Modelling Resin Swelling in Mixed Solvents and Its Applications

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MSc by Research

University of York

Chemistry

December 2018

Abstract

The resin swelling of Merrifield and HypoGel™200 resins in different volume/volume ratios of binary solvents was investigated. The results show that there is usually not a linear variation of resin swelling on changing the ratio of two solvents. High, medium and low swelling regions for each resin can be determined within the Hansen solubility parameter (HSP) 3D space model. If the line connecting two solvents goes through the high resin swelling region in HSP space, then there will be mixtures of the two solvents that will make the resin swell more than either pure solvent.

To illustrate the significance of this effect, binary mixtures of two green solvents were predicted which could replace the traditional organic solvents used in solid-phase peptide synthesis. The experimental results confirm that appropriate ratios of the solvent mixtures give better synthetic results than either pure solvent. In another application of this model, binary solvents were used to dissolve polystyrene. Generally, mixtures of two solvents at an appropriate ratio were found to more rapidly dissolve polystyrene than the parent solvents. Comparison of the resin swelling results obtained on the same resin backbone with different functional groups show that the functionality does not influence the magnitude of resin swelling. However, it could influence the optimised ratio of two solvents needed to optimally swell the resin. In addition, the resin swelling experiments demonstrate that some binary mixtures of two solvents have strong solvent-solvent interactions which prevent the mixed solvent from interacting with the resin matrix.

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Acknowledgements

Time flies very fast. Until now, I have stayed at York for one year. Thinking back to the first day I arrived at York, I felt extremely helpless as it was my first time to go abroad for a long time by myself. But now, everything has become better and I feel grateful for everything and everyone who has helped me in my research life. In the past, I was a person without dream and had no passion for life. However, everything has been changed since I met Michael North who is my supervisor. He is the first person I want to say thank you to for teaching me to be enthusiastic and dedicated to my work. When I feel frustrated about my research work, he always gave me a lot of concerns and good suggestions. I appreciated what he did for me. It is he who made my goal for my life clearer. Secondly, I would like to say thank you to Ian Ingram who is my lab supervisor. During my research, he gave me a lot of guidance for my lab work. He also taught me to use a lot of software, analyse ^{1}H NMR COSY spectra and how to do academic writing. He is a very good supervisor, caring about my study and life. I think I could not have finished my project successfully without him.

Then I want to appreciate Han Li, the only classmate for me; she has given me much assistance in my experiments and much emotional support over this year. Thanks must also go to Xiao Wu, who taught me how to analyse ^{1}H NMR patiently and helped me to translate what I could not understand from Mike and Ian. Thank you to Yang Gao, Xiangju Meng, Long Zhou and Hao Xia, they taught me how to do lab duty and always helped me to do lab duty together. They are like my family and make me not feel lonely abroad. I would also want to thank Maria del Prado, she gave me the happiest time abroad. She has taught me to balance work and life. She said she hoped I would not forget her when she went back to Spain. I want to say "of

course, we are sisters”. Thank you, my best friend. Thank you to Anna Zhenova for teaching me English every week. She let me know a lot of very funny and native English slangs. Wenting You and Li Chen are also people I want to thank for showing me a lot of concern and helping me.

Thank you to other people in the Green Chemistry Centre of Excellence, Roxana Milescu, Fergal Byrne, Katie Lamb, James Sherwood, Yann Lie and Hannah Briers. In the past year, they gave me a lot of advice for my experiments and helped me to analyse my samples many times. I could not have finished my project without them. I have met so many nice people in York who make me feel happy, and I have had an impressive experience here.

Finally to my parents, my aunt and my boyfriend who gave me financial and spiritual support so that I could have the opportunity to come here to study and have courage to overcome difficulties.

Declaration

I declare that this thesis was written by myself and all experiments were done by myself, except where acknowledged in it and for some suggestions obtained from my supervisors. I have never submitted this thesis for a degree or any other purpose previously.

Yanrui Ran

December 2018

1. Introduction

1.1. The significance of green chemistry

In our recent industrial past, vast quantities of pollutants have been released into the air, land and water upon which our ecosystems and we ourselves depend.[1] A variety of industrial sectors are to blame for this pollution, with chemical manufacturing being amongst the worst offenders.[1] As issues such as air pollution, water pollution, and climate change are drawing increasing attention, more legislation is being enacted to attempt to mitigate pollution and problematic aspects of chemical processing.[1] Inevitably, the chemical industry will need to continue , as it is a necessary part of science and its advancement impels the progress of society. Hence the field of “Green Chemistry” has arisen over recent decades as chemists and manufacturers of chemical products begin to think about the use of more sustainable and environmentally benign methods and materials to reduce environmental impact and keep pace with a changing regulatory framework.[1]

Since the 1990s, creative and innovative chemists have focused on new methods which not only address environmental problems, but also have high chemical yields. By using a lot of data from previous experience, chemists can avoid toxic substances, and choose more environmentally-friendly reagents and solvents which have fewer effects on human health and fewer ecological impacts. On the other hand, by analysis of the synthetic route and calculating the atom efficiency, chemists can rapidly evaluate the potential waste of a given reaction and get alternative, more efficient, routes to their target products.[2] Simply stated, green chemistry is about using more benign techniques and methodologies to reduce or eliminate hazards from chemical processes resulting in positive effects upon the environment whilst increasing atom utilization to get high yields of products with reduced waste.[1] In 1998, Paul Anastas first stated the 12 principle of green chemistry, and these principles have become basic criteria for green chemistry, especially when we design reactions or during chemical processes:[3]

1. Waste prevention is much more significant than waste management when a chemical reaction is carried out.
2. When a chemical synthetic method is designed, the atom utilization should be maximised.
3. Fewer or no hazards should be generated wherever chemical syntheses occur.
4. Chemicals should be designed with less toxicity and appropriate function.
5. Auxiliary substances should be avoided during chemical processes if possible, and if needed should have little or no toxicity.
6. Try to minimize energy use and it is better to carry out chemical reactions at ambient temperature and pressure if possible.
7. It is a priority to choose renewable raw materials rather than use non-renewable resources.
8. Minimize or avoid derivatives such as unnecessary intermediate products, protecting groups and by-products.
9. Give preference to catalysts rather than use of stoichiometric concentrations of compounds.
10. Chemical products should have the desired function and be degradable.
11. Use instantaneous analysis including real-time monitoring and control in the development of chemical operation aiming to reduce or prevent pollutants and toxicants.

12. When choosing chemical substances to be used in chemical reactions, select the ones which are less volatile, less explosive and less flammable to avoid chemical accidents.

By integrating these 12 principles, green chemistry aims at designing more benign ways for chemical production.

1.2. The urgent need for greener solvents

Alternative solvents as an important part of green chemistry, have been investigated for about 50 years, but “Green Chemistry” emerged as a subject only since 1998 when Paul Anastas set out the foundational principles for it.[3] The term ‘green solvents’ means those that are less toxic; have reduced environmental impact, including impacts from their disposal; or derive from bio-based feedstocks which have a reduced environmental and especially greenhouse-gas footprint associated with their production.[1] Although it is difficult to select greener solvents, there are still a lot of chemists developing some guides on the basis of safety, health, environmental quality and industrial constraints. Following these guides and advice,[4,5,6] chemists can select a “green” or sustainable solvent.

In traditional organic chemistry, solvents play a crucial role. In pharmaceutical and in fine chemical processing, solvents typically make up 80-90% of the total mass of the reaction mixture.[7] Furthermore, organic solvents are also extensively used in a variety of industrial processes such as paint manufacturing, spray painting, shoe making and clothes production.[8] Many conventional solvents are not environmentally-friendly and are known to be reprotoxic. For example, before the late 1980s, carbon tetrachloride was widely used in cleaning and degreasing processes because it can evaporate quickly and dissolve large amounts of organic compounds, as well as having low flammability and good stability; but later its use was phased out under the Montreal Protocol to prevent damage to the ozone layer.[9] Also, according to a lot of studies, carbon tetrachloride damages the liver in humans and animals.[10] Dichloromethane is a widely used chlorinated solvent in laboratories, chemical production and the pharmaceutical industry. However, since the 1980s, studies have shown that it has potential carcinogenicity, tumorigenicity and genotoxicity for people exposed to it.[11] Even more seriously, benzene was used in cosmetics before it was assessed to have carcinogenicity.[12]

Conventional solvents used in solid-peptide synthesis such as dimethylformamide (DMF) are also regarded as being highly toxic.[6,13] Many other traditional solvents (like diethyl ether) have high volatility, high flammability, low boiling points and strong odours, which may pose more issues.[13] Solvents or chemicals which are used in lacquer, acrylic and marker removers have even been found in the fresh water systems which are essential for human beings and animals to survive, and these chemicals do permanent damage to aquatic organisms.[14] Therefore, there is an obvious need for “greener” alternatives.

1.3. The development of resins which are used as a solid-phase in organic synthesis

Since 1963,[15] solid phase synthesis has been an option for chemists. Solid (polymers) supported methods are used in peptide synthesis during which the peptide chain is attached onto the solid-phase during the synthetic process. Or in other areas, enzymes or catalysts, for example, are immobilized on a solid-phase[16] (Figure 1-1 and Figure 1-2). Although conventional solution phase synthesis has developed over many years, it needs a lot of complicated and time-consuming processes, such as distillations, recrystallizations, and many complex purifications.[17] A series of these procedures could give low yields of products and generate multiple hazards. Compared to synthesis carried out in solution, solid-phase synthesis has apparent advantages. For instance, solid-phase organic synthesis has simple and rapid purification and often an easier work-up. In addition, Wei Zhang and Berkeley W. Cue stated in 2012 that solid-supported catalysts are vital for most flow synthetic processes as they can accelerate syntheses and purifications.[18]

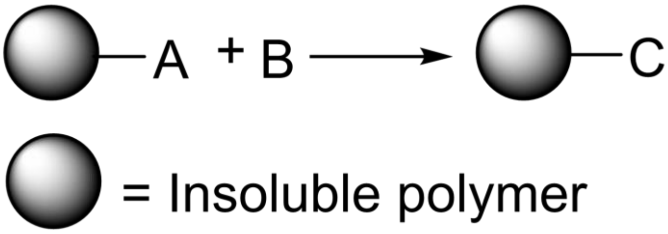


Figure 1-1: Conceptual figure of solid-phase organic synthesis

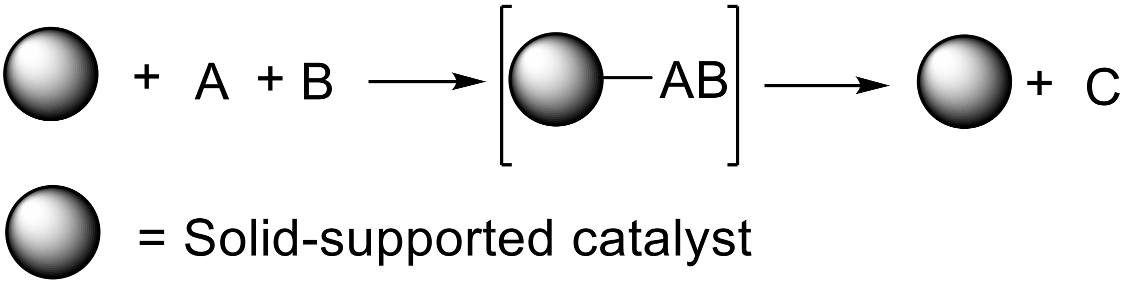
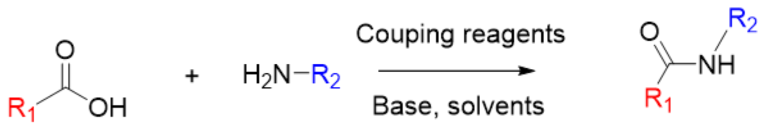


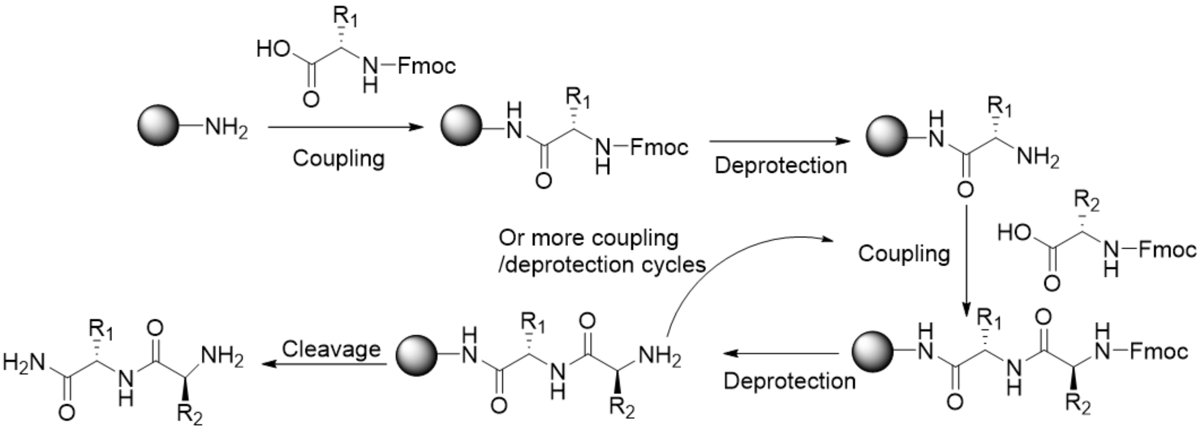
Figure 1-2: Conceptual figure of solid-supported catalysts for organic synthesis

There have been many significant contributions to the development of solid-phase organic synthesis. Professor R. Bruce Merrifield[17] at Rockefeller University and

Professor Robert Letsinger[19] developed the solid supports simultaneously. Resins, which means polymers which can be utilized as solid supports, have different backbones and functionalities. For use as a solid-support in solid-phase peptide synthesis (a peptide, by definition, is a polymer or oligomer made up of a sequence of amino acids.[16]), resins should be insoluble in all solvents which are to be used in reactions, while they have to contain reactive functionalities which could be used to attach amino acids by a covalent bond.[17] For example, in 1963, a chloromethylated copolymer of styrene and divinylbenzene was found which could meet these two requirements and work very well.[15] Now it is called Merrifield′s peptide resin and is used extensively in solid-peptide synthesis. However, products obtained by this technique are, in general, difficult to purify, and the resin is not applicable to all synthetic peptides.[20] For example, when peptide synthesis is carried out between aspartic acid and glutamic acid, there is a transesterification side reaction which generates toxic side products (imides).[20] Thus, although in some cases the efficiency of purification for peptides could be increased by using complicated and time-consuming techniques, such as selective proteolysis[21] or affinity chromatography,[22] a new resin needed to be developed. Based on the work of R. B. Merrifield, another new resin, which is p-alkoxybenzyl alcohol resin ($HOCH_2C_6H_4OCH_2C_6H_4$ resin), was developed by Su-Sun Wang, it is called Wang resin and gave more satisfactory results in the formation of peptides with a C-terminal carboxylic acid.[23] The general schemes of solid-phase peptide synthesis are shown in Scheme 1 and Scheme 2, with the peptide chain growing on the solid-phase.



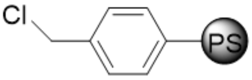
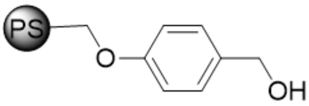
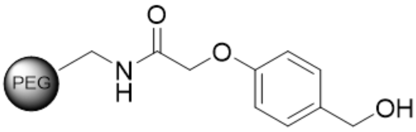
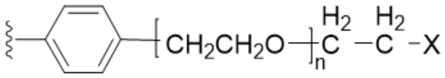
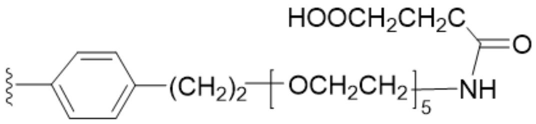
Scheme 1: The general scheme of peptide synthesis



Scheme 2: General mechanism of solid-phase peptide synthesis; amino acids are usually protected with protecting groups, such as N-α-(9-fluorenylmethyl)oxycarbonyl (Fmoc, in solid-phase peptide synthesis), t-butyloxy-carbonyl (t-Boc in solution-phase peptide synthesis) and the carboxyl group of one amino acid needs to be activated for forming the peptide bond.

As Merrifield resin and Wang resin are both polystyrene-based resins, they are both hydrophobic, and this is a limitation for solid-phase organic synthesis because it will prevent polar solvents from entering into the polymer matrix.[24] This limitation impelled chemists to design more hydrophilic resins which have polyethylene glycol-polystyrene backbones.[24] Many PEG-PS resins which have different lengths of the PEG chains are now commercially available.[24] Owing to the combination of hydrophobic polystyrene and hydrophilic polyethylene glycol and the differing lengths of the PEG chains in different resins, these resins can perform very well in both polar and nonpolar solvents.[24] However, they also have some drawbacks: for example, TentaGel, which was developed by Bayer and Rapp[25], is usually synthesized by reacting the oligooxyethylene units with p-aminomethylated polystyrene: 1% divinylbenzene copolymer beads or by grafting the polyethylene glycol-polymer to polystyrene beads. It has been shown that proteins would be immobilised on the surface of it during peptide synthesis because it is polyporous. In addition, at most 15% of the functional groups are on the surface so that some amino acids may not access to all of the reactive groups, resulting in the peptide sequence being truncated.[26] Another resin was developed which has five polyethylene glycol units on the PEG-PS backbone, terminating with carboxylic acid functionalities, and it was named HypoGel™200-COOH resin.[27] When it was applied in peptide synthesis, it was reported that the coupling efficiency went down compared to other PEG-PS resins.[26] A totally PEG resin was developed by Meldal[28,29] and Andreu[30], and named as ChemMatrix resin. By comparison to PEG-PS resins, it has a lot of advantages, such as helicity of its structure, both hydrophilicity and hydrophobicity and it can be swollen in most polar and nonpolar solvents.[24] （Table 1-1）

Table 1-1: Chemical architectures of different resins

Resin name	Year	Structural formula
Merrifield resin	1963	
Wang resin	1972	
Wang-ChemMatrix® resin	1996	
TentaGel® resins	1997	 X: different functionalities
HypoGel™200 resin	2008	

When discussing solid-phase organic synthesis, the most important thing which needs to be considered is resin swelling. Due to the resin's reactive functionalities which are always blocked within its polymer matrix, it should be swollen to provide access to the reactive functionalities.[31] Thus, it is crucial to find a good solvent to swell a specific resin as poor solvents result in poor accessibility and will diminish reaction rates and yields.[32]

1.4. Greener solvents for resin swelling used in SPOS/SPPS

Due to the growing need for more sustainable, less hazardous solvents, more and more greener solvents are being applied to different aspects of organic synthesis including solid phase synthesis.[33] Water has drawn the attention of chemists in synthetic chemistry.[34] However, water is difficult to use, especially in SPPS, because many protecting groups are insoluble in it and there can be issues with hydrolysis.[34] Acetonitrile has been studied by Jad *et al.* as an alternative to DMF/NMP in peptide synthesis and was shown to give good yield and purity with reduced environmental impact.[35] However, it still has defects in that twenty percent (v/v) of piperidine in DMF was used to do deprotections of Fmoc groups and acetonitrile is not considered to be very "green" as it is toxic, not bio-based, and has an unreliable supply.[34]

Recently in our own group, Lawrenson evaluated more sustainable solvents for use in solid phase peptide synthesis.[31] For instance, cyclic carbonates, especially propylene carbonate, which may be produced with 100% atom economy by the reaction of epoxides with carbon dioxide, have been investigated as replacements for conventional polar aprotic solvents. It was also shown that cyclic carbonates could be used in solid-phase peptide synthesis.[13] Also, Lawrenson *et al.* studied the ability of 25 common “green” solvents and conventional solvents (DMF, NMP and DCM) to swell nine resins that were commonly used in solid-phase peptide synthesis, which helps inform the search for more suitable sustainable solvents that could be applied in peptide synthesis.[31] Three categories of solvents are classified by the rough guideline: swelling below 2 mL g^{-1} is a poor solvent, between 2 mL g^{-1} to 4 mL g^{-1} is a moderate solvent and higher than 4 mL g^{-1} is a good solvent.[32] For example, 2-methyltetrahydrofuran, which is derived from a sustainable resource, could replace tetrahydrofuran.[36] It shows good swelling ability for polystyrene-based resins.[31] Cyclopentanone, which is assessed with a high score in the GSK green solvents guide[4], can also swell the nine resins studied in his project.[31] Other solvents, such as CPME and anisole, are also regarded as good solvents in some resin swelling experiments.[31]

It is common to see solvent blends in chemical procedures. For example, column chromatography needs to use an eluent, such as mixtures of ethyl acetate and petroleum ether.[37] Mixed solvents extensively exist in the natural world, such as petroleum.[37] In recent years, people began to study the different properties of mixed solvents because researches have shown that a mixture of solvents could perform better in some chemical and physical properties than pure solvents.[37]

Due to environmental effects, the use of volatile solvents needs to reduce.[38] Benjamin Laux *et al.* owned a patent that used a non-volatile solvent mixture composed of glycol ether and petroleum distillate to remove grease and oil and make them emulsify into water then give a clean aqueous solvent system with high efficiency.[38] Mixed solvents are also applicable in our common life elsewhere. As we know, graffiti is a problem affecting the beauty of a city. Therefore, it is very useful to have graffiti removal systems which are less toxic and highly efficient. Robinson and Tonawanda have developed a more benign and faster graffiti removal system which can also be used in general surface cleaning applications.[14] This removal system was composed of different percentages of propylene carbonate, soy methyl ester and ethoxylated alcohols C9-11 and different proportions of the solvent mixture are applied in different pH ranges.[14] Mixed solvent systems have also found applications in lithographic printing and blanket washes[39] and in extraction of natural products, such as a mixture of n-hexane and methanol which was used for extracting the oil and separating the resin from Calophyllum seeds.[40]

In summary, binary solvent mixtures often allow access to solvent properties that are either not accessible with a pure solvent or allow replacement of pure solvents that are problematic.

