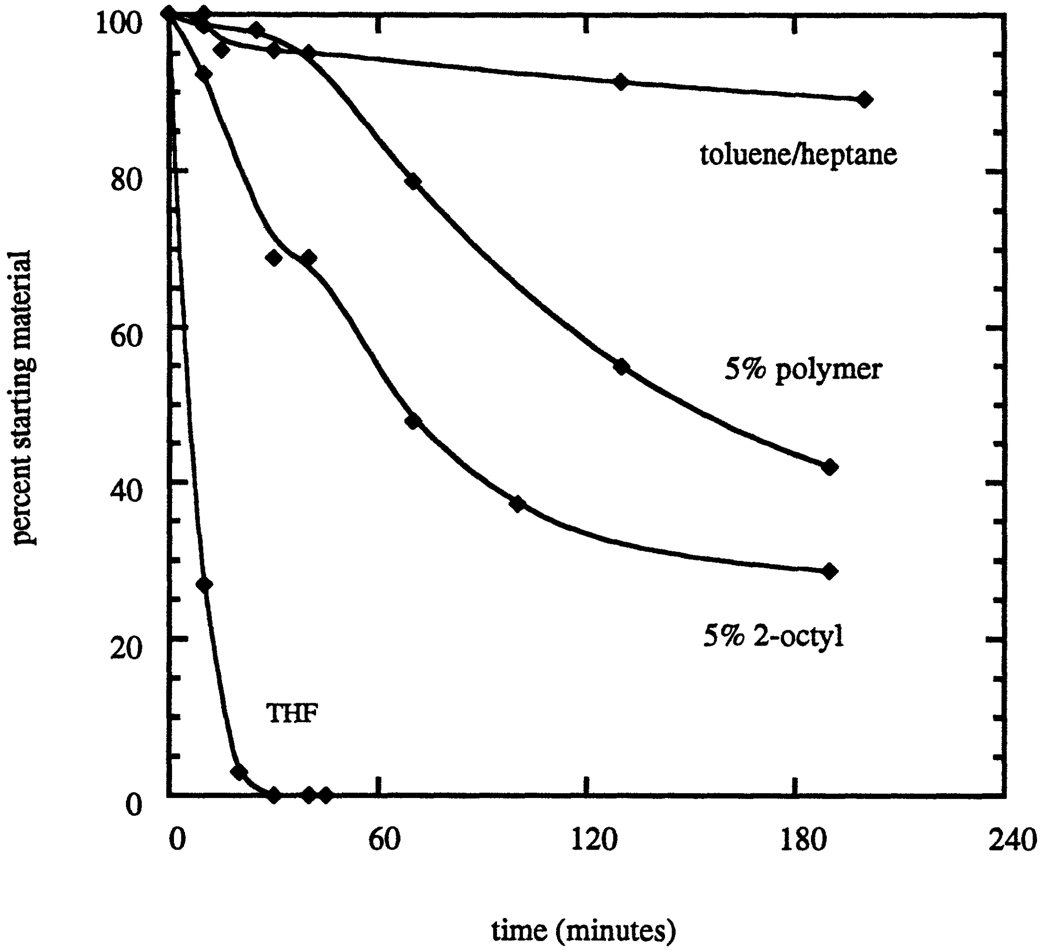

Figure 1. Percent starting material vs. time for THF, 5% n-octyl tetrahydrofurfuryl ether, and 5w/w% poly[3-vinylbenzyl tetrahydrofurfuryl ether] in toluene/heptane diluent.