1.5. Hansen solubility parameters of solvents and HSPiP Software

Hansen solubility parameters (HSP) define solvent properties in terms of the dispersion forces between molecules, the energy from the dipolar intermolecular force between molecules, and the energy from hydrogen bonds between molecules, using δD, δP, and δH respectively.[41] In 1967, a book written by Charles M. Hansen set out this method of calculating the three dimensional solubility parameter.[42] The

HSP model is widely used in the polymer chemistry and solvent fields.[41] The advantage of the use of HSP is that the HSP of a mixed solvent system can be calculated by using weighted averages for each component, allowing mixed solvent systems to be optimised and plotted in three dimensional HSP space. This can permit mixtures of “green” solvents to be suggested as replacements for undesirable conventional solvents where no single “green” replacement exists.[41] HSP can also be combined with cutting edge methodologies in the industries of relevance to solvents and polymers as a powerful way to help chemists and technologists to understand, predict and even solve problems in these areas, such as solubility, compatibility, stability, efficacy and dispersibility.[43] When we want to use the HSPiP software to predict the optimal HSP for a polymer, we should set one to six different scores on the basis of the solubility.[43] The scores are input into the HSPiP software so that the software can help us to generate the round surface for this target polymer.[43] Also, other solvents or solvent mixtures which have good locations in HSP-3D space can help to confirm a clearer boundary.[43] By this means, the distance between poor or good solvents and the target polymer can be determined. What is more, HSPiP software has a variety of methods that can be used to calculate and predict other properties including, sedimentation, dissolution and ODC tests.[43] Previously, chemists needed to prepare a few samples before using the software to do modelling. However, when there is a large quantity of samples needed to test, this is a tough task. Recently, Sander van Loon combined HSP with high-throughput methods, which can test hundreds of samples quickly, to predict formulations which may contain more than 10 ingredients.[43]

In the work of Stefan Lawrenson *et al*.,[31] green solvents as well as DMF, NMP and dichloromethane were chosen as a set to establish the modelling of HSP.[31] These 18 solvents were divided into 4 to 6 groups by their ability to swell each resin, then the HSPiP software predicted the optimised HSP of each polymer.[31] Also, he used this software to predict the optimised ratio of solvents blends.[31] However, there are some drawbacks of HSPiP software. Firstly, its prediction is based on a set of experimental results. Unfortunately, scientists and technologists usually focus on the solvents they are interested in and they could not do a lot of basic experiments. This means that the prediction of this software may sometimes be incorrect. Also, the values are changed by classifying solvents into different groups. Furthermore, the spherical model predicted by this software is not always valid, especially for copolymers or resins with surface functionalities. Thus, a lot of experiments had to be done to get the data for HSPiP modelling, and then the predictive results of this software had to be proven or not by more practical experiments.

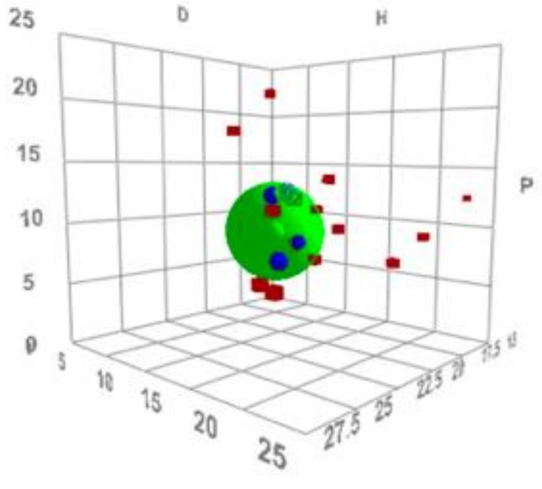


Figure 1-3*:* 3D plot for Merrifield resin using 5 solvent groups taken from the literature.[31] The green ball shows the predicted area of the polymer, blue balls show good solvents, and red balls show poor solvents.

1.6. Coupling agents used in solid-phase peptide synthesis

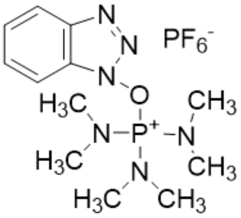
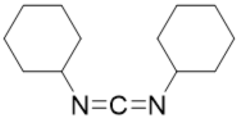
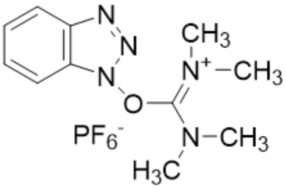
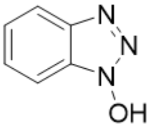
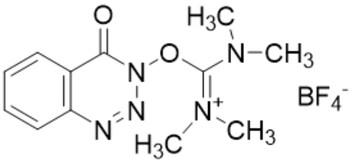
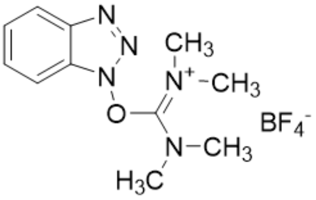
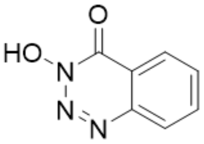
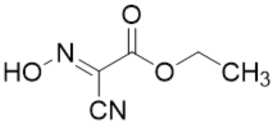
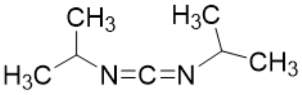
Peptides, which are formed by peptide linkages between amino acids, are crucial for life. For example, proteins are components of the cytoskeletons of all eukaryotic cells and a few prokaryotic cells, and so are essential components for all life. Likewise, biological enzymes that are the catalysts in metabolic reactions are proteins. Furthermore, peptides are increasingly widely used in multifarious medications, like antihypertensives, antidepressants, contraceptives and antibiotics.[44] In view of this importance, peptide synthesis has been an interesting research field for chemists for many years. Compared to isolating natural proteins, synthesising the peptide has many merits, because chemists can design the peptide chain structure in advance and evaluate the bioactivity or pharmacological effect of this peptide.[45]

Referring to peptide synthesis, the most important things to consider are coupling reagents. However, it is not enough to use only coupling reagents because of the risk of losing stereochemical purity when activating the amino acid. Thus, another chemical called a coupling additive is used to allow formation of a good yield whilst maintaining the configuration of each activated amino acid, i.e. minimizing racemization.[45]

Benzotriazol-l-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) was the first coupling reagent developed for solid-phase peptide synthesis; it had a lot of advantages compared to DCC, which was usually used in solution phase synthesis. However, the side production of extremely toxic hexamethylphosphorotriamide makes this reagent problematic. Thus, it should be substituted by other reagents. HBTU (3-[bis(dimethylamino)methyliumyl]-3H-benzotriazol-1-oxide hexafluorophosphate) which was first used in solid-phase peptide synthesis in 1989, shows excellent properties as a coupling agent.[46] In addition, HOBt (1-hydroxybenzotriazole) could be used together with HBTU to reduce the racemization and make the peptide synthesis process smoother as the byproducts are harmless and soluble in water or organic solvents.[46] There are also other coupling reagents which show good abilities for peptide synthesis, such as TDBTU, but it has a dangerous side reaction to generate 2-azido-benzoic acid.[46]

N-(1-H-benzotriazol)dimethylamino)methylene]N-methylmethanaminium tetrafluoroborate N-oxide (TBTU) is another coupling reagent which is suitable for solid-phase peptide synthesis.[46] For the coupling additives, 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HODhbt) shows better ability than HOBt, and it is possible to judge if the acylation is completed by the change of colour.[45] However, it has a series side reactions.[44] Another common coupling additive is ethyl 2-cyano-2-(hydroxyimino)acetate (OxymaPure). In the synthesis of α-ketoamides, which are interesting compounds in organic chemistry and pharmaceuticals, OxymaPure/DIC gave better purity and yield than HOBt/DIC or carbodiimide alone.[47] These chemicals' structural formula are shown in Table 1-2.

Table 1-2: Structural formula of common coupling reagents and additives

Abbreviation	Structure
BOP	
DCC	
HBTU	
HOBt	
TDBTU	
TBTU	
HODhbt/HOOBT	
Oxymapure	
DIC	

There are many coupling agents, and they have different advantages and disadvantages. For different peptide synthesis, they have shown different purities and yields. For example, HBTU/HOBt is one of the popular coupling agents used in solid-phase peptide synthesis, but solubility is a big problem for HBTU. HBTU can dissolve in some conventional organic solvents such as DMF and DCM very well. In recent years, more chemists are focusing on using greener solvents to replace these traditional solvents for peptide synthesis. HBTU does not dissolve in greener solvents such as ethyl acetate and TMO (2,2,5,5-tetramethyloxolane). Thus, there is a need to study the purity and yields of different coupling agents in greener solvents, and the first step is to test the solubility of coupling agents in different greener solvents.

1.7. Solute–solvent and solvent–solvent interactions in mixed binary solvents

As discussed above, in recent years, binary solvents have been found to be superior to pure solvents in some chemical or physical properties. For mixed solvents, there are more complex interactions between solvent and solvent and between solute and solvent than in pure solvents. For chemical processes occurring in solution, the polarity of solvents affects them strongly.[48] In 1994, Yizhak Marcus used multiple chemical probes to explore the polarity and hydrogen bonding of mixed non-aqueous solvents.[37] It was a novel way to measure the chemical properties of solvent blends. However, this method may not be correct in some cases as it usually converted the practical data to another quantity to describe the polarity[37] and the parameters are not only influenced by preferential solvation, but also the interaction of the probes and solvents. Thus, it is very hard to choose probes which have little interaction with each component in the binary solvent, similar parameters, aggregation, and no interference in the solvents, mutual interaction whilst also having extensive applicability in other solvent systems.[37] Following this study, he also studied using the chemical probes in aqueous solvent mixtures.[49] As aqueous solvents are totally different from the non-aqueous solvents, the measuring methods of parameters, such as Kamlet-Taft dipolarity-polarizability, hydrogen bond accepting parameter, etc. were also different. In the aqueous solvents study, Yizhak Marcus compared the different values of these parameters from those reported by other researchers.[49] Finally, he thought out an optimal calculation for these values and the preferential solvation.[49] A preferential solvation model can be used to explain the polarity in binary dipolar hydrogen bond acceptor solvents.[50] In 1995, Rosés *et al.* used the preferential solvation of solvatochromic indicators to test the interaction between solute and solvent and also between solvent and solvent.[50] 2,6-Diphenyl-4-(2,4,6-triphenyl-l -pyridinio)-1-phenolate (or $E_T(30)$ dye) is an extensively used solvatochromic indicator.[48] In general, this indicator could analyse the preferential solvation of solute by any of the studied mixed solvents.[50] On the other hand, the results were also influenced by solvent-solvent interactions.[50] However, this model only used one solvation parameter and did not take into account hydrogen bonding in the solvation shell so that it could not explain the polarity variation well.[50]

Another study was for the influence of changing temperature on the $E_T(30)$ parameters of mixed solvents of dipolar hydrogen-bond acceptor solvents such as alcohols and water to mix with excellent hydrogen-bond donor solvents like dimethyl sulfoxide, acetonitrile and nitromethane.[51] According to the results of this study, there was a very strong synergism of these binary mixtures, which means binary solvents are usually more polar than their pure solvents, and this synergism would decrease on increasing temperature because temperature had a huge impact on the hydrogen bonding between the two pure solvents.[51] Dimethyl sulfoxide and water could be the most extraordinary example as they were influenced by temperature much more than other binary solvents that could form hydrogen-bonded complexes (in alcohol and water).[51]

In addition, some research showed that the liquid structure of water could be enhanced by adding a small amount of alcohol into it, e.g. 2-methylpropan-2-ol, propan2-ol, ethanol or methanol because water had a tendency to aggregate around the hydrophobic groups of these alcohols to form low entropy structures and get longer forming hydrogen bonding when the solvents had low concentrations of alcohols.[52] By rearranging these hydrogen bonds to enhance the structure of water, these binary solvents showed growing polarizability and acidity and declining basicity.[52] The longer the carbon chain of the alcohol, the lower its enhancing ability for water.[52] Moreover, solvent blends of formamides (formamide, N-methylformamide and N,N-dimethylformamide) and hydroxylic solvents (water, methanol, propan-2-ol, 2-methylpropan-2-ol) have been studied.[53] By analysis of experimental results, the solvatochromic indicator was preferentially solvated less in each solvent mixture with less amide, but generally it was strongly solvated by the hydrogen-bonded complexes formed by amides and alcohols, and also the synergism and polarity were similar in these mixtures.[53]

For solvation, the essence is the interplay of solute-solvent and solvent-solvent interactions, and the solute-solvent interaction is the most important.[54] The solubility has been proved to be associated with solute-solvent interactions. Then based on the measured solubility, the Hildebrand solubility parameter (solvent-solvent interaction) and also HSP for solvents can be caculated.[55] The Gibbs free energy varies depending on the how many solvent molecules there are around the solute.[55] Nevertheless, the interaction of solute and solvent in binary solvents is different from that in the pure solvent, and for binary solvents they usually have different preferential solvation ability for the solute compared to the average ability of the pure solvents.[56]

In conclusion, some binary solvents have superior physical chemistry properties and are significant to study. Due to the toxicity and hazards of some traditional solvents, it is very significant to try to avoid them and adopt much greener solvents. However, pure greener solvents often perform worse than traditional organic solvents to some extent. For this reason, it is worthwhile to explore the different properties and abilities of binary mixtures of greener solvents.

1.8. Polystyrene dissolving and recycling

Polystyrene is a polymer made up of the monomer styrene.[57] It is a thermoplastic polymer with a glassy solid state at room temperature, but it can be solid or foamed as needed for applications in our common life. Hence it is widely used in plastics, packages, disposable cutlery and making models that produce millions of tonnes of waste every year.[58-59] As a result of the slow biodegradation of polymers such as polystyrene, which are harmful to the environment, some plastic bags are even found in the bellies of Marine life.[60] Thus, it is very urgent to take action to prevent or reduce polystyrene use. There are some laws about restricting plastics, and many countries have begun to ban them or force consumers to pay for them.[61] However, these countries focus on plastic bags mostly, another serious problem is caused by polystyrene foam (including expanded polystyrene (EPS) and extruded polystyrene (XPS)) which also requires more attention.[62] Polystyrene foam waste is extremely prevalent in fast food restaurants, cafeterias, supermarkets and as packaging for protecting household appliances or other fragile goods in transit.[62]

In recent years, chemists and environmentalists have started to think about methods to recycle polystyrene foam. Polystyrene recycling is very meaningful because the recycled polystyrene can be reused in manufacture and other applications such as: plant pots, plastic bags, and modelling materials.[62] At the same time, the pollution of the environment including fossil fuel consumption and greenhouse gas emissions from landfill can be reduced. There are many ways to recycle polystyrene including: mechanically, pulverizing; chemically, solvent dissolving; and thermally (Figure 1-4).[63]

For mechanical recovery, Shino, *et. al.* invented a machine to process and separate polystyrene from mixed or contaminated waste such as paper.[62] The recycling process was that polystyrene foam waste was milled into small particles, then a rotary trommel and air classifier were used to screen out the different sizes of polystyrene and paper particles, then the mixture went through water to remove the paper so that finally only foamed polystyrene was left.[62] Although this method is novel, polystyrene foam has a large volume and a low density. If we adopt this method, we need to spend a lot of human, energy and financial resources to transport and recycle it.

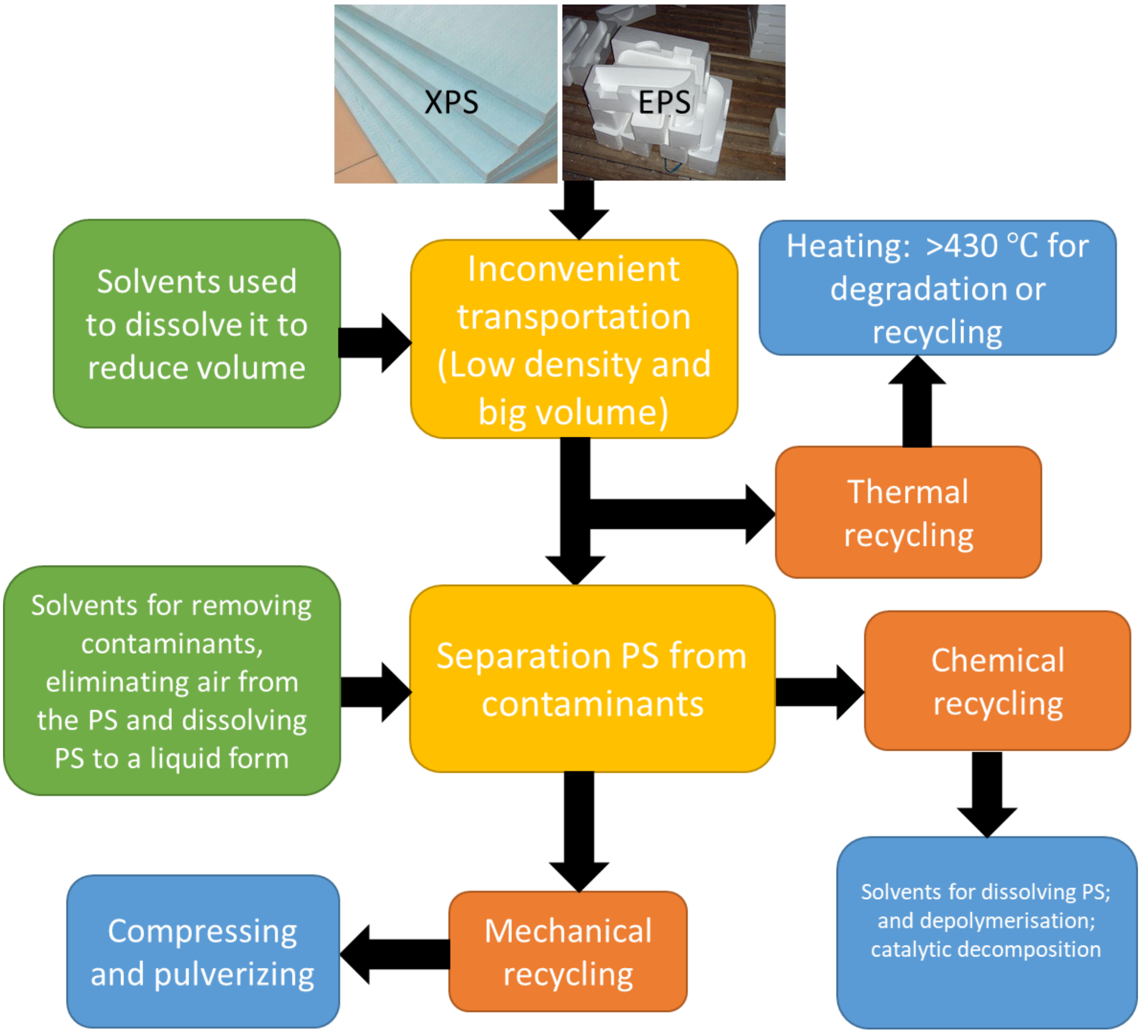


Figure 1-4: Concept for different recycling methods for polystyrene foam

For thermal treatment, in Sapporo, Japan, the municipal waste plastics are put into an apparatus at 430 ℃ and at atmospheric pressure to decompose thermally.[64] In a laboratory or pilot plant scale, a fluidized bed is usually used to test large scale thermal cracking.[65,66] However, many factors such as heterogeneity of plastic materials, the synergy of different compositions in cracking and restricted transfer of heat and mass influence the kinetics of pyrolysis, so accurate values of the kinetics cannot be obtained. Heating can also reduce the physical properties, and this is why cracking the plastic waste is not able to be applied into industry.[66] In the meantime, using pyrolysis does not give either polystyrene or monomer back.[67]

Since mechanical and thermal recycling have limitations, chemical methods are being considered more by chemists and environmentalists. Using a catalyst to promote the degradation of polystyrene has been studied for many years.[68] This method is superior because the monomer styrene can be obtained at low temperature with a high selectivity.[68] There are many catalysts used in degrading polystyrene, such as Fe-base catalysts, MgO, CaO, BaO, K_2O, SiO_2/Al_2O_3, several solid acids and active carbonate catalysts.[63] Other studies showed that supercritical solvents could also disassemble the polystyrene into styrene monomers efficiently.[69]

The chemical methods above are all converting polystyrene into styrene monomer. However, there is a better recycling method that not only can maintain the polymer state, but also reduce the volume of the polystyrene foam: it is polystyrene dissolving using organic solvents. Another advantage of using solvents to dissolve the polystyrene is that it does not make the physical properties deteriorate.[70] A lot of solvents have been used to dissolve polystyrene. For example, the traditional organic solvents, benzene, toluene, tetrahydrofuran and chloroform have particularly good abilities to dissolve polystyrene foam, but we try to avoid these solvents as they are extremely toxic and do harm to the bodies of the people who use them and the environment.[71] In consequence, more chemists are begining to explore greener solvents to take the places of these traditional solvents. D-Limonene, which is extracted from citrus, has shown excellent ability to dissolve polystyrene foam. However, due to its very strong citrus odour, volatility, low flash point as well as its instability with respect to transformation into para-cymene, it is not good for the environment.[70] Glycol ethers (diethylene glycol dimethyl ether, diethylene glycol diethyl ether and dipropylene glycol dimethyl ether) have high flash points over 100 ℃

and good dissolving abilities for polystyrene foam. There is an innovative feature that adding water into them makes the solution become non-flammable.[70] One drawback for this method is the price of glycol ethers which are so expensive that they cannot be applied in industry. Dissolving polystyrene foam can decrease its volume and make it easier to transport.

These thermal, mechanical and chemical methods are combined with each other during a recycling process. However, solvents are usually used in pre-treatment processes or reactions for these three methods. Thus, looking for alternative greener solvents to dissolve polystyrene foam is interesting and meaningful research work.

1.9. Project aims

In this project, we will explore the swellings of two different resins used in peptide synthesis: Wang resin, which is polystyrene based resin, and Hypogel™200 resin, which is a mixed system containing both polystyrene and polyethylene glycol components. We will then compare the differences by using 3D plots. Through resin swelling experiments with different mixed solvent systems, we hope to map the swelling of these resins in four dimensions, using three dimensional HSP space plus extent of swelling data, to arrive at a robust and predictive understanding of what solvent properties swell these resins and how they differ based on their different structural and chemical motifs. Furthermore, the model could potentially be used to predict which pairs of green solvents have a maximum resin swelling capability when they mix together and to predict the optimised ratio of green solvents pairs.

Once this has been adequately established, we aim to validate our model by choosing suitable mixtures of green solvents to apply in solid-phase peptide synthesis. Prior work of Lawrenson in our group detailed the synthesis of the peptide TFA·H-Leu-Ala-Phe-OH in propylene carbonate on ChemMatrix resin,[31] and this tripeptide will be used as our case study using the same coupling reagents and similar conditions. However, to take full advantage of our solvent modelling work, we will use Wang resin, which was shown to swell poorly in some single suitable "green" solvents. We will choose two moderate or poor solvents to mix with each other and optimise their ratio to perform the tripeptide synthesis. Then, by comparing the synthetic results of using two pure solvents and their optimised ratio mixture, it may prove that our solvent modelling will allow a suitable mixed solvent system to be chosen for peptide synthesis.

Polystyrene foam recycling attracts more attention by chemists recently. Once we have succeeded to use binary greener solvents in solid-phase peptide synthesis, we aim to make this model more meaningful by predicting the greener binary solvents to apply in polystyrene dissolution.

Thus, in this project, not only the modelling of the high swelling area in HSP space for Wang and HypoGel™200 resins will be investigated, but also the different applications of the modelling will be explored.

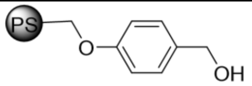
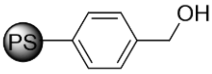
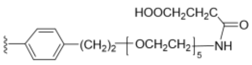
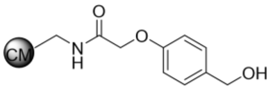
2. Results and discussion

2.1. Investigating the high swelling area for Merrifield and HypoGel™200 resins

2.1.1. Repeating resin swelling experiments from the literature

In the prior work of Stefan Lawrenson *et al.*, nine resins were selected to predict the optimised ratio of two mixed solvents. Solvent swelling experimental results indicated that some mixtures might have a maximum, some blends might have a minimum, and other mixtures had no significant change at the optimised ratio.[31] Thus, it became apparent that the simple software predictions of mixed solvent systems for resin swelling were inadequate.

Table 2-1: The predicted optimised ratio of four resins. The data are from the literature. [31]

		Predicted	
Resin	Structural formula	Solvent 1 (%)	Solvent 2 (%)
Merrifieid		2-MeTHF (52)	CPME (48)
ParaMax		dimethyl isosorbide (95)	ethylene carbonate(5)
HypoGel™200		cyclopenetanone(9-1)	Water (9)
ChemMatrix		Cyrene (80)	dimethyl isosorbide (20)

The predictions[31] for the four resins (Merrifield, ParaMax, HypoGel™200 and ChemMatrix) were interesting so that they required further study. Thus, the swelling of these four resins in mixtures of the specified solvents (miscibility may be an issue in some cases) would be studied using ten percent (or smaller if necessary) steps around the solvent ratio that gives maximum or minimum swelling in order to investigate the trend of resin swelling in these mixed solvent systems.

It is believed that this prediction arises from the assumption made by the HSPiP software of a spherical region of high swelling in HSP space for different polymers. This approximation is usually valid for small molecular solutes, but due to the inhomogeneity of crosslinked resins, which contain surface functionality, a variety of monomers, and may have a core-shell architecture, the spherical assumption breaks down for polymeric resins. Thus, in this project, the relevance of HSP to resin swelling was investigated in more detail than in previous work.

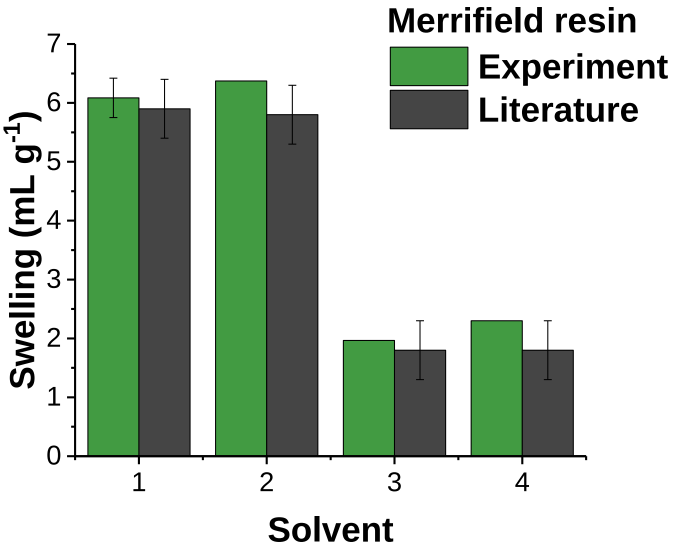


Figure 2-1: Repeat of literature experiments[31] for Merrifield resin (Wang linker) was swollen in 4 green solvents; solvent 1: dimethyl isosorbide, solvent 2: 2-methyltetrahydrofuran, solvent 3: propylene carbonate and solvent 4: D-limonene; the supporting information seen in Appendix A (Table 5-1).

In order to verify the resin-swelling methodology, one commercially available resin-Merrifield resin (Wang linker) was swollen using various green solvents previously reported with this resin and the results were compared with those obtained in the prior work.[31] The results are shown in Figure 2-1 with the green bars showing the results obtained in this project, and the black bars representing the literature data. In each case, the experimental observation was judged to be acceptably close to the previously published values,[31] and the swelling proved reproducible upon repetition. These experimental results established the foundation to implement this project.

2.1.2. Background to this project and the modelling methodology

Two commercially available resins have been chosen for this study; Merrifield's crosslinked polystyrene resin functionalised with the Wang linker (4-hydroxybenzyl alcohol),[23] and HypoGel™200 resin with a backbone of polystyrene glycol grafted onto polyethylene, functionalised with carboxylic acid groups.[26] These two resins were chosen because they have contrasting backbones and functionalities. Thus, by studying these two resins, we could obtain more detailed insight into the relationship between resin swelling, resin structure and solvent HSP values.

HSPiP [41] is a software which can establish a 3D model for a polymer on the basis of a large number of solubility experiments and then help scientists to predict good solvents for this polymer. According to the modelling, we can know the location of good solvents and poor solvents for this polymer in HSP-3D space. Therefore, in order to attempt to understand more details of the resin swelling properties in HSP-3D space, δD, δP, δH were set as X, Y, Z to draw 3D scatter graphs, with points for each pure solvent and binary solvent with data points colour coded to represent the degree of swelling. Three categories of solvents are defined by the rough guidelines: swelling below 2 mL g^{-1} is a poor solvent, between 2 mL g^{-1} to 4 mL g^{-1} is a moderate solvent and higher than 4 mL g^{-1} is a good solvent.[32] This guideline provided the scale for the colour map in 3D graphs. The swelling data and HSP (δD, δP, δH) for all the solvents used in Lawrenson's work,[31] except for the ionic liquid, are presented in Table 5-2 in Appendix A. The values of δD, δP and δH of cyrene could not be found using the HSPiP database, so they were determined by the Y-MB method.[72] From Figure 2-2 it is apparent that the single-solvent swelling data obtained previously hints at regions of high and low swelling, but by necessity such discrete and separate data points lack resolution. Therefore, the use of more solvents, and especially mixed solvent systems, was proposed. The mixed solvents' HSP calculation principle is set out in the HSPiP software guidebook.[41]

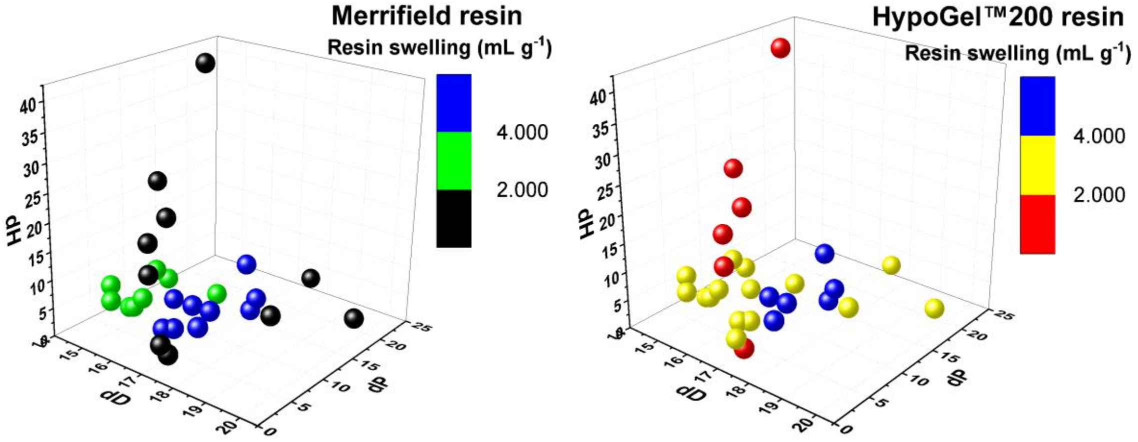


Figure 2-2: 3D graph of Merrifield resin and HypoGel™200 resin, showing swelling data obtained previously by Lawrenson[31] and plotted according to the Hansen solubility parameters of 27 solvents. The black, green, blue (Merrifield) or red, yellow and blue (HypoGel™200) points represent the resin swelling below 2 mL g^{-1}, between 2 mL g^{-1} to 4 mL g^{-1} and beyond 4 mL g^{-1} respectively.

Therefore, to find the shape and edge of the high swelling region for each resin, all binary mixtures of two parent solvents were chosen such that their connecting line passed through regions of HSP-3D space for which data from single solvents were lacking, and the resin swelling properties of mixtures at several different ratios for each pair were tested. In most cases, in addition to the parent solvents, ratios of

25:75 (v/v), 50:50 (v/v), and 75:25 (v/v) were initially evaluated, with additional data points being selected on a case by case basis to clarify the trends. By inspection of the data presented in Figure 2-2, high swelling areas for HypoGel™200 and Merrifield resins do seem to exist in HSP space. Clearly, the extent and shape of this high swelling region is important both practically; as high swelling is a prerequisite for successful SPOS, and theoretically; as a study into the relationship between resin structure and/or functionality and the properties of the solvents requires insight into swelling.

Table 2-2: 21 pairs of solvents chosen for HypoGel™200 resin

Solvent 1	Solvent 2
cyclopentanone	water
propylene carbonate	ethanol
propylene carbonate	diethyl carbonate
propylene carbonate	dimethyl carbonate
propylene carbonate	isopropanol
propylene carbonate	methanol
propylene carbonate	ethyl acetate
propylene carbonate	isobutyl acetate
propylene carbonate	cyclopentyl methyl ether
methanol	isobutyl acetate
methanol	dimethyl isosorbide
1,2-dichlorobenzene	dichloromethane
1,2-dichlorobenzene	dimethylformamide
acetonitrile	toluene
propylene carbonate	1,2-dichlorobenzene
1,2-dichlorobenzene	heptane
propylene carbonate	acetonitrile
isopropyl acetate	acetonitrile
furfuryl alcohol	cyclopentanone
water	dimethylformamide
TMO	cyclopentanone

Thus, pairs of solvents were chosen for which the connecting line could go across the putative high swelling area and define its boundaries. Initially, for HypoGel™200 resin, several pairs of solvents were selected and their swelling data plotted, after which further binary pairs were selected to complete the emerging picture of the high-swelling boundary. One pair of solvents chosen initially was cyclopentanone and water, but these were found to be only fully miscible in certain ratios. In order to fill the gap (δD=17-19, δP=5-15, δH >20) where cyclopentanone and water did not mix, two additional pairs of solvents were chosen. They were cyclopentanone and furfuryl alcohol; and water and DMF. 2,2,5,5-Tetramethyloxolane (TMO),[73] which is an emerging green solvent, was also chosen to mix with cyclopentanone to test if the mixture would have a maximum resin swelling ratio. In the end, 21 pairs of solvents were chosen for resin swelling experiments and they are shown in Table 2-2. The same methodology and calculating principle were applied to find the high resin swelling area for Merrifield resin. In this case, 20 pairs of solvents were used for swelling experiments and they are given in Table 2-3.

Table 2-3: 20 pairs of solvents chosen for Merrifield resin

Solvent 1	Solvent 2
2-MeTHF	CPME
ethanol	cyclopentanone
propylene carbonate	dimethyl carbonate
propylene carbonate	ethyl acetate
cyclopentanone	methanol
cyclopentanone	isopropanol
1,2-dichlorobenzene	dichloromethane
1,2-dichlorobenzene	dimethylformamide
acetonitrile	toluene
propylene carbonate	1,2-dichlorobenzene
1,2-dichlorobenzene	heptane
propylene carbonate	acetonitrile
isopropyl acetate	acetonitrile
furfuryl alcohol	cyclopentanone
water	dimethylformamide
TMO	cyclopentanone
propylene carbonate	TMO
propylene carbonate	D-limonene
propylene carbonate	acetone
propylene carbonate	isopropyl acetate

The chosen pairs of solvents for these two resins were slightly different. The values of δD, δP, δH of the pure solvents were obtained from the HSPiP software database except cyrene and TMO because cyrene and TMO are not included in this database. The parameters of cyrene were calculated by the Y-MB method,[72] and values of TMO were determined by the work of Fergal Byrne.[73] All values of δD, δP, δH of pure solvents, their solvent blends and the corresponding resin swelling are shown in Table 5-4, Table 5-5 and Table 5-6 in the Appendix A.