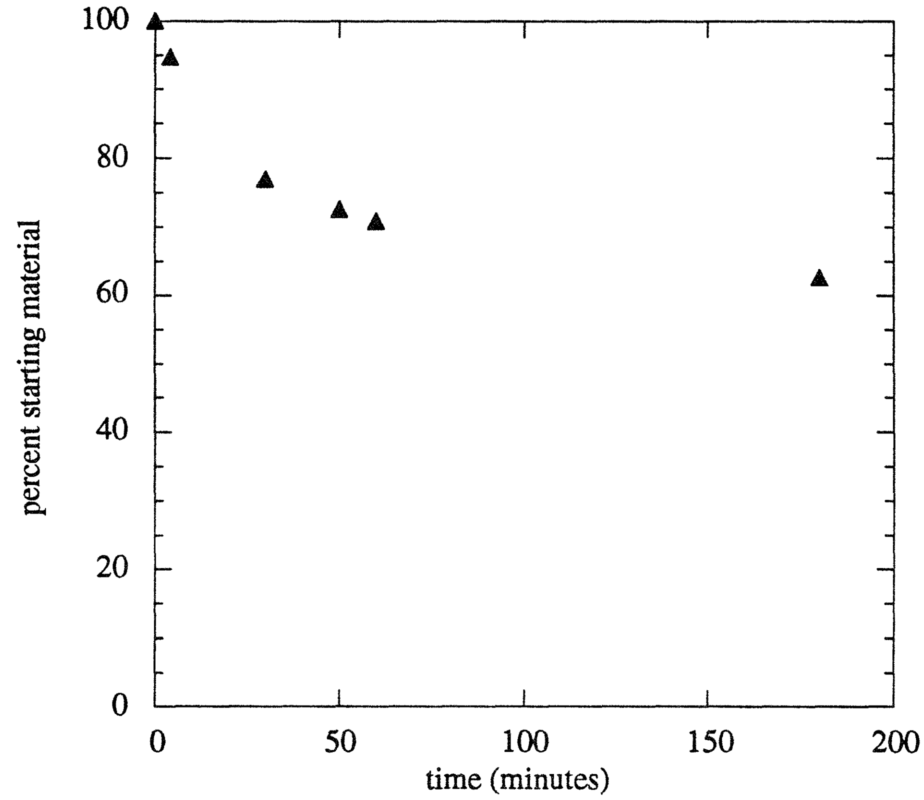

Figure 2. Percent starting material vs. time (minutes) for 20% polymer solution at T=-30 °C.

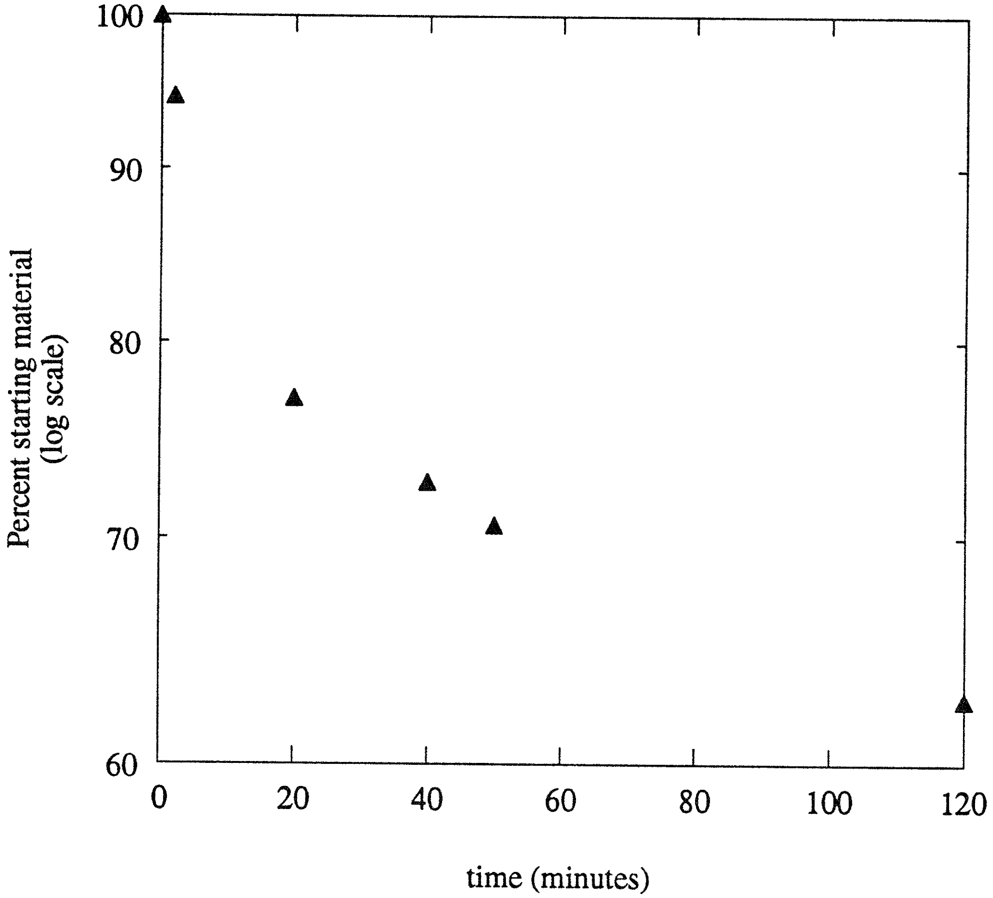

Figure 3. Percent starting material (log scale) vs. time for 20% polymer solution at T=-30 °C.

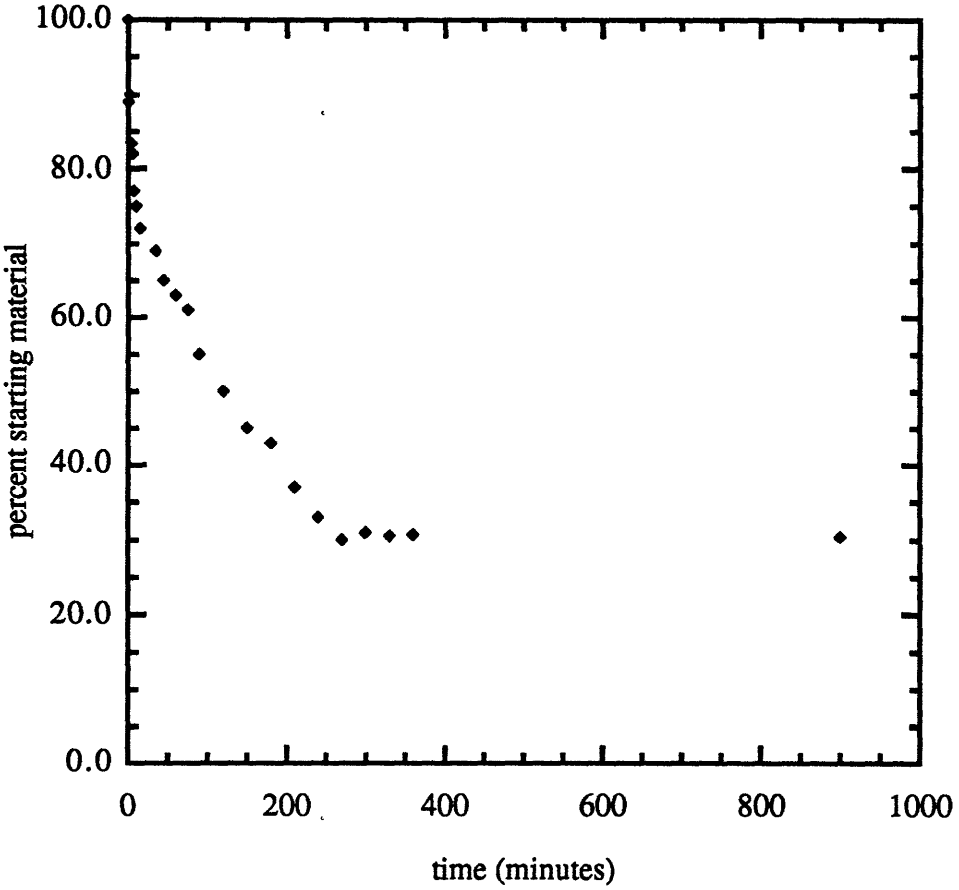

Figure 4. Percent starting material vs. time (minutes) for 10% polymer solution at T=-10 °C.