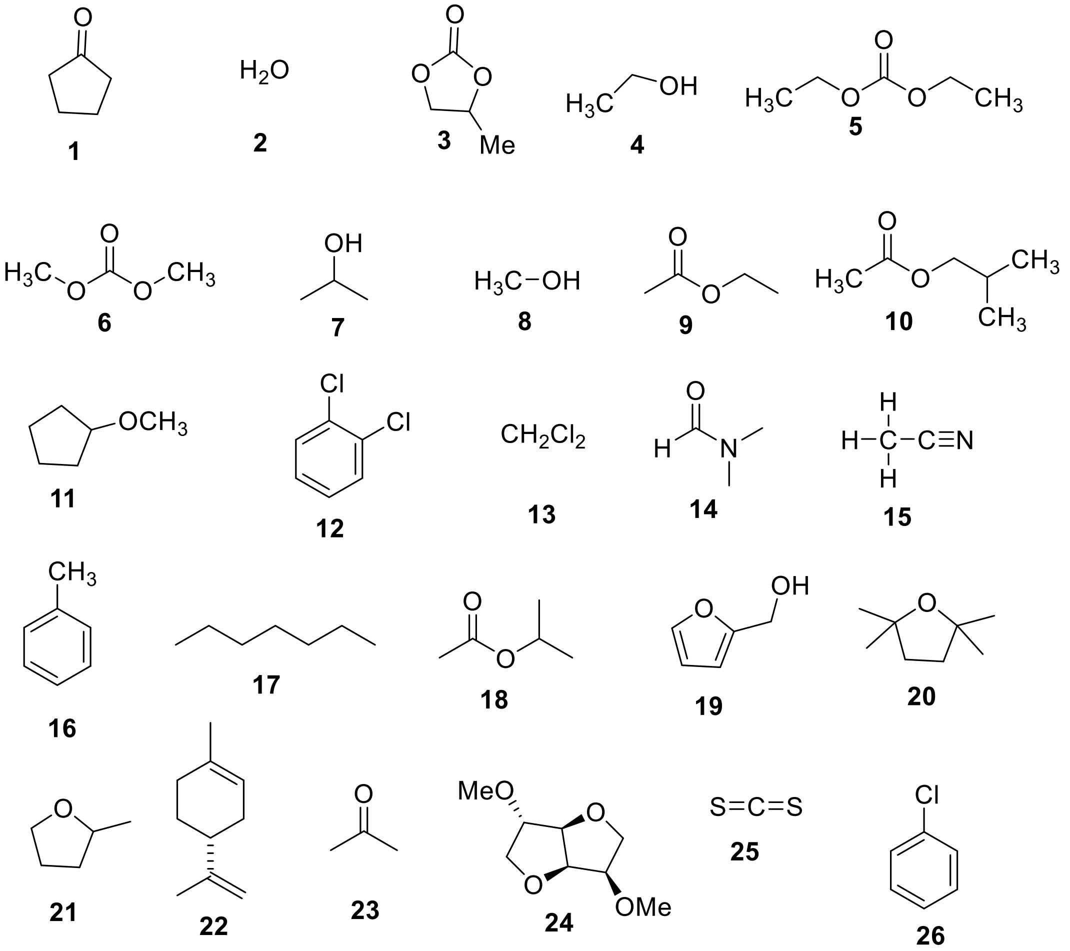


Figure 2-3: Structures of solvents used in this project; 1. cyclopentanone; 2. water; 3. propylene carbonate; 4. ethanol; 5. diethyl carbonate; 6. dimethyl carbonate; 7. Isopropanol; 8. methanol; 9. ethyl acetate; 10. isobutyl acetate; 11. cyclopentyl methyl ether; 12. 1,2-dichlorobenzene; 13. dichloromethane; 14. Dimethylformamide; 15. acetonitrile; 16. toluene; 17. heptane; 18. isopropyl acetate; 19. furfuryl alcohol; 20. 2,2,5,5-tetramethyloxolane (TMO); 21. 2-Methyltetrahydrofuran; 22. D-limonene; 23. acetone; 24. dimethyl isosorbide; 25. carbon disulphide; 26. chlorobenzene

The resin swelling performances of mixed solvent systems were classed into four types: Type 1 (including Type 1a where the solvents cannot mix together at all ratios) means that the solvent mixtures have a better swelling ability at some ratios than their pure solvents; Type 2 systems show a steadily increasing or decreasing line which does not go through a maximum and where no mixture has better resin swelling than either parent solvents; Type 3 are flat because the swelling ability of the two solvents are similar and there is no significant increase or decrease in swelling upon using mixed systems; and Type S represents some special cases for these two resins, but these situations only appeared once. Schematic graphs corresponding to each of these mixed solvent types are presented below (Figure 2-4).

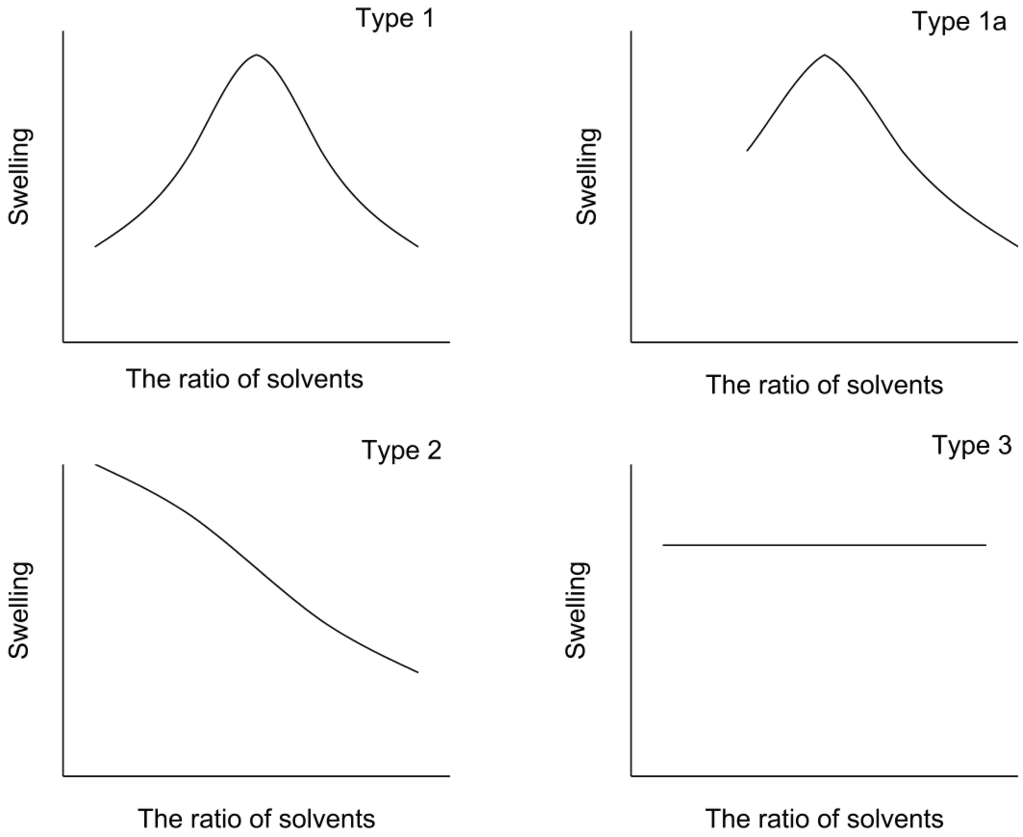


Figure 2-4: Schematic graphs of three types of mixed solvent systems for Merrifield and HypoGel™200 resin swelling

2.1.3. Resin swelling in green binary solvents and the high swelling area in HSP-3D Plots

2.1.3.1. High resin swelling area for Merrifield and HypoGel™200 resins

For Merrifield resin and HypoGel™200 resins, the solvent blends' HSP calculation principle is followed based on the percentage contribution of each component.[41] All values are presented in Table 5-4 and Table 5-5 in Appendix A and all error bars of resin swelling were +/- 0.3 mL g^{-1}. Using all these values to draw graphs, the high resin swelling area for each resin can be visualised. To fill the gaps in the corners and confirm the boundary of the high swelling area, other solvents, such as carbon disulphide (δD=20.2, δP=0, δ=0.6) and chlorobenzene (δD=19, δP=4.3, δH=2) were also chosen because of their good positions in HSP space. Using different colours to represent different degrees of resin swelling, different visual methods were adopted to make the high resin swelling area clearer. A high resin swelling area for these two resins became apparent as shown in Figure 2-5 and Figure 2-6. For the 3D scatter graph of Merrifield and HypoGel™200 resin, the axes are δD: the energy from dispersion forces between molecules as X; δP: the energy from dipolar intermolecular force between molecules as Y; and δH: the energy from hydrogen bonds between molecules as Z. The values of the axes are: X: δD= 14.7~20; Y: δP=0~21.7; and Z: δH=0~42.3.

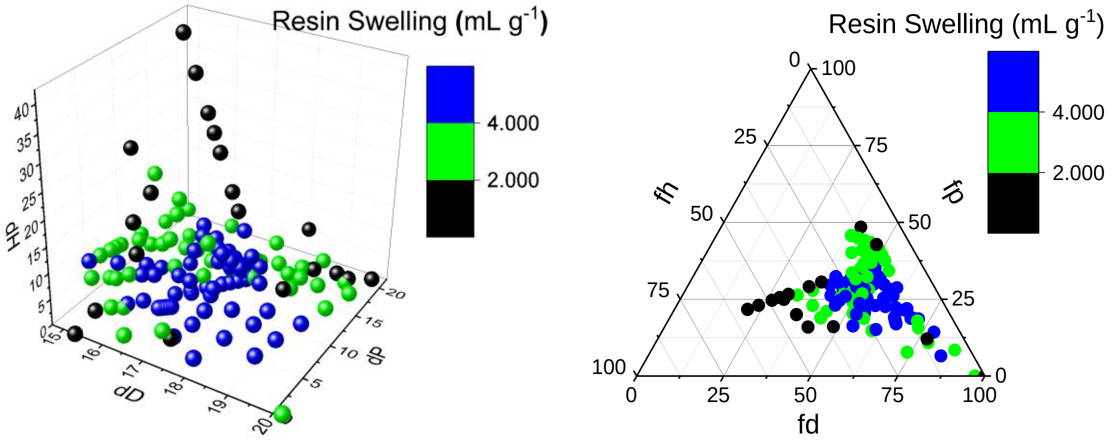


Figure 2-5: 3D scatter graph and Teas plot[74] of Merrifield-Wang-OH resin. Resin swelling data of 22 mixed solvent systems and a few pure solvents, with swelling depicted by colour coding, plotted according to solvent Hansen solubility parameters in the 3D scatter graph or fractional parameters for Teas plot. The black, green and blue colours represent resin swelling below 2 mL g^{-1}, between 2 mL g^{-1} to 4 mL g^{-1} and beyond 4 mL g^{-1} respectively.

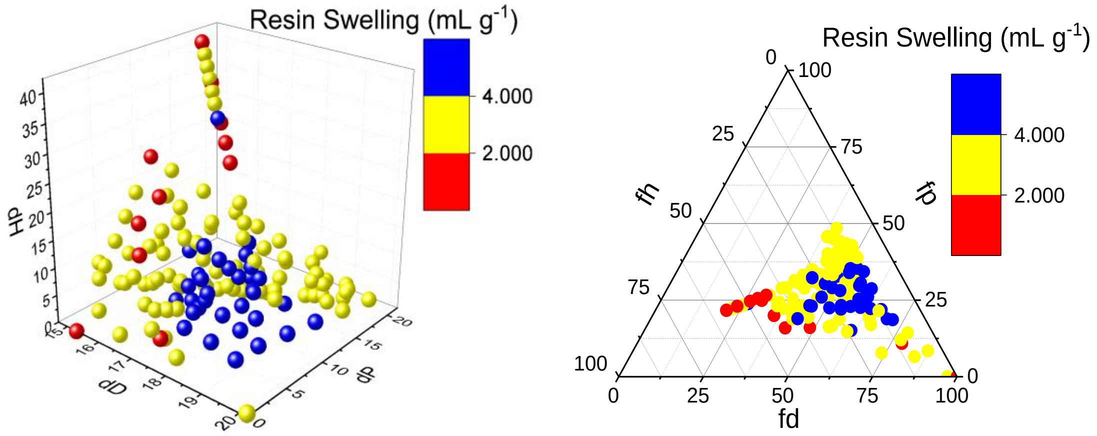


Figure 2-6: 3D scatter graph and Teas plot[74] of HypoGel™200 resin. Resin swelling data of 20 mixed solvent systems and a few pure solvents, with swelling depicted by colour coding, plotted according to solvent Hansen solubility parameters in the 3D scatter graph or fractional parameters for Teas plot. For better identification, for HypoGel™200 resin another colour scale was chosen, red, yellow and blue.

In order to improve clarity when the data is presented on paper where the 3D scatter plots cannot be rotated and observed from multiple angles, a ternary graph, also called a Teas plot, was also generated as it can show the correlation of HSP parameters in 2D.[74] The ternary graph is different to the 3D scatter graph due to its use of fractional parameters (fd, fp and fh) as axes rather than straight HSP parameters. The formulae for the generation of fd, fp and fh are as below:

$$\mathrm{fd} = \frac{\delta\mathrm{d}}{\delta\mathrm{d}+\delta\mathrm{p}+\delta\mathrm{h}} \qquad \mathrm{fp} = \frac{\delta\mathrm{p}}{\delta\mathrm{d}+\delta\mathrm{p}+\delta\mathrm{h}} \quad \mathrm{fh} = \frac{\delta\mathrm{h}}{\delta\mathrm{d}+\delta\mathrm{p}+\delta\mathrm{h}} \cdots\cdots\cdots\cdots\cdots \text{Equation 1}$$

$$\mathrm{fd} + \mathrm{fp} + \mathrm{fh} = 100 \quad \cdots\cdots\cdots\cdots\cdots \text{Equation 2}$$

The triangular graph was used first by Jean P. Teas in 1968,[74] the fractional parameters are calculated from the three Hansen solubility parameters and they show the percentage contribution of these three parameters to the whole Hildebrand value. Adding fd, fp and fh together will equal 100. The Hansen solubility parameters are also related to the Hildebrand solubility parameter as shown in Equation 3:

$$\delta\mathrm{t}^2 = \delta\mathrm{d}^2 + \delta\mathrm{p}^2 + \delta\mathrm{h}^2 \cdots\cdots\cdots\cdots\cdots \text{Equation 3}$$

$$\delta\mathrm{t}^2 = \text{total Hildebrand parameter squared}$$

$$\delta\mathrm{d}^2 = \text{dispersion force squared}$$

$$\delta\mathrm{p}^2 = \text{dispersion force squared}$$

$$\delta\mathrm{h}^2 = \text{hydrogen bonding squared}$$

Thus, a ternary graph can help to identify the relationship of resin swelling to Hansen solubility parameters rather than to Hildebrand parameters. All fractional parameters of solvents for these two resins are given in Table 5-3, Table 5-4, Table 5-5 and Table 5-6 in the Appendix A. It must be noted that the assumption that the fractional contributions add up to a uniform total that is the same for different solvents has no genuine physical basis and is an approximation necessary for 2-dimensional visualisation of 3D data. Therefore, whilst Teas plots are a very helpful visual aid, conclusions must not be drawn directly from the Teas plot without confirming any correlation by close inspection of the corresponding 3D scatter plot. It is impossible to reduce the dimensionality of data without loss of information, and in this case this is justified for visual clarity on paper on the understanding that Teas plots are strictly illustrative rather than accurate.

Additionally, as can be seen in Figure 2-5 and Figure 2-6, the boundaries of the high swelling region (containing all the blue points) have been established, with the exception of impractical regions requiring self-contradictory solvent properties. The essentially complete three-dimensional model of these data is shown in Figure 2-5 and Figure 2-6, where swelling defined as “good” has been coded in blue for clarity. The results for Merrifield resin and HypoGel™200 resin are distinct areas, corresponding to the different properties of these two resins. It is worth noting that in these plots, some “impossible” areas exist, especially corresponding to solvents which have low polarity, are highly dispersive, and have a large degree of hydrogen bonding. Clearly such properties are mutually exclusive, at least in practical solvents, so an absence of data in such a region is to be expected. In the 3D scatter graph of Figure 2-6 for HypoGel™200 resin, we can see that there was a good solvent system well above all the others. This is the mixture of cyclopentanone: water=31: 69 (v/v). It is a special case which will be discussed in detail later.

2.1.3.2. More visualisations to investigate the high swelling area for Merrifield resin

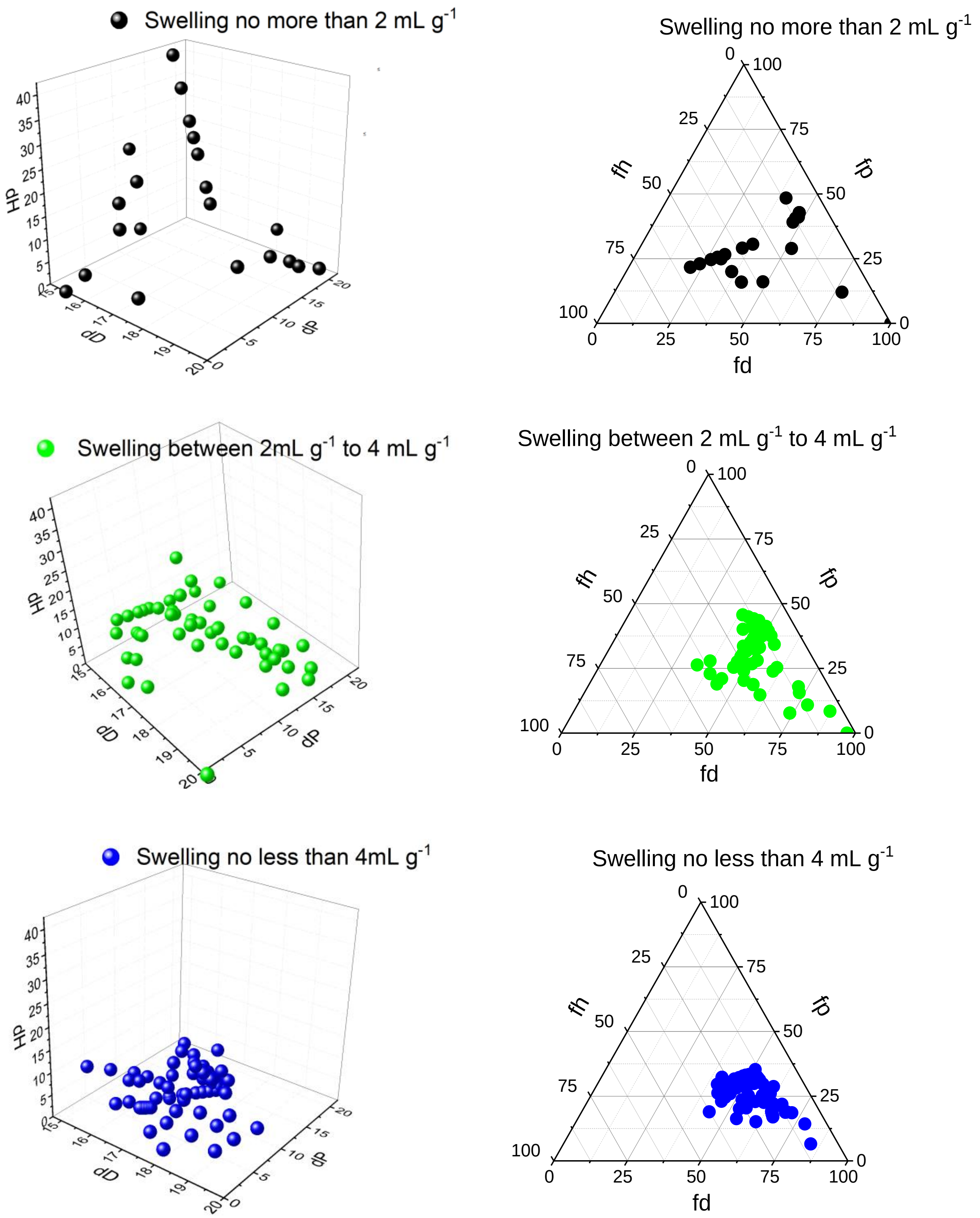


Figure 2-7: 3D scatter graph and ternary graph of different regions for Merrifield resin; resin swelling coded by different colours

Additional visualisations were helpful to analyse the high swelling area of Merrifield resin. 3D scatter graphs and ternary plots were drawn for each resin swelling range.

As is evident from Figure 2-7, the two graphs of solvents that result in resin swelling of no more than 2 mL g^{-1} identify that poor solvents are usually located in high hydrogen bonding (>10), lower dispersion force (<16), and higher polarity (>15). Spatially these comprise a shell scattered outside the boundaries of the high swelling area. However, moderate solvents in which the resin swelling is between 2 mL g^{-1} to 4 mL g^{-1} appear closer to the blue area. Thus, the high swelling area is relatively well defined in HSP space, and its boundaries are clear enough to allow the possibility of closely predicting which ratio of an unknown pair of solvents will swell the resin best.