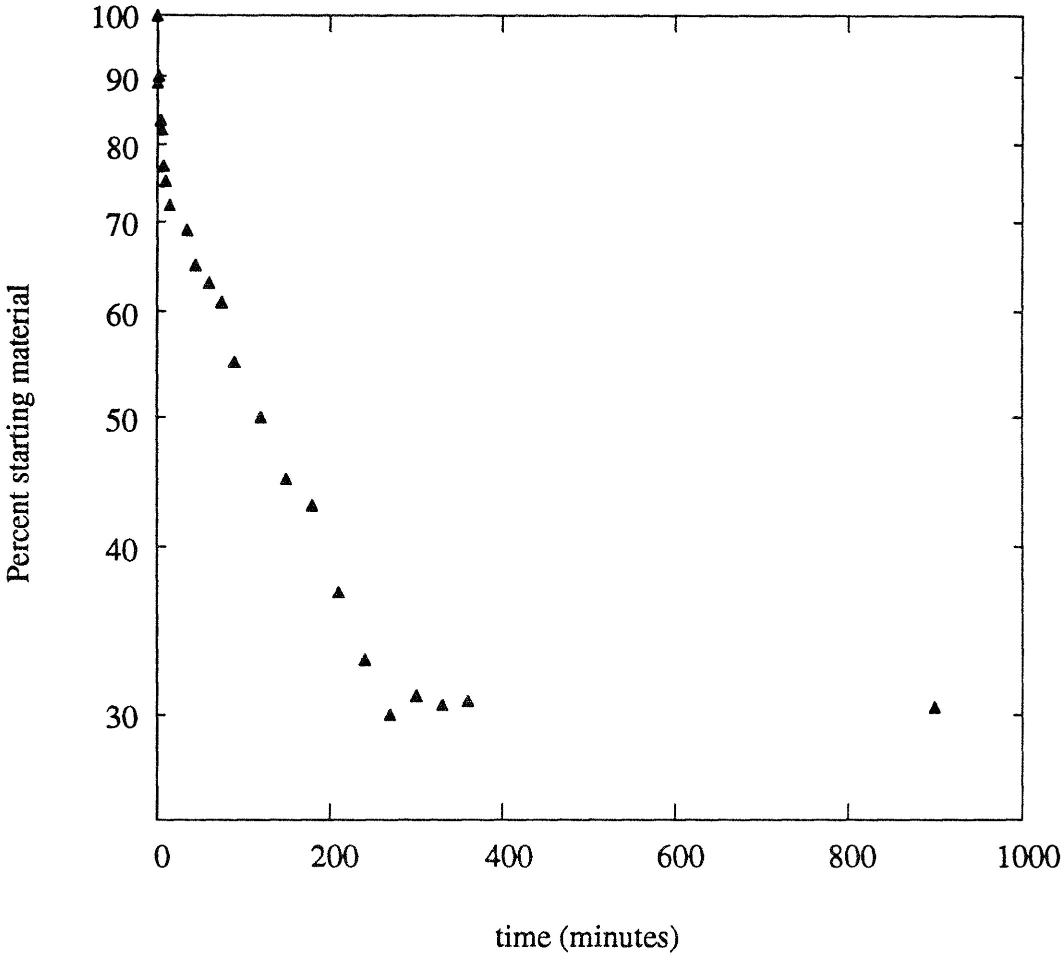

Figure 5. Percent starting material (log scale) vs. time for 10% polymer solution at T=-10 °C.