Additionally, by comparing the 3D scatter graph of resin swelling between 2 mL g^{-1} and 4 mL g^{-1} with that of resin swelling above 4 mL g^{-1} in Figure 2-7, we can see that the green points seem to intermingle with the blue points because most green solvents are mixtures. The resin swelling scales were set as smaller values which could help to observe this more clearly in Figure 2-8. Propylene carbonate (δD=20, δP=18, δH=4.1, swelling=1.80 mL g^{-1}) is commercially available and has a good location in HSP-3D space so that we often chose propylene carbonate in the bottom right corner of Figure 2-8 to mix with a moderate solvent on the opposite side of the high resin swelling area. Thus, their mixtures could be located in the blue area. All these solvent systems have a maximum resin swelling (they are Type 1) and details can be seen in Table 5-4 in Appendix A. Figure 2-8 also shows that the blue points gather very closely together, and the yellow, green and black points are outside of the blue area.

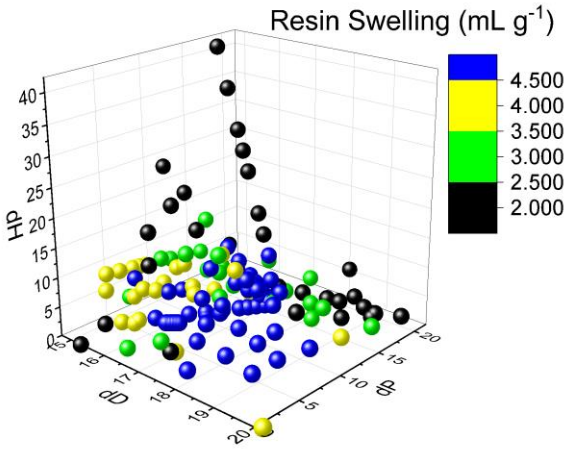


Figure 2-8: 3D scatter graph for Merrifield resin; the resin swelling scales are: black: resin swelling below 2.5 mL g^{-1}; green: resin swelling between 2.5 mL g^{-1} and 3.5 mL g^{-1}; yellow: resin swelling between 3.5 mL g^{-1} and 4.5 mL g^{-1}; and blue: resin swelling above 4.5 mL g^{-1}

The 3D scatter graphs and ternary graphs both have disadvantages. For example, it is difficult to see some detailed properties of this 3D model in 3D scatter graphs viewed on 2D paper or screens. The ternary graphs distort the Hansen parameters as they are put into the two-dimensional graph so that they are not ideal to learn about the relationship between resin swelling and HSP parameters of a solvent. Therefore, to enable the high resin swelling area for Merrifield resin to be visualised more clearly, another plot type was used. This is a contour graph which could show more details by cutting the whole 3D model into slices. According to analyses of the 3D scatter graphs and ternary graphs of Merrifield resin, it is apparent that almost all solvents with high hydrogen bonding will be poor solvents for this resin. Therefore, hydrogen bonding will have only a slight contribution to the resin swelling. Hence, the contour graphs were plotted by different ranges of hydrogen bonding as presented in Figure 2-9.

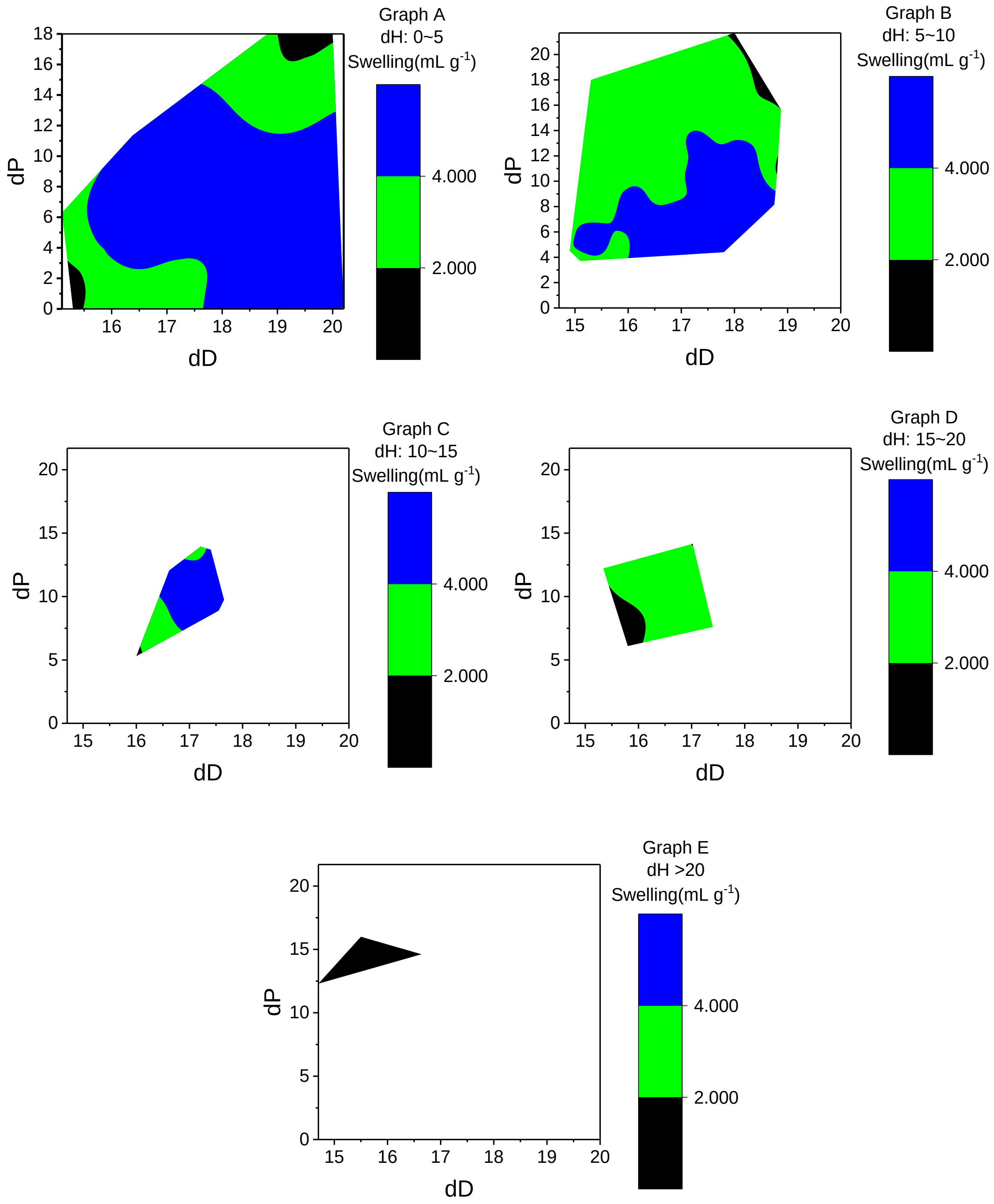


Figure 2-9 Contour graphs of Merrifield resin divided by different range of hydrogen bonding

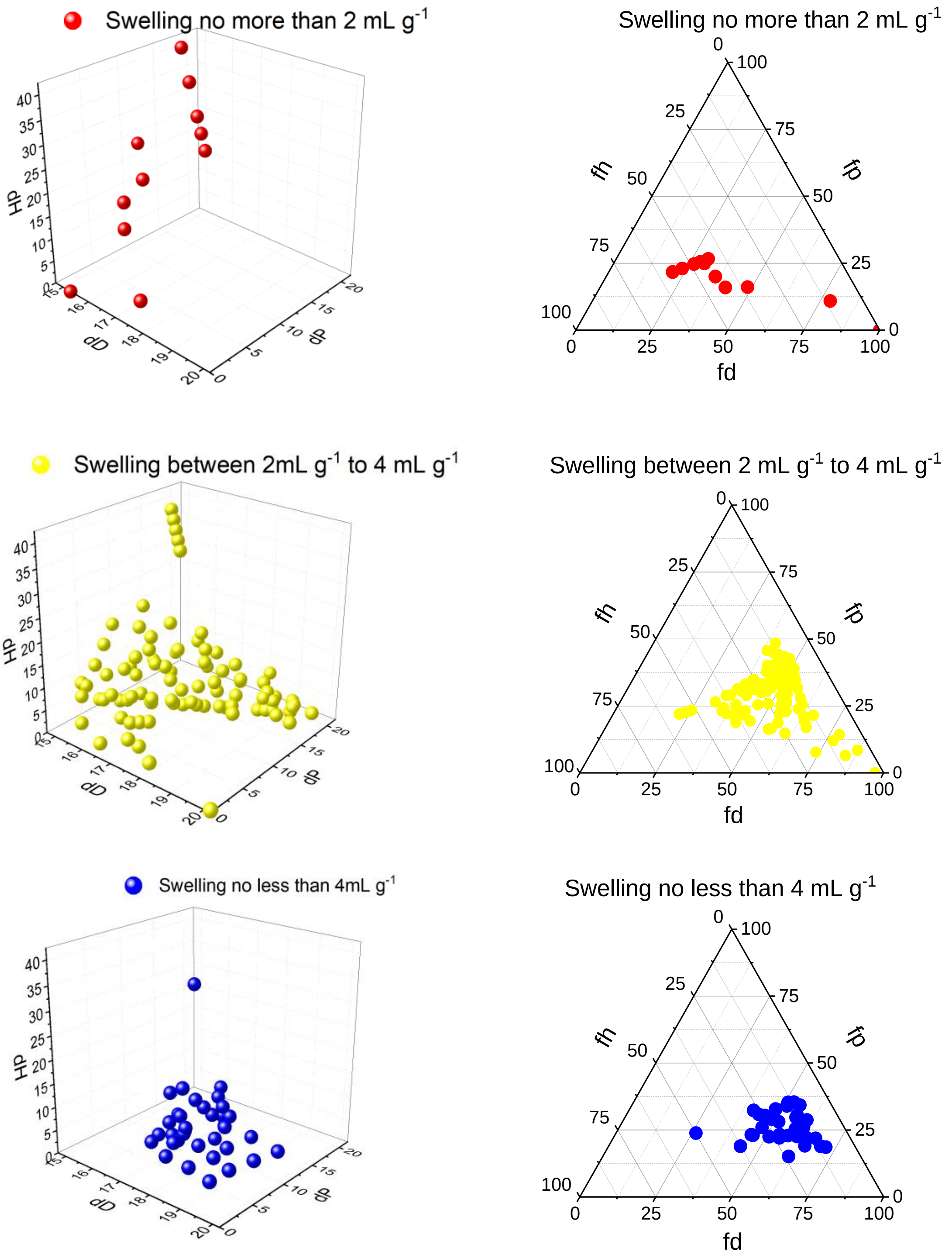
In the HSPiP software solvent database, all solvents are in the range of: δD: 10.6~26.0, δP: 0~ 36.2 and δH: 0~23.5. Inspection of Figure 2-9 shows that the high swelling area was located in regions with medium dispersion force (15~20), low to medium polar force (0~14) and low hydrogen bonding (0~15).

To be specific, in graph A: at hydrogen bonding parameter between 0 and 5, the blue zone occupies the largest area of this graph, and this illustrates that the high resin swelling area is more concentrated in the area where the hydrogen bonding is below 5. Out of the blue zone, the black zone is where the moderate solvents are located. Outside of the black zone, the grey zone represents the poor solvents area. In graph B, compared to graph A, the blue area remarkably decreases to half the area. When hydrogen bonding increases to between 10 and 15, the high swelling area declines steeply and disappears when the hydrogen bonding parameter is over 15. According to these contour graphs, this high swelling region is definitely not spherical. This validates the practicability of the visualisation methods we use to investigate the high resin swelling area rather than just using HSPiP software to predict a maximum based on its spherical assumption.

2.1.3.3. More visualisations to investigate the high swelling area for HypoGel™200 resin

To explore more details of the high resin swelling area of HypoGel™200 resin, the same visualisations as for Merrifield resin were used. The first was to draw the 3D graphs and ternary graphs for different ranges of resin swelling. Based on the values of the HSP for all the solvents used, the axes' ranges for HypoGel™200 resin plots are: X: δD =14.7~20.2, Y: δP=0~21.7, Z: δH=0~42.3.

Comparing the graphs of shows that poor solvents gather around the high hydrogen bonding and low dispersive force area. However, moderate solvents were the major solvents for HypoGel200 resin, and surrounded the small blue area. The other visualisation method was use of contour graph plots to analyse the high resin swelling area as shown in Figure 2-11. Since the hydrogen bonding force does not contribute much to the resin swelling, the map plot was again categorized by different ranges of hydrogen bonding force. The ranges are: δH=0~5, δH=5~10, δH=10~15, δH=15~20 and δH >20.



● Swelling no more than 2 mL g^{-1}

Swelling no more than 2 mL g^{-1}

● Swelling between 2mL g^{-1} to 4 mL g^{-1}

Swelling between 2 mL g^{-1} to 4 mL g^{-1}

● Swelling no less than 4mL g^{-1}

Swelling no less than 4 mL g^{-1}

Figure 2-10: 3D scatter graph and ternary graph of different regions of resin swelling for HypoGel™200 resin

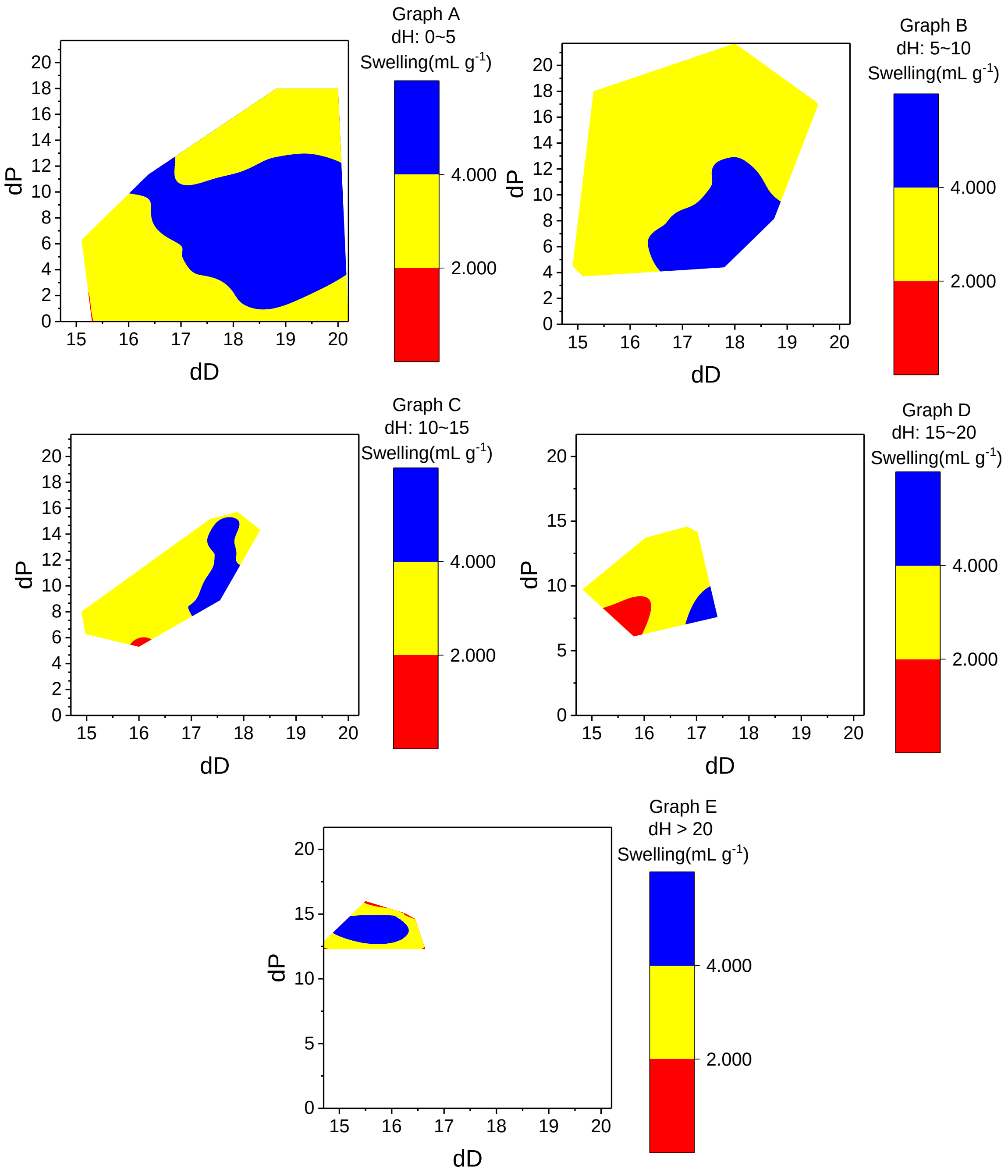


Figure 2-11: Contour graphs of HypoGel™200 resin divided into different ranges of hydrogen bonding

Compared to Merrifield resin, HypoGel™200 resin has fewer poor solvents, and moderate solvents are the majority. However, HypoGel™200 resin has good solvents located on the δH > 15 slice whilst there was no high swelling area in this slice for Merrifield resin. Merrifield resin for which the backbone is polystyrene only swells well in moderately polar and low hydrogen bonding solvents, such as 2-

methyl-THF, anisole, dimethyl isosorbide and cyclopentyl methyl ether, etc.[31] However, HypoGel™200 resin[26] is composed of PEG grafted onto polystyrene and also has good swelling in 2-methyl-THF and anisole, but also swells better in higher hydrogen bonding solvents than Merrifield resin. In the previous literature study, it was shown that resin swelling was dependent on the backbone of the resin not the linker.[31] That means that it is the PEG of the backbone for HypoGel™200 resin that helps it to swell in higher hydrogen bonding solvents as PEG chains can make the resin more hydrophilic.

These experiments have defined a distinct high-swelling region in HSP space for each resin. Now that this is known it is possible to predict mixtures of solvents which will swell the resins even if the pure solvents do not, with a high degree of confidence. This vastly expands the library of solvents available for use in solid phase (peptide) synthesis with these resins to include many more “green” solvents than would be possible without this information.

2.1.3.4. Resin swelling in green binary solvents for Merrifield resin

For Merrifield resin, the mixed systems of Type 1 all had a maximum at a particular ratio. The two mixed systems of cyclopentanone with methanol, and ethyl acetate with propylene carbonate are representative and are shown in Figure 2-12 and Figure 2-13. The line graphs were drawn so that the X-axis is the volume/volume ratio of the two solvents and the Y-axis is the resin swelling. Dotted lines were used to help compare the resin swelling tendency achieved by changing the volume/volume ratios.

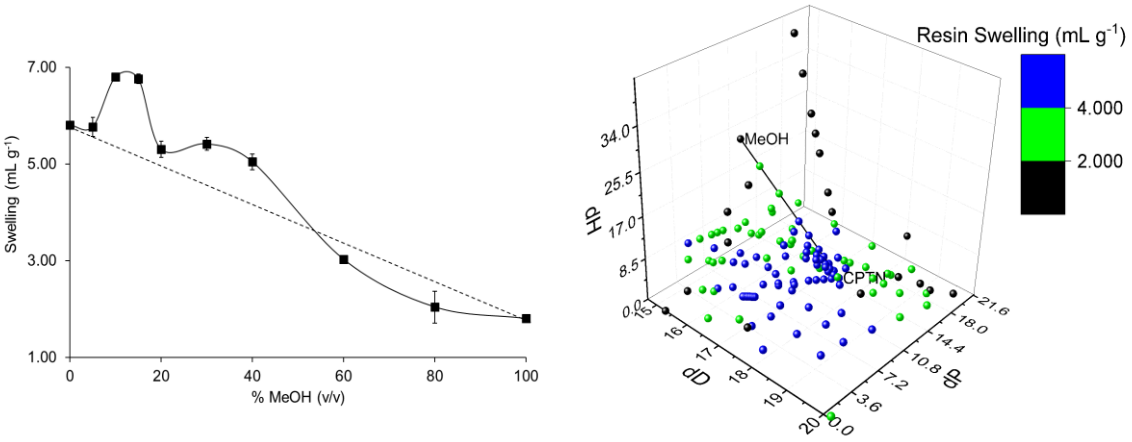


Figure 2-12: Line graph and 3D trajectory graph of the solvent system of cyclopentanone & methanol for Merrifield resin. Line graph is the resin swelling at various cyclopentanone: methanol (v/v) ratios; 3D trajectory graph shows that the cyclopentanone (CPTN) & methanol (MeOH) solvent system is connected by a black line in 3D space

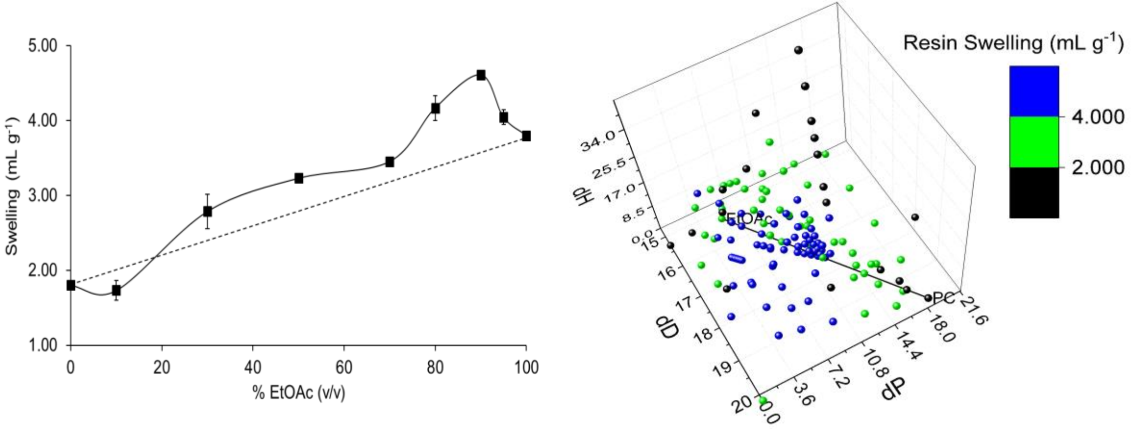


Figure 2-13: Line graph and 3D trajectory graph of the solvent system of propylene carbonate & ethyl acetate for Merrifield resin. Line graph is the resin swelling at various propylene carbonate: ethyl acetate (v/v) ratios; 3D trajectory graph shows that the propylene carbonate (PC) & ethyl acetate (EtOAc) solvent system is connected by a black line in 3D space

As detailed in Figure 2-12 and Figure 2-13, both of these solvent pairs serve as good examples of Type 1 swelling behaviour, with maxima for a certain mixture that exceeds the swelling for either parent solvent. There is a marked rise from pure cyclopentanone (swelling=5.80 mL g^{-1}) to cyclopentanone:MeOH=90:10 (swelling=6.80 mL g^{-1}). At the point of cyclopentanone:MeOH= 90: 10, a maximum value appears. Then the swelling decreases to pure MeOH (swelling=1.80 mL g^{-1}). In Figure 2-12, we can see that the line of MeOH and cyclopentanone from the high resin swelling area (cyclopentanone) to poor resin swelling area (methanol) of

Merrifield resin. From a lot of experimental results, almost every set of cyclopentanone and an alcohol could have maximum value as all the connecting lines of them went through this high swelling area.

Similarly, propylene carbonate is itself a poor solvent (swelling=1.80 mL g^{-1}) and is outside the blue area whilst ethyl acetate is a moderate solvent (swelling=3.80 mL g^{-1}) and is also outside the high swelling area. When connecting them by a black line as shown in Figure 2-13, this line goes right through the high swelling area, predicting that a certain mixture would give resin swelling above 4 mL g^{-1}. From Figure 2-13, we can see that the optimised ratio is at propylene carbonate:ethyl acetate=10:90 (swelling=4.61 mL g^{-1}). This indicates that the resin swelling will increase when the mixtures' positions are close to the core of the blue area.

For Type 2 and Type 3 solvent mixtures, although they have different line graphs (Type 2 has increasing or decreasing trend and Type 3 is flat), they are all indicative that their mixed solvents have no resin swelling over their pure solvents. The line of Type 2 will go from outside of the high resin swelling area to inside of this area. Type 3 will not change the resin swelling region. Although Type 2 and Type 3 cases did not have maximum resin swelling for Merrifield resin that exceeded their parent solvents, they are beneficial to determine the boundaries of the high swelling area. 1,2-Dichlorobenzene with DMF, and propylene carbonate with 1,2-dicholorobenzene exemplify these solvent types.

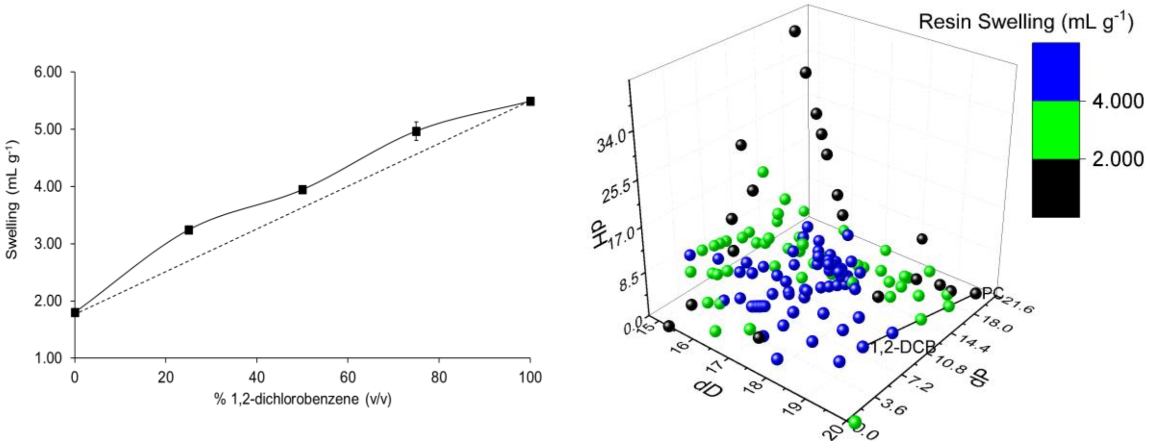


Figure 2-14: Line graph and 3D trajectory graph of the solvent system of propylene carbonate & 1,2-dichlorobenzene for Merrifield resin. Line graph is the resin at various propylene carbonate: 1,2-dichlorobenzene (v/v) ratios; 3D trajectory graph shows that the propylene carbonate (PC) & 1,2-dichlorobenzene (1,2-DCB) solvent system is connected by a black line in 3D space

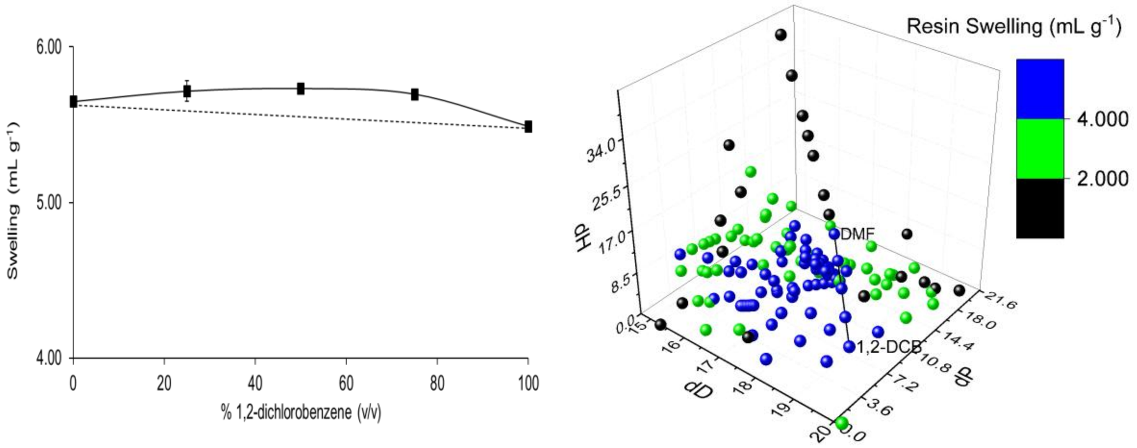


Figure 2-15: Line graph and 3D trajectory graph of the solvent system of DMF (dimethylformamide) & 1,2-dichlorobenzene for Merrifield resin. Line graph is the resin swelling at various DMF: 1,2-dichlorobenzene (v/v) ratios; 3D trajectory graph shows that the DMF & 1,2-dichlorobenzene (1,2-DCB) solvent system is connected by a black line in 3D space

As indicated in Figure 2-14, propylene carbonate was a poor solvent for Merrifield resin, but 1,2-dichlorobenzene was a good solvent. This solvent system provides useful information about the exact boundary of the high resin swelling region along a particular vector in HSP space, even though it does not include a maximum with greater swelling than 1,2-dichlorobenzene itself. Figure 2-15 illustrates that the swelling ability of 1,2-dichlorobenzene, DMF and their mixture solvents (75:25, 50:50, 25:75) are similar for Merrifield resin so that the line presents as flat. As shown in

Figure 2-15, this set of solvents fits within the blue high swelling area and this establishes that, within this region at least, no significant maximum swelling exists.

2.1.3.5. Resin swelling in green binary solvents for HypolGel™200 resin

To show the generality of our approach, HypolGel™200 resin in which the backbone consists of polyethylene glycol grafted onto polystyrene, with a carboxylic acid linker as discussed previously, was also chosen to study using the same methodology as the Merrifield resin.

As discussed above for Merrifield resin, Type 1 solvent mixtures have a maximum swelling mixture. Propylene carbonate with cyclopentyl methyl ether; and toluene with acetonitrile are examples of Type 1 solvent mixtures for HypoGel™200 resin. These solvent pairs are meaningful, because not only do their mixtures go through the high resin swelling area, but also their mixtures become good solvents (swelling beyond 4 mL g^{-1}). The graphs for these solvents are presented in Figure 2-16 and Figure 2-17.

It can be seen from Figure 2-16 that propylene carbonate and cyclopentyl methyl ether are moderate solvents for HypoGel200 resin giving resin swellings of 2.20 mL g^{-1} and 2.80 mL g^{-1} respectively. However, their mixtures become good solvents at ratios between PC:CPME = 40:60 and PC:CPME= 85:15. At the optimised ratio, the swelling has markedly increased to 4.71 mL g^{-1}. Propylene carbonate, cyclopentyl methyl ether and their mixtures are connected by a black line in the 3D trajectory graph.

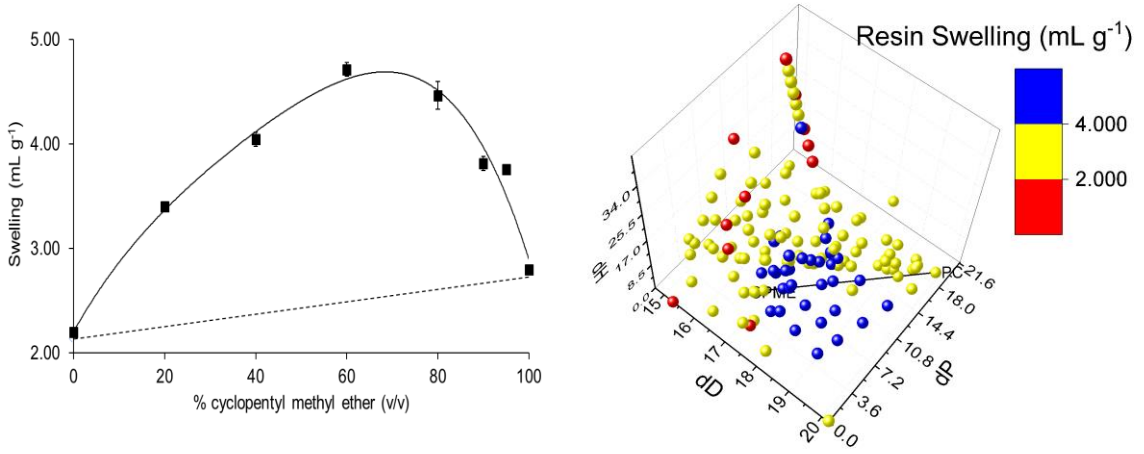


Figure 2-16: Line graph and 3D trajectory graph of the solvent system of cyclopentyl methyl ether & propylene carbonate for HypoGel™200 resin. Line graph is the resin swelling at various propylene carbonate: cyclopentyl methyl ether (v/v) ratios; 3D trajectory graph shows that the cyclopentyl methyl ether (CPME) & propylene carbonate (PC) solvent system is connected by a black line in 3D space

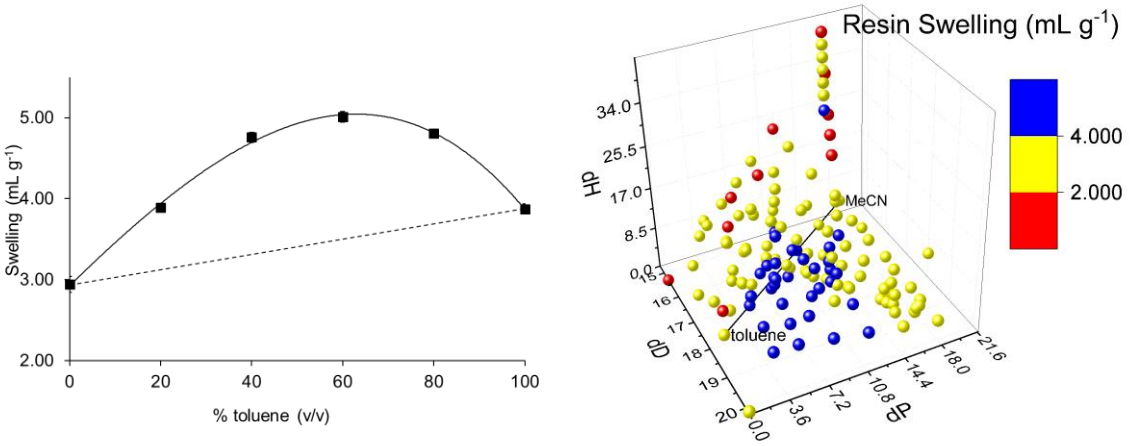


Figure 2-17: Line graph and 3D trajectory graph of the solvent system of acetonitrile & toluene for HypoGel™200 resin. Line graph is the resin swelling at various acetonitrile: toluene (v/v) ratios; 3D trajectory graph shows that the acetonitrile (MeCN) & toluene solvent system is connected by a black line in 3D space

As a second example, along a very different vector in HSP space to the CPME/PC solvent mixtures discussed above, toluene and acetonitrile also showed Type 1 behaviour, with their swelling going through a maximum (acetonitrile:toluene=40:60 (v/v), swelling=5.01 mL g^{-1}) significantly higher than either toluene or acetonitrile alone (2.94 mL $g^{-1}$and 3.87 mL g^{-1} respectively) (Figure 2-17)

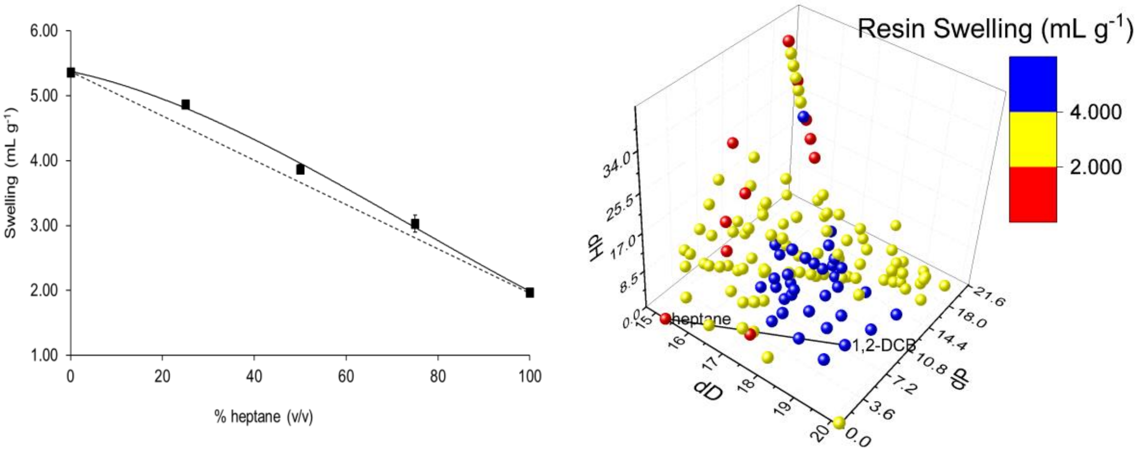


Figure 2-18: Line graph and 3D trajectory graph of the solvent system of heptane & 1,2-dichlorobenzene for HypoGel™200 resin. Line graph is the resin swelling at various 1,2-dichlorobenzene: heptane (v/v) ratios; 3D trajectory graph shows that the heptane & 1,2-dichlorobenzene (1,2-DCB) solvent system is connected by a black line in 3D space

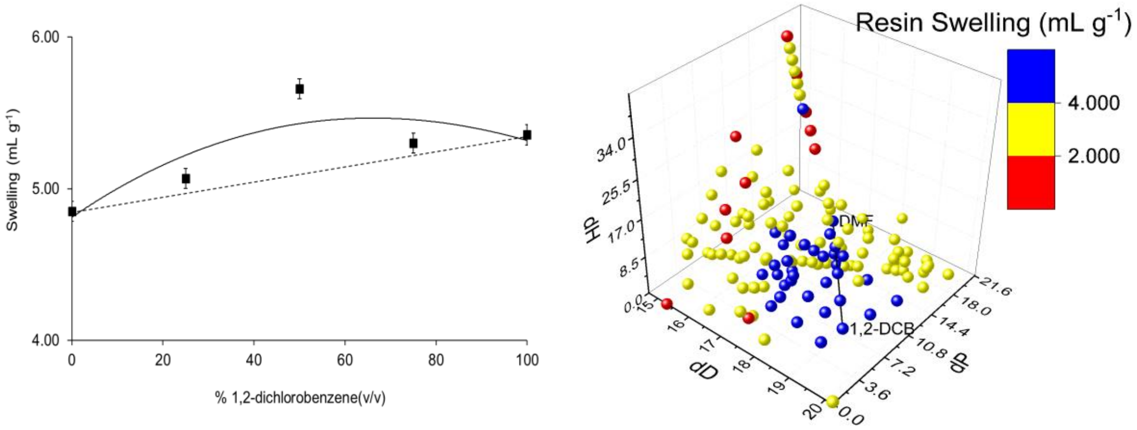


Figure 2-19: Line graph and 3D trajectory graph of the solvent system of dimethylformamide & 1, 2-dichlorobenzene for HypoGel™200 resin. Line graph is the resin swelling at various dimethylformamide: 1,2-dichlorobenzene (v/v) ratios; 3D trajectory graph shows that the dimethylformamide (DMF) & 1,2-dichlorobenzene (1,2-DCB) solvent system is connected by a black line in 3D space

For this resin, the solvent system of heptane with 1,2-dichlorobenzene is representative of a Type 2 solvent system and DMF with 1,2-dichlorobenzene represents Type 3. There is no evident maximum to the curve for a mixture of 1,2-dichlorobenzene and heptane as can be seen in Figure 2-18, because this pair of solvents does not go right across the high resin swelling area. The 1,2-dichlorobenzene and DMF system is shown in Figure 2-19. Although there is slightly more swelling at 50: 50 (v/v), it is still regarded as flat and all points are in the high resin swelling area. Similarly, these pairs of solvents are advantageous to get the boundary of high swelling area. Even if DMF, heptane and 1,2-dichlorobenzene are not perfect solvents in green chemistry, they are common organic solvents and they can be helpful to explore the high resin swelling area.