Chapter 6

Summary and Future Work on Low Molecular Weight and Polymer-Based Replacement Solvents

Many application opportunities exist in the area of organic synthesis. Solvent replacement of THF is an interesting area to study because it is a rather ubiquitous reaction medium. For instance, THF is used for metal hydride, Grignard, acid chloride addition to amines, and methylation reactions. One important reason for trying to replace THF is the fact that THF is fully miscible with water. This poses problems in the bigger picture of the reaction, extraction and isolation sequence for the synthesis of products. In a typical sequence, a reaction carried out in THF is extracted with water to remove salts and polar substituents. This may cause some of the product to be "dragged" into the aqueous phase. The product must then be isolated, which involves a switch to a solvent in which the product will crystallize. It is this continuous switching of solvents which is problematic in pharmaceutical processing. Solvent changes are time-consuming, introduce potential pollutants which must be removed, and produce a large amount of waste.

In developing new solvent systems for THF there are several important characteristics to keep in mind. The solvent system should be inert, non-foaming (this may be a problem if polymers are eventually used), non-explosive, and nontoxic. THF can form peroxides which is a safety and a practical issue because it cannot be contained in large volume tanks and therefore leads to waste removal problems. In addition, it should be immiscible with water so it is not necessary to add a non-solvent in the extraction process to get a phase split. Also, since THF is used for very exothermic reactions that rarely go above 25 °C and sometimes are run at -20 to -70 °C, the new solvent system should be able to provide the requisite solvation properties at these temperatures. Another factor which must be considered is the target concentration of the solute. For the reactions considered it is roughly estimated that the new solvent system should be 50% THF-like meaning it must be able to solubilize a certain concentration of solute.

The development of new solvents will present new challenges in the separation and work-up of products. It is envisioned that our replacement solvents can be part of an intelligent reaction/separation sequence that improves upon currently used sequences in terms of both environmental impact and productivity. The low molecular weight n-octyl tetrahydrofurfuryl and tetrahydro-3-furan methane ether solvents have the advantage that they will not be lost to the water phase during the work-up as would tetrahydrofuran, but they may have to be distilled from the products in some cases. As discussed in Chapter 2.4, it may sometimes be possible to add the recrystallization solvent (i.e. hexanes) directly to the mixture of derivatized solvent and product. The polymeric-based solvents provide more opportunities for facile separation trains because they will not be lost to the water phase during work-up and because of their higher molecular weight they can be ultrafiltered in order to separate them from the product. The use of polymer systems in production is appealing to industry since membrane separations are rated as the cheapest unit operation in pharmaceutical production facilities. Polymeric solvents can be part of an integrated reaction, product recovery and solvent regeneration process whereby the polymeric solvents are diluted in the recrystallization solvent for the product. Thus, after filtration the product is left in its recrystallization solvent for isolation and purification and the polymeric solvent can be regenerated for reuse.

Molecular Modelling

Molecular modelling will be an important component of this work, as it will enable us to evaluate the solvation properties of the different polymers *a priori* to aid in the design of new solvent systems. Commercially available computer packages from Biosym will be used for this purpose. The Solvation module (see Biosym User's Guide DelPhi and Solvation manual, Version 2.5, December 1993) will be used to build a chemical structure library of our THF derivatives and other solvent substitutes and to examine their solvation properties in water and other organic solvents. Thus, with this program we would be able to test various THF derivatives in both water and hexanes to find those structures with minimal water solubility and maximum solubility in hexanes. It would be useful to determine if there exist any differences in solubility for the two and three position alkyl ethers. With complementary experimental data we may also be able to use Biosym to determine the structure of the solution that forms when our THF derivatives are added to water or hexanes, i.e. clustering or micelle formation. Thus, with these programs we can determine the solvation energies and do conformational analyses at the pertinent temperatures.

Engineering Aspects/ Cost Analysis

The criteria for performance evaluation cannot be formulated solely on the basis of the reaction parameters themselves, but must be put in the broader perspective of an integrated reaction, product recovery and solvent regeneration process. Thus, while it is possible that the intrinsic reaction step may be less than optimal in the new solvent systems, the gains to be made in subsequent downstream processing steps could be expected to more than compensate for any reduction in reactor productivity. For this reason, it will be necessary to adopt a systems engineering approach for the evaluation of the entire reaction/separation sequence. This will depend on the availability of appropriate systems models, which will be constructed as required, and when warranted by progress in the polymeric solvent synthesis and reaction parameter determination. The systems models will rely on the capabilities inherent in commercial packages such as ASPEN, using standard models for the various unit operations and using physical property information generated during the course of this research.

Other related areas of research include determining the cost-effectiveness of replacing THF with n-octyl tetrahydrofurfuryl ether. Because THF is fully miscible with water, it is necessary to distill them apart for removal of THF from waste streams and/or regeneration of THF. This is a costly and time-consuming procedure because THF and water form a minimum boiling azeotrope at a THF concentration of 84%.

Physical characterization of polymer-based solvent systems

Some of the most important future work will be the physical characterization of the polymer-based solvents. Viscosity measurements will be crucial in determining the upper concentration limits of polymer that can be handled on an industrial scale. These measurements can be done in the same way as described for the low molecular weight THF derivatives. Phase diagram determination so that the solution structure of the polymer will be known over the temperature range of interest will also be important so that we are not working in a regime where phase separation has occurred.

Other application areas

Other potential applications are in differential precipitation of products, as solvents for extraction and absorption operations, as vessel cleaning agents, and as microreactors. Generally, vessels are cleaned by several solvent flushes. These solvents may also contain detergents or surfactants. Solvent flushes are very ineffective for cleaning steroids from the vessels and result in a significant down time for the use of the equipment. In addition, the current system creates a large volume of solvent waste. Polymeric solvents may be able to solubilize and concentrate the waste removed. Polymer micelles acting as microreactors could be useful in applications where the organic molecules used in the synthesis are not soluble in water, but it is advantageous to run the reaction in an aqueous environment. The micelles would solubilize the biomolecules to enable the reaction to be carried out in aqueous media. Our THF replacement solvents may be useful in reactions which are run in a mixture of THF and water. This is done so unwanted byproducts such as salts move to the water phase. The problem is that some THF is also lost to the water phase. Thus, our non-watersoluble THF replacements may prove to be useful. This could also be helpful in extractions processes. Other ideas include our replacement solvents made with chiral centers for use in chiral synthesis. Finally, it is anticipated that the concepts developed in this thesis would be applicable to other organic solvents as well.

Appendix A

Kinetic data for low molecular weight replacement solvents

Table A.1 Raw data from Chapter 2, Figures 5-7. HPLC monitoring of allylation reaction using various solvents and solvent mixtures. Values given are percent of acetonide starting material remaining as monitored by HPLC and are an average value determined from at least three experimental trials.

time min.	THF	2-octyl	3-octyl	MTBE	50:50 2-octyl	25:75 2-octyl	10:90 2-octyl	5:95 2-octyl	heptane	50:50 THF	10:90 THF
0.0000	100.00	100.00	56.500	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
10.000	26.900	17.400			20.430	93.610	89.470	92.330	99.400	35.700	
15.000			54.000								
20.000	3.0000	7.1000			16.360	53.230				8.9400	
30.000	0.0000		52.000	99.520	9.2700	47.890	60.500	68.970		6.4000	
40.000	0.0000				4.8800	23.530			97.320	5.8000	
45.000			40.950	98.500							84.300
50.000		2.4000				17.980	43.280			5.2000	
60.000				94.830	2.4900	14.250					
70.000		0.0000			1.0900	10.820	28.470	47.990	93.560		
80.000					0.510		24.800				
85.000						6.9400					
100.00							19.590	37.300			71.300
120.00						5.2900					
130.00						1.9800	12.720		91.490		
150.00											62.300
180.00			4.3000	80.190			4.0800				
190.00								28.700	91.000		
200.00						0.0000	2.3000				55.700
240.00											54.800

Table A.2 Raw data from Chapter 2 Figure 8. Comparison of model reaction results for THF and 2-octyl at T=-30 °C and with excess allyl bromide (10 eq). Values given are percent of acetonide starting material remaining as monitored by HPLC and are an average value determined from at least three experimental trials.