2.1.4. Special cases of resin swelling

2.1.4.1. Solvent system of cyclopentanone and water for HypoGel™200 resin

As cyclopentanone and water are only miscible in certain ratios, the use of this solvent system created an interesting special case for resin swelling. As shown in Figure 2-20, there is a blue ball which is far away from the main blue area; this is one of the mixtures of cyclopentanone and water. The limits of cyclopentanone and water miscibility were found to be up to 14% water (v/v) in cyclopentanone or up to 31% cyclopentanone in water at room temperature. Cyclopentanone and water are not miscible between this gap. Therefore, some solvents whose positions are in the gap area (δD=17-19, δP=5-15, δH>20) were searched for in the database of the HSPiP software to fill the gap. Unfortunately, there were no suitable candidates. All suggested chemicals either had high melting points or were extremely expensive.

Resin swelling is high for pure cyclopentanone, and this does not change significantly on addition of small quantities of water. However, starting from pure water, as the limit of miscibility is approached by adding cyclopentanone to water, swelling increases rapidly, with 31% cyclopentanone in water having a swelling value of 4.48 mL g^{-1}. As can be seen in Figure 2-20, this high swelling behaviour is anomalously far away from the main high-swelling region in HSP space. From the prediction of Stefan Lawrenson, *et al.*, cyclopentanone and water had an optimised swelling ratio at 91: 9 (v/v).[31] It was suspected that this effect is the result of the resin preferentially capturing cyclopentanone out of the solvent mixture, giving swelling behaviour more similar to cyclopentanone than the ratio of the mixture would indicate.

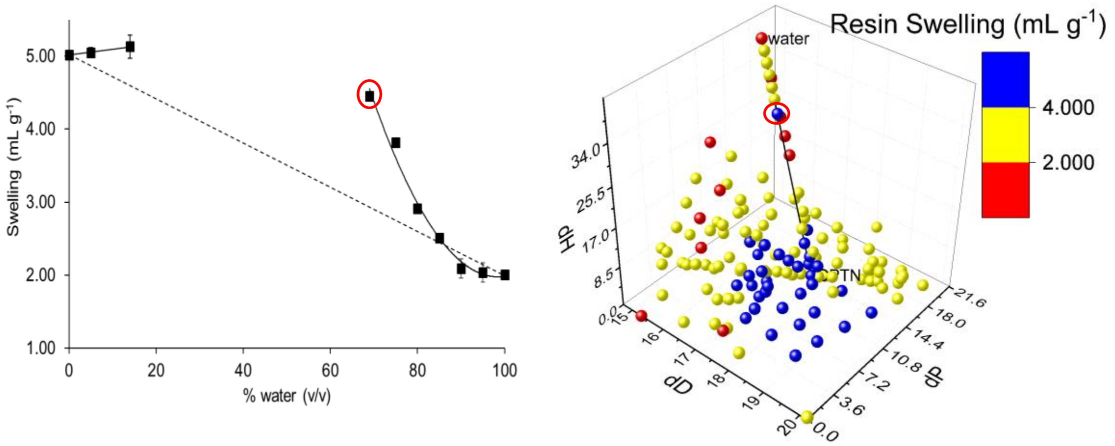


Figure 2-20: Solvent system of cyclopentanone and water for HypoGel™200 resin; the red cycle is the cyclopentanone: water=69: 31 mixture

^{1}H NMR spectroscopy with an internal standard method was chosen to prove the ability of HypoGel™200 resin to selectively capture cyclopentanone from a water & cyclopentanone mixture. Mesitylene was employed as internal standard because it has only two peaks in its ^{1}H NMR spectrum which do not overlap the signals for cyclopentanone. The methodology was: spectra were recorded of pure cyclopentanone, pure mesitylene, the mixed solvent before resin swelling and the mixed solvent remaining above the swollen beads after resin swelling. A known volume of mesitylene was added to mixed solvent samples taken before and after resin swellings as an internal standard to allow calculation of how the cyclopentanone:water ratio changes. The standard was added to the aliquots taken for NMR only, it was not present for the swelling experiment itself. For full spectra, see Appendix C.

Table 2-4 gives the test results and the mesitylene: cyclopentanone ratio is determined by dividing the mesitylene aromatic CH integral by 3, then summing the integrals for the two cyclopentanone signals between 1.88 and 2.20 ppm and dividing the sum by 8. The amount of mesitylene added as an internal reference was identical for entries 1 and 2, and for entries 3 and 4 respectively. A water: cyclopentanone=30:70 (v/v) mixture was used initially as this was known to swell the HypoGel™200 resin. The ^{1}H NMR data were: mesitylene (1,3,5-trimethylbenzene): 6.81-6.71 and 2.50 ppm; cyclopentanone: 2.20-2.09 and 2.00-1.88 ppm; water: 1.61 ppm. A peak at 4.85-4.77 ppm was due to PEG from the HypoGel™200 resin. As can be seen from Table 2-4, the concentration of cyclopentanone in the residual solvent relative to the mesitylene standard was reduced after swelling, indicating that the resin has preferentially taken up cyclopentanone over water in the mixture.

Table 2-4: ^{1}H NMR analysis of cyclopentanone: water mixtures before and after swelling of HypoGel^{TM}200 resin. The ^{1}H NMR spectra are in Appendix C

Entry	Initial cyclopentanone to water ratio (v/v)	Before / after swelling of resin	Mesitylene to cyclopentanone ratio
1	30:70	before	1:0.40
2	30:70	after	1:0.28
3	90:10	before	1:0.14
4	90:10	after	1:0.06

To confirm this result, another solvent ratio: cyclopentane: water=90:10 (v/v) was also chosen to do the same test, and the results are also displayed in Table 2-4. By comparison of the mesitylene to cyclopentanone ratio before and after swelling it again shows the removal of cyclopentanone from the solvent after resin swelling. However, the degree of decrease of concentration of cyclopentanone in the 90:10 solvent blend is considerably more than in the 30:70 solvent blend as the 90:10

(resin swelling=4.9 mL g^{-1}) is a better solvent for HypoGel™200 resin than the 30: 70 (resin swelling= 4.48 mL g^{-1}). These results have shown that in the solvent system of cyclopentanone and water only cyclopentanone swells the HypoGel™200 resin.

2.1.4.2. Solvent system of DMF and water for HypoGel™ 200 and Merrifield resins

The DMF and water system was chosen to fill a gap at δD=17-19, δP=5-15, δH >20. Although DMF is not a green solvent, it is commercially available and miscible with water. Water is a poor solvent for these two resins while DMF is good solvent for these two resins, therefore, it was hoped that this data set would establish the boundary of the high swelling region along this vector (Figure 2-22). Line graphs of swelling against solvent composition are shown in Figure 2-21. As is shown in these two figures, there is no significant increase or decrease in swelling from 100% water to water:DMF= 20:80. However, beyond water:DMF= 20:80, the amount of swelling has a dramatic growth for HypoGel™200 resin. But for Merrifield resin, addition of even 10% water reduces the swelling of the resin to the same level observed using pure water. In the area (δD=17-19, δP=5-15, δH >20) which can be seen in the full 3D graphs (Figure 2-22) of these two resins, the mixtures of DMF and water are black points for Merrifield resin and red points for HypoGel™200 resin which means they give poor swelling. As DMF was in a high swelling area, these results can help to get a clearer definition of the high swelling area. In the middle area of this 3D graph, other solvents (such as furfuryl alcohol) are also poor solvents which means that all solvents in this area were not good solvents.

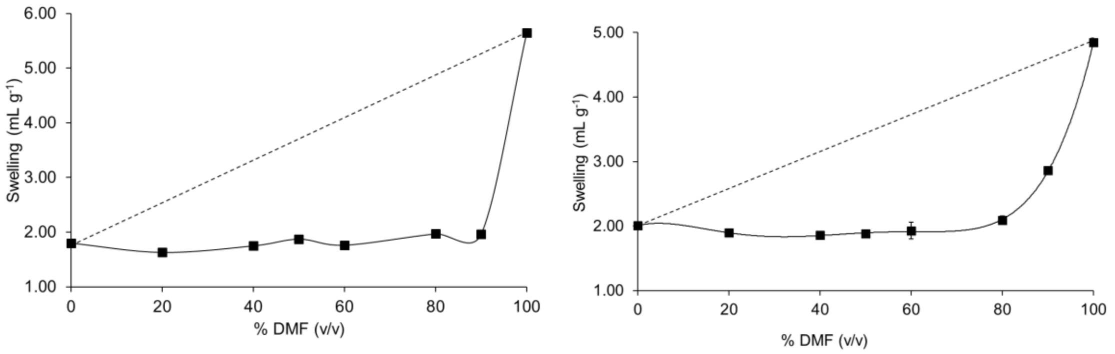


Figure 2-21: Solvent system of dimethylformamide (DMF) and water for Merrifield resin and HypoGel™200 resin; the first line graph is belong to Merrifield resin and the second ling graph is belong to HypoGel™200 resin

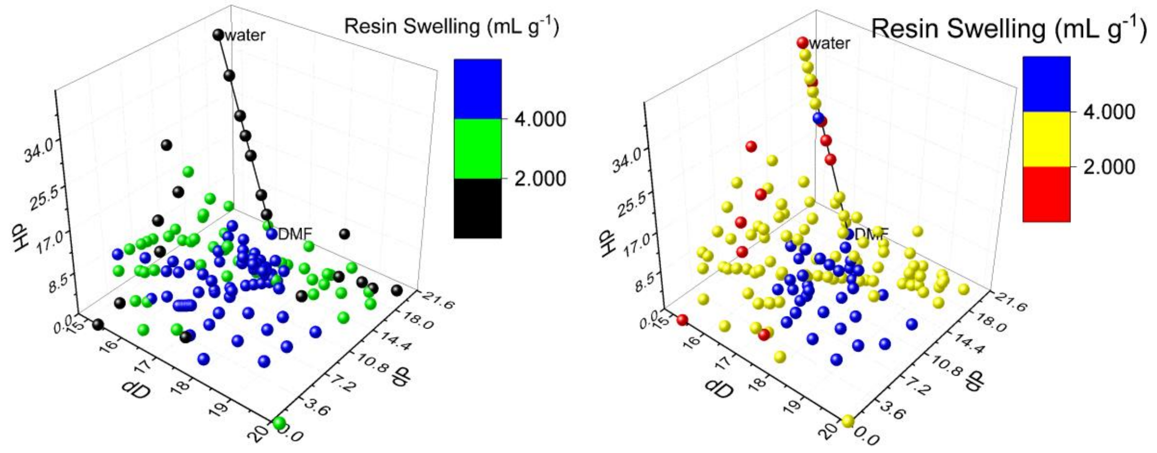


Figure 2-22: 3D trajectory graph of the solvent system of DMF and water for Merrifield resin and HypoGel™200; the first 3D trajectory graph is belong to Merrifield resin and the second 3D trajectory graph is belong to HypoGel™200 resin

Dimethylformamide is polar and a good acceptor of hydrogen bonds, and water is dipolar and a good donor of hydrogen bonds. When dimethylformamide mixes with water, this solvent system will form hydrogen-bonded complexes by the interaction of the amide and hydroxylic cosolvents.[75] For this reason, the interaction of solvent and solvent is very large, and prevents DMF from swelling the resin. However, when the percentage of DMF exceeded 80%, only part of the DMF combined with water to form hydrogen-bonded complexes and the remaining part of the DMF can swell the HypoGel™200 resin as it is more hydrophilic than Merrifield resin. This is the reason why the line graphs of dimethylformamide (DMF) and water for Merrifield and HypoGel™200 resins have an unusual shape.

2.1.4.3. Solvent system of 2-MeTHF and cyclopentyl methyl ether for Merrifield resin

Another special case is 2-MeTHF and cyclopentyl methyl ether for Merrifield resin (Figure 2-23). In the study of Lawrenson, HSPiP software predicted that the optimised ratio for these two solvents was 2-MeTHF:CPME=52:48 (v/v).[31] In this study, we found that 52% 2-MeTHF (swelling of 6.27 mL g^{-1}) mixed with 48% CPME (swelling of 5.67 mL g^{-1}) gave swelling of 5.33 mL g^{-1}, lower than either pure solvent. The Hansen solubility parameters of 2-MeTHF (δD=16.9, δP= 5, δH=4.3) and CPME (δD=16.7, δP= 4.3, δH=4.3) are very similar which means that their positions in 3D space are very close. In Figure 2-23, the circle in red encompasses all this solvent system: both pure solvents and their mixtures are located in the high resin swelling area. This solvent system is a case of solvent system which has a minimum resin swelling, and it indicates that the solvent-solvent interactions may not only have positive synergy (maximum resin swelling) but can also have negative synergy (minimum resin swelling). This phenomenon needs further investigation.

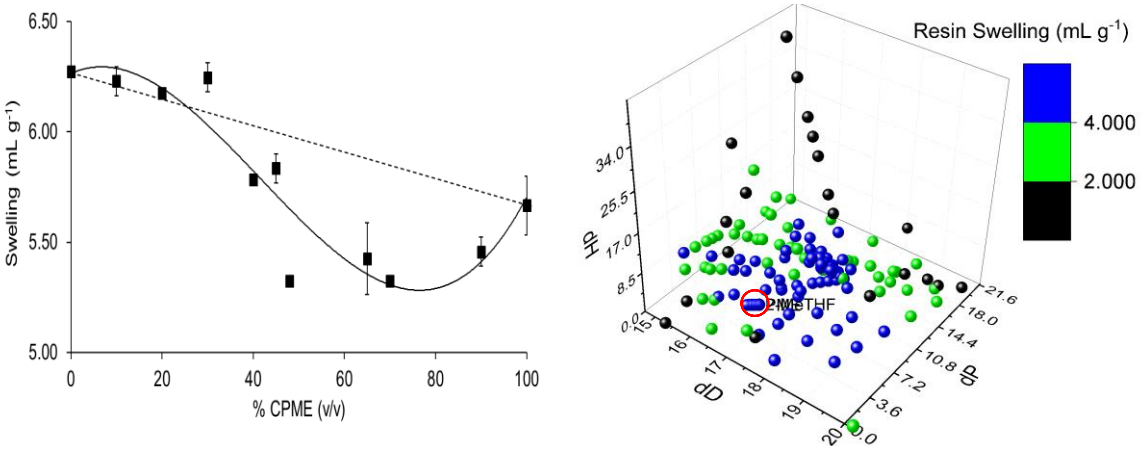


Figure 2-23: Solvent system of 2-methyltetrahydrofuran (2-MeTHF) and cyclopentyl methyl ether (CPME) for Merrifield resin (circled in red)

2.1.4.4. Solvent system of propylene carbonate and TMO for Merrifield resin

The solvent system of propylene carbonate and TMO is another special case for Merrifield resin because they are immiscible from PC:TMO=65:35 (v/v) to PC:TMO=10:90 (v/v) at room temperature, which is shown as a gap in Figure 2-24. However, data from the 3D graph in Figure 2-24 indicate that the solvent system of TMO and propylene carbonate goes through the high swelling area (the blue area) of Merrifield resin. In the line graph of Figure 2-24, their miscible mixtures (black points) show the ability to make Merrifield resin swell beyond 2 mL g^{-1} and even close to 4 mL g^{-1} though propylene carbonate and TMO are both poor solvents with resin swelling below 2 mL g^{-1}. It was apparent that the PC:TMO=10:90 (v/v) mixture has a maximum resin swelling (3.82 mL g^{-1}). To investigate this further, other ratios (red points) which cannot be mixed together were also used to swell Merrifield resin, and gave similar results in terms of resin swelling. These systems formed two layers and gas chromatography (GC) was used to analyse each layer to determine their mol/mol ratio. The results are presented in Table 2-6.

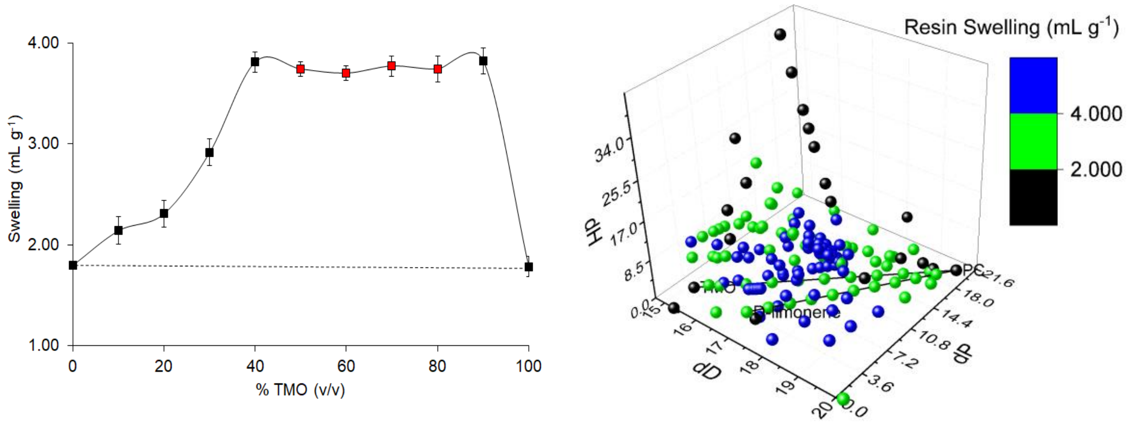


Figure 2-24: Solvent system of propylene carbonate and TMO for Merrifield resin

GC is a widely used chromatography in analytical chemistry, and it can separate components of a mixture by the different time of peak elution. According to Appendix D, acetone was used as blank and eluted at 1.186 min in the chromatogram, followed by TMO and propylene carbonate at 1.765 min and 2.819 min respectively. A miscible mixture of these two solvents (PC:TMO=80:20 (v/v)) was chosen as a calibrant, then other mixtures were calibrated using the same response factor (Rf) to get the mol/mol ratio of each blend. The results varied depending on which GC instrument was used. The calibration results are given in Table 2-5. The formula used is below:

$$\frac{PC(mol\%)}{TMO(mol\%)} = \mathrm{Rf}\frac{PC(Area)}{TMO(Area)} \quad \cdots\cdots\cdots\cdot \text{ Equation 4}$$

Table 2-5: Calculating response factors (Rf) from different gas chromatography instruments

Machine	PC (v%)	PC (V%)	PC (mol%)	TMO (mol%)	PC Area (PA *s)	TMO Area (pA *s)	Rf
1	80	20	88.30%	11.70%	12669	4808.9043	2.863453
2	80	20	88.30%	11.70%	7926.79492	3153.14453	3.000769

After the GC calibration, the real mol/mol ratio was determined. Data in Table 2-6 suggest that for immiscible blends, more TMO existed in the top layer and more propylene carbonate was present in the bottom layer. At the same time, we can also observe that the top layers of PC:TMO=20:80, 30:70, 40:60, 50:50 and 60:40 (v/v) contained 14-16 mol% propylene carbonate and 84-86 mol% TMO which are similar to the composition of the PC:TMO=10:90 (v/v) solvent blend. Correspondingly, the bottom layers of all the immiscible mixtures contained 76-77 mol% propylene carbonate and 23-24 mol% TMO which matches the molar composition of the 65:35 (v/v) mixture. This suggested that it was the top layer of the immiscible mixtures which was responsible for the resin swelling.

Table 2-6: The results of propylene carbonate and TMO mixtures for Merrifield resin after GC calibration

					GC results				
Testing Part	PC(v%)	TMO(v%)	PC(mol%)	TMO(mol%)	PC(Area pA*s)	TMO(Area pA*s)	Rf	PC(mol%)	TMO(mol%)
Suspension	10	90	17.32%	82.68%	478.39	7800.95	2.86	14.94%	85.06%
Top	20	80	32.04%	67.96%	1059.21	17904.60	2.86	14.49%	85.51%
Bottom	20	80	32.04%	67.96%	7666.45	6605.79	2.86	76.87%	23.13%
Top	30	70	44.70%	55.30%	1110.32	19194.10	2.86	14.21%	85.79%
Bottom	30	70	44.70%	55.30%	7524.83	6504.19	2.86	76.81%	23.19%
Top	40	60	55.70%	44.30%	951.05	16372.00	2.86	14.26%	85.74%
Bottom	40	60	55.70%	44.30%	7823.83	6719.13	2.86	76.93%	23.07%
Top	50	50	65.35%	34.65%	703.28	11937.90	2.86	14.43%	85.57%
Bottom	50	50	65.35%	34.65%	7750.32	6669.02	2.86	76.89%	23.11%
Top	60	40	73.88%	26.12%	701.40	11041.80	3.00	16.01%	83.99%
Bottom	60	40	73.88%	26.12%	8900.46	8179.28	2.86	75.70%	24.30%
Suspension	65	35	77.79%	22.21%	7216.28	5964.92	2.86	77.60%	22.40%
Miscible	68	32	80.03%	19.97%	10061.40	7796.25	2.86	78.70%	21.30%
Miscible	70	30	81.48%	18.52%	7775.30	5246.31	2.86	80.93%	19.07%
Miscible	80	20	88.30%	11.70%	12669.00	4808.90	2.86	88.30%	11.70%
Miscible	90	10	94.44%	5.56%	12072.70	2089.69	2.86	94.30%	5.70%

To confirm this interpretation, the immiscible solvent blends of PC:TMO=20:80 (v/v) and PC:TMO=50:50 (v/v) were selected to test the swelling ability of their top and bottom layers. The experimental method was to separate the top layers and bottom layers of these two solvent blends and test them separately. GC was applied to analyse the variation of mol/mol percentage of the top and bottom layers before and after resin swelling so as to investigate which layer swelled Merrifield resin as well as which solvent swelled the resin, and results are displayed in Table 2-7.

Table 2-7: GC to test the capturing ability of Merrifield resin in PC+TMO solvent system

	Solvent(v/v)		Solvent(mol/mol)		GC results			
Test	PC	TMO	PC	TMO	PC Area (pA *s)	TMO Area (pA *s)	PC (mol%)	TMO (mol%)
Top before swelling					850.88269	14269.3	15.18%	84.82%
Top after swelling	20	80	32.04 %	67.96 %	419.04117	15715.8	7.41%	92.59%
Bottom before swelling					6117.58105	5335.81836	77.48%	22.52%
Bottom after swelling					6432.0791	3397.47363	85.03%	14.97%
Top before swelling					764.07281	13117.6	14.88%	85.12%
Top after swelling	50	50	65.35 %	34.65 %	751.15051	14505.5	13.45%	86.55%
Bottom before swelling					6104.40283	5112.06445	78.18%	21.82%
Bottom after swelling					7147.79297	3625.61133	85.54%	14.46%

As can be seen from Table 2-7 for these two solvent mixtures, both of their top layers after swelling have an evidently decreased percentage of propylene carbonate and increased TMO compared to the percentage of propylene carbonate and TMO before swelling. On the contrary, the percentage of propylene carbonate goes up sharply and TMO reduces in their bottom layers after swelling by contrast with the percentage before swelling. Therefore, using this method can identify that both the top and bottom layer of the mixtures have swelling abilities for Merrifield resin. However, the top layers have better abilities than the bottom layers to swell the resin. In other words, in the immiscible solvents, the solvents of the top layers go into the interface of the resin faster. Thus, Merrifield resin prefers to swell in a propylene carbonate:TMO mixture which contains more TMO than is present in the bottom layer and which corresponds to that found in the top layer.

In summary, propylene carbonate and TMO are poor solvents for Merrifield resin, but their mixture can become moderate solvent. This means that it is a synergistic effect of propylene carbonate and TMO that makes the resin swell. However, the case of propylene carbonate and TMO illustrates that although two solvents are poor solvents and are well separated in HSP-3D space, when their mixture can be located in the high resin swelling area, their mixture would have better swelling ability than either pure solvent. This situation was also apparent for the mixture of propylene carbonate and D-limonene, which is perhaps unsurprising as D-limonene (δD=17.2, δP=1.8, δH=4.3) has very similar Hansen solubility parameters to TMO (δD=15.4, δP=2.4, δH=2.1).

2.1.5. Miscibility tests of potential solvent pairs for Merrifield resin

Based on the 3D graphs, various other pairs of solvents whose mixtures will pass through the high resin swelling area of Merrifield resin can be predicted. However, in view of the above results, the miscibility of these solvent pairs was investigated. Table 2-8 shows the miscibility of solvent A and solvent B when their volume to volume ratio is 50 to 50. DMF and water is a special case for Merrifield resin and HypoGel™200 resin because they can form hydrogen-bonded complexes as discussed previously. Usually, when chemists test the miscibility of two solvents, the ratio v/v=50/50 is chosen. From the solvent system of propylene carbonate and TMO, however, we know that sometimes even though they cannot mix at v/v=50/50, they still can be miscible at some ratios which are usually close to pure solvent A or pure solvent B.

Table 2-8: Miscibility tests of potential solvent pairs which would have maximum swelling for Merrifield resin

Solvent A	Solvent B	A: B=50: 50(v/v)
dimethylformamide	water	+
dimethyl sulfoxide	TMO	-
ethylene carbonate	TMO	-
acetonitrile	carbon disulfide	-
cyclopentanone	TMO	+
cyclopentanone	water	-
propylene carbonate	TMO	-
propylene carbonate	heptane	-
propylene carbonate	D-limonene	-
propylene carbonate	p-cymene	-
propylene carbonate	dimethyl carbonate	+
propylene carbonate	acetone	+
propylene carbonate	isopropyl acetate	+
propylene carbonate	diethyl carbonate	+
propylene carbonate	isobutyl acetate	+

2.1.6. Conclusions for resin swelling in greener binary solvents for Merrifield and HypoGel™200 resins

At this stage of this project, two commercially available resins: Merrifield resin with Wang linker and HypoGel™200 resin with different backbones and linkers had been studied. This project started with the study of Lawrenson in our group. Hundreds of resin swelling experiments have defined that high resin swelling areas exist in HSP-3D space for both HypoGel™200 resin and Merrifield resin. Additional studies investigated interesting special cases for non-miscible solvent mixtures (water/cyclopentanone and PC/TMO), or a mixture with very large solvent-solvent interactions (water/DMF). This now provides a robust, predictive model for selection of binary mixed solvent systems for solid phase peptide synthesis using either of these resins, as well as giving some insight into the fundamental resin-solvent interaction in each case. Next, to make these models be of more significance, their applications were taken into consideration. Thus, some greener binary solvents were selected to study if they could be applied in solid phase peptide synthesis.

2.2. Solid-phase peptide synthesis in greener binary solvent mixtures

2.2.1. Background of greener binary solvents and repeated literature experiments: a tripeptide prepared in propylene carabonate on Wang-ChemMatrix®resin

Peptides are important in the pharmaceutical industry as therapeutic peptides have high efficiencies as antihypertensives, antidepressants, contraceptives and antibiotics.[45] As they have large economic and practical values, peptide synthesis is a crucial step for the manufacture of these drugs.[45]

Solution-phase peptide synthesis is a common reaction in chemistry, but it is gradually being discarded due to disadvantages such as difficult purification and low yield. Solid-phase peptide synthesis has been adopted by industry as it is a quick and easy procedure.[17] Traditional organic solvents like DMF are usually used in solid-phase peptide synthesis as they have good swelling abilities for commercially available resins.[17] However, there is an urgent need to find alternative solvents which are more environmentally friendly.

In Chapter of 2.1 of this thesis, two common resins, Merrifield resin and HypoGel™200 resin were investigated to determine if they had high swelling areas in HSP-3D space. This hypothesis was confirmed and their 3D models were almost fully established. Thus, it was appropriate to think about the application of these two models. As this project started with greener solvents which could potentially be applied in SPPS,[13] SPPS was used as a target to test if the models were useful.

Propylene carbonate is a green solvent synthesized from carbon dioxide and propylene oxide.[76] Recently, Lawrenson studied the use of propylene carbonate in solid-phase peptide synthesis and it performed well.[13] The tripeptide (H-Leu-Ala-Phe-OH) was used as a target and the synthesis was started with preloaded H-Phe-HMPB-ChemMatrix® resin, adding Fmoc-Ala-OH and Fmoc-Leu-OH in sequence.[13] However, to date, using solvent blends to do peptide synthesis had not been investigated. In this project, greener solvent blends were hence applied in solid-phase peptide synthesis. Use of Merrifield resin was set as the research objective because Merrifield resin is more prevalent in solid-phase peptide synthesis than HypoGel™200 resin. The tripeptide, H-Leu-Ala-Phe-OH was again used as the target peptide chain to test if greener binary solvents could also work well in solid-phase peptide synthesis. As detailed in Chapter 2.1.3.4, many green binary solvents have been shown to have maximum resin swellings for Merrifield resin at optimised ratios. Thus, two pairs of solvents: ethyl acetate and propylene carbonate, TMO and propylene carbonate, whose mixtures have better swelling than each pure solvent, were selected to apply in the synthesis of this tripeptide.

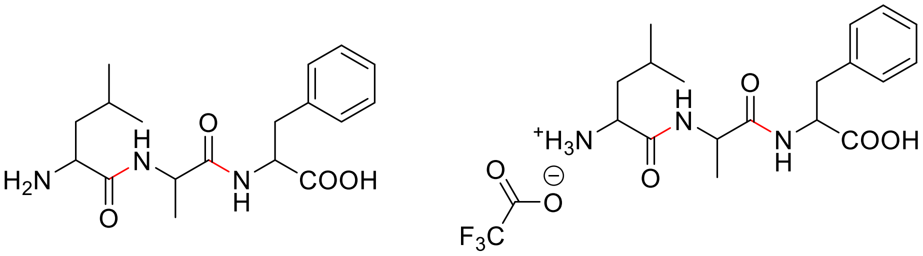


Figure 2-25: The first chemical structure is the tripeptide (H-Leu-Ala-Phe-OH), the second chemical structure is this tripeptide as its trifluoroacetate salt

The synthesis of H-Leu-Ala-Phe-OH in propylene carbonate on Wang-ChemMatrix® resin was repeated to prove the reproducibility of the literature synthesis,[13] and the product characterizations are shown in Figure 2-26 to Figure 2-28. Compared with the literature data,[13] Figure 2-26 is an identical ^{1}H NMR spectrum. The spectrum of H-Leu-Ala-Phe-OH was recorded in TFA-d NMR solvent, TFA-d: δ = 7.26-7.16 (m, 3H, ArH), 7.14-7.08 (m, 2H, ArH), 5.01-4.96 (m, 1H, Phe-NCH), 4.71-4.61 (m, 1H, Ala-NCH), 4.31-4.24 (m, 1H, Leu-NCH), 3.30 (dd *J* 14.3, 4.3 Hz, 1H, CH_2Ph), 3.09 (dd *J* 14.3, 8.5 Hz, 1H, CH_2Ph), 1.80-1.60 (m, 3H, Leu-CH_2CHMe_2), 1.39 (d *J* 6.3 Hz, 3H, $NCHCH_3$), 0.93 (t *J* 6.0 Hz, 6H, $CH(CH_3)_2$). In Figure 2-27, the mass spectrum shows $[M+H]^+$ at 350.2070 $[M+H]^+$ and $[M+Na]^+$ at 372.1889. The HPLC trace in Figure 2-28 illustrates that this tripeptide elutes at 14.122 min, and the purity is ≥ 98%. The sample was a white solid.

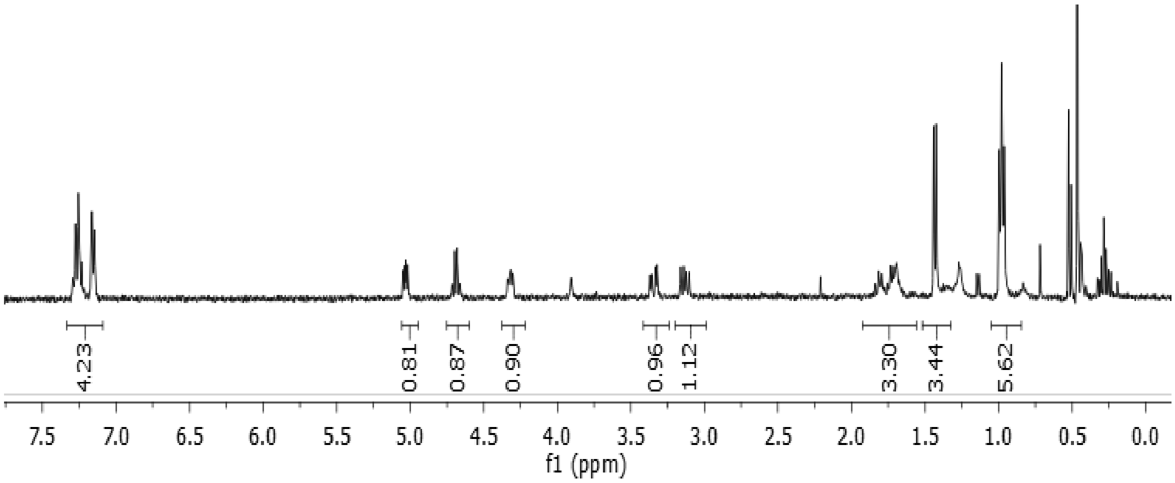
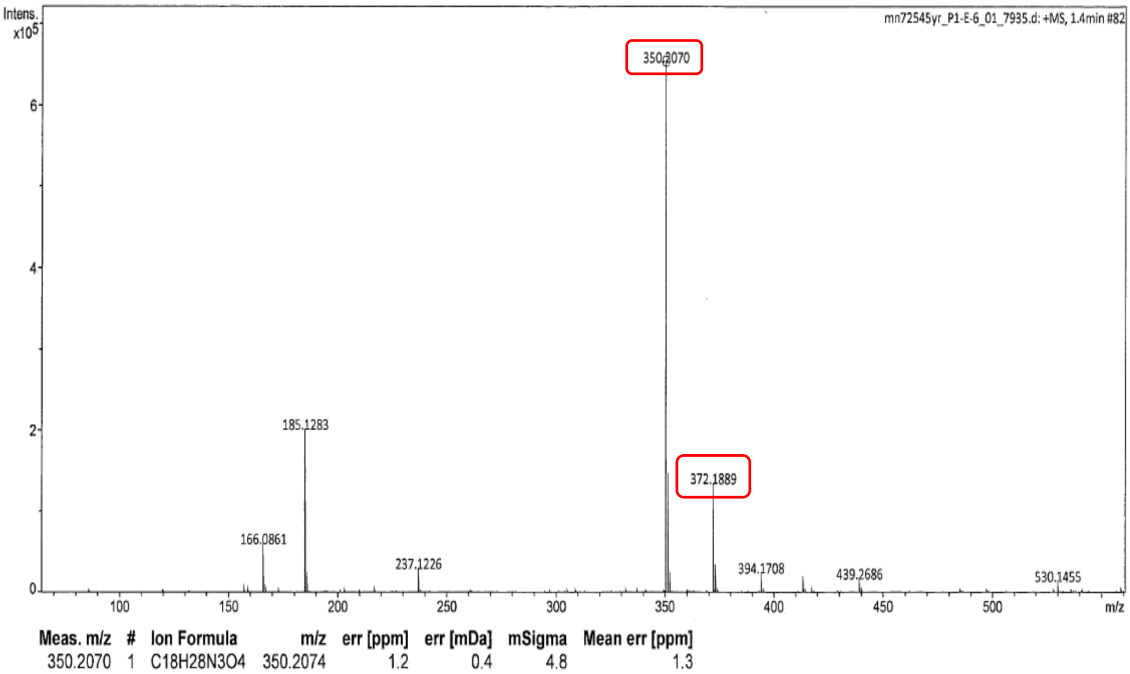
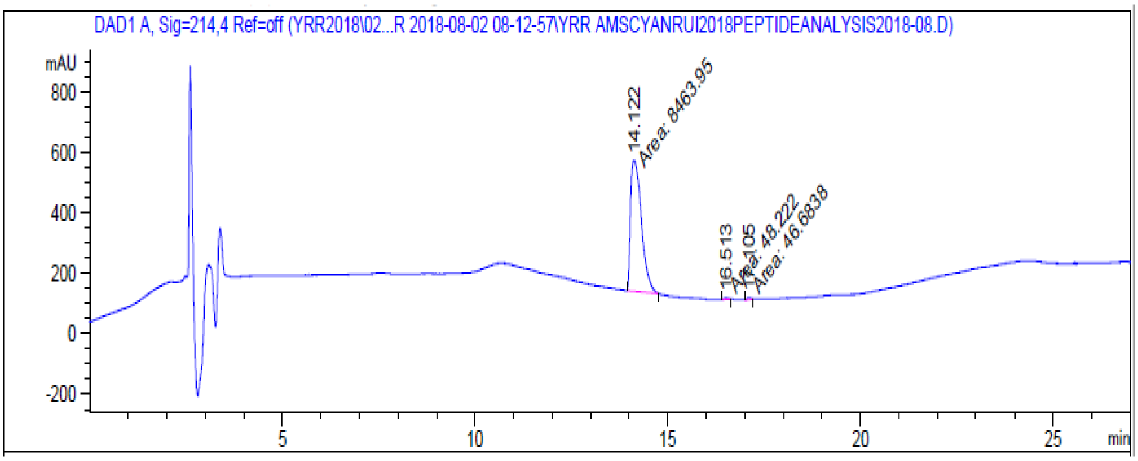


Figure 2-26: ^{1}H NMR spectrum (TFA-d) of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate on ChemMatrix resin



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2070	1	C18H28N3O4	350.2074	1.2	0.4	4.8	1.3

Figure 2-27: Mass spectrum of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate on ChemMatrix resin



HPLC Chromatogram Report

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.122	MM	0.3245	8463.95215	434.72705	98.891
2	16.513	MM	0.111	48.222	7.23913	0.5634
3	17.105	MM	0.1062	46.68384	7.32693	0.5454

Figure 2-28: HPLC trace of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate on ChemMatrix resin

2.2.2. Tripeptide synthesis in propylene carbonate & ethyl acetate solvent system with Merrifield resin (HBTU/HOBt)

As the peptide synthesis had been repeated successfully, Merrifield resin with Wang linker (also just called Wang resin) was used as the solid-phase to synthesize the same tripeptide, following the sequence in Figure 2-29. In this project, H-Leu-Ala-Phe-OH was set as the target peptide to test if binary solvents could be applied in solid-phase peptide synthesis as well as if they could work better than their pure solvents. As reported before, the solvent system of propylene carbonate (PC) (swelling=1.80 mL g^{-1}) and ethyl acetate (EA) (swelling=3.80 mL g^{-1}) has a maximum Merrifield resin swelling at a ratio of PC:EA=10:90 (v/v) (swelling=4.61 mL g^{-1}). Thus, the tripeptide was synthesized in propylene carbonate, ethyl acetate and a PC:EA=10:90 mixture on Wang resin to compare which solvent was better for solid-phase peptide synthesis. The synthetic method mainly followed literature,[13] but some processes were changed (Figure 2-29), as peptide synthesis was started with Fmoc-Phe-Wang resin (Figure 2-30). Firstly, a freshly prepared 20% (v/v) solution of piperidine in pure solvents or binary solvent was used for deprotection. Three equivalents of HBTU/HOBt (3-[bis(dimethylamino)methyliumyl]-3H-benzotriazol-1-oxide hexafluorophosphate/hydroxybenzotriazole) as the coupling agents and six equivalents of DIPEA (diisopropylethylamine) were dissolved in 5 mL of solvent to pre-activate three equivalents of Fmoc-amino acid. Coupling reactions were performed at ambient temperature for 1 hour. A mixture of TFA (trifluoroacetic acid), TIPS (triisopropylsilane) and H_2O with the ratio at 95:2.5:2.5 (v/v/v) was adopted to cleave the peptide chain from the resin and it was then precipitated with cold diethyl ether. The last step was to use vacuum to dry the peptide. All syntheses were repeated twice and gave the same results. After each step, the resin was washed