time (seconds)	2-octyl	THF
0.0000	100.00	100.00
5.0000	78.000	
10.000		80.000
30.000	69.000	66.000
60.000	61.600	55.000
120.00	55.000	41.000
180.00	51.000	34.000
240.00	46.000	29.000
300.00	42.500	25.000
360.00	38.400	
420.00	34.100	
480.00	34.700	
540.00	32.600	
600.00	31.020	
900.00	26.500	
1200.0	21.800	
1800.0	17.000	

Table A.3 Raw data from Chapter 2, Figure 9. Comparison of THF kinetics for 10 and 20 eq of allyl bromide. Values given are percent of acetonide starting material remaining as monitored by HPLC and are an average value determined from at least three experimental trials.

time (seconds)	10 eq	20 eq
0.0000	100.00	100.00
10.000	80.000	76.000
30.000	66.000	65.000
60.000	55.000	54.000
120.00	41.000	37.000
180.00	34.000	29.000
240.00	29.000	24.000
300.00	25.000	
600.00	16.000	

Table A.4 Raw data from Chapter 2, Figure 10. Influence of temperature on model reaction run in THF at T=-15 °C, -30 °C, and -45 °C. Values given are percent of acetonide starting material remaining as monitored by HPLC and are an average value determined from at least two experimental trials.

time(seconds)	T=-15 °C	T=-30 °C	T=-45 °C
0.0000	100.00	100.00	100.00
5.0000	71.500	81.400	91.000
15.000	59.200	70.700	76.700
30.000	54.800		69.800
40.000	51.100		
60.000	46.300	58.600	58.700
120.00	32.700	43.000	47.400
180.00		31.000	36.000
240.00		19.000	31.300
300.00			24.900
360.00			
420.00			20.230

Table A.5 Raw data from Chapter 2, Figure 11. Rate constants for Arrhenius plots from model reactions run in THF at T=-15, -30, and -45 °C, and in 2-octyl ether and 2-octyl ether diluted with heptane at T=0, -15, and -30 °C.

T (°C)	1/T (K)	k, THF	k, 2-octyl	k, 50:50	k, 25:75	k, 10:90
0.0000	0.0037000		0.0030000	0.0014550	0.00072300	0.00029340
-15.000	0.0039000	0.0060000	0.0026000	0.0012470	0.00066700	0.00025470
-30.000	0.0041000	0.0051000	0.0021500	0.0010950	0.00052480	0.00021200
-45.000	0.0044000	0.0040000				

Appendix B

Physical property data for low molecular weight replacement solvents

Table B.1 Raw density data from Chapter 3, Figures 4 and 5. Densities (g/mL) of n-alkyl tetrahydrofurfuryl and tetradydro-3-furan methanol ethers as a function of percent volume of replacement solvent in hexanes.

vol% solvent	THF	3-butyl	3-octyl	2-butyl	2-hexyl	2-octyl
0.0000	0.66960	0.66680	0.66690	0.66650	0.66650	0.66670
10.000	0.68750	0.69360	0.69410	0.69120	0.68950	0.69310
20.000	0.70980	0.71670	0.71440	0.71750	0.72060	0.71550
30.000	0.72860	0.74270	0.74060	0.74050	0.74130	0.74340
40.000	0.74910	0.76850	0.75980	0.76270	0.76600	0.76910
50.000	0.77230	0.79240	0.78140	0.78960	0.78620	0.78940
60.000	0.79370	0.82020	0.80570	0.81270	0.81290	0.82520
70.000	0.81700	0.85000	0.82640	0.83280	0.83440	0.83800
80.000	0.83960	0.86700	0.84810	0.86240	0.86010	0.86010
90.000	0.85920	0.88910	0.87070	0.88580	0.87740	0.87230
100.00	0.88260	0.91170	0.88890	0.90700	0.89570	0.88730

Table B.2 Raw surface tension data from Chapter 3, Figure 6. Surface tension (dynes/cm) for a given mole percent of THF or replacement solvent in hexanes.

mol% THF	THF	mol% 2-butyl	2-butyl	mol% 2-hexyl	2-hexyl	mol% 2-octyl	2-octyl
0.0000	18.800	0.0000	18.800	0.0000	18.800	0.0000	18.800
7.0000	18.900	4.0000	18.900	6.0000	19.300	3.7000	19.200
14.000	18.900	7.0000	19.100	11.000	19.600	5.6000	19.500
24.000	19.400	13.000	20.050	19.000	20.500	12.000	20.200
32.000	19.800	21.000	20.500	27.000	21.300	20.000	20.850
40.000	20.400	28.500	21.000	38.000	22.100	26.000	21.400
52.000	20.900	37.000	21.700	43.000	22.800	35.000	22.100
61.000	21.300	46.000	22.500	55.000	23.400	39.000	23.000
74.000	22.100	58.000	23.100	65.000	23.500	44.000	23.400
88.000	23.600	69.000	23.200	79.000	23.600	52.000	23.400
93.450	24.500	78.700	23.500	83.000	23.700	61.000	23.850
100.00	26.500	85.000	23.600	88.000	23.900	76.000	24.000
		92.000	23.700	94.000	24.000	81.000	24.300
		100.00	24.400	100.00	24.500	87.000	24.500
						93.000	25.200
						100.00	25.900

Table B.3 Raw data from Chapter 3, Figures 9-13. I_1/I_3 ratios of the fluorescent probe pyrene in n-butyl tetrahydrofurfuryl ether, THF and mixtures of n-butyl tetrahydrofurfuryl ether and THF with hexanes.

mol% in hexanes	2-butyl T=-10 °C	2-butyl T=10 °C	2-butyl T=25 °C	THF T=-10 °C	THF T=10 °C	THF T=25 °C
0.0000	0.77000	0.72000	0.59200	0.81000	0.74000	0.66500
0.15000				0.96000	0.85000	
0.15700	1.0000	0.89000	0.85000			
0.28400						0.88000
0.33000	1.1000	1.0700	1.0100			
0.40100				1.1300	1.0400	
0.51000						1.0700
0.53000	1.2900	1.2500	1.1250			
0.61200				1.2900	1.2100	
0.70000						1.2200
0.75000	1.4000	1.3400	1.2500			
0.78000				1.4100	1.3450	
0.86000						1.3500
0.93000				1.5400	1.4700	
1.0000	1.4700	1.4500	1.3500	1.6000	1.5250	1.4500

Appendix C

Kinetic data for polymer-based replacement solvents

Table C.1 Raw kinetic data from Chapter 5, Figure 1. Values given are percent of acetonide starting material remaining as monitored by HPLC and are an average value determined from at least three experimental trials.

time (minutes)	5% polymer in toluene	toluene control
0.0000	100.00	100.00
10.000	98.500	100.00
15.000		95.430
20.000		
25.000	97.990	
30.000		95.430
40.000	95.000	
45.000		
50.000		
60.000		
70.000	78.700	
75.000		
80.000		
85.000		
90.000		
100.00		
120.00		
130.00	55.000	91.400
150.00		
180.00		
190.00	42.000	
200.00		89.200

Table C.2 Raw kinetic data from Chapter 5, Figures 2-5. Values given are percent of acetonide starting material remaining as monitored by HPLC and are an average value determined from at least three experimental trials.

time (minutes)	10% polymer T=-10 °C	20% polymer T=-30 °C
0.0000	100.00	100.00
1.0000	89.000	
2.0000	90.000	
4.0000	83.400	94.600
5.0000		
6.0000	82.000	
8.0000	77.000	
10.000	75.000	
15.000	72.000	
20.000		
30.000	77.000	
35.000	69.000	
45.000	65.000	
50.000		72.700
60.000	63.000	70.600
75.000	61.000	
90.000	55.000	
120.00	50.000	
150.00	45.000	
180.00	43.000	62.700
210.00	37.000	
240.00	33.000	
270.00	30.000	
300.00	31.000	
330.00	30.500	
360.00	30.700	
900.00	30.400	

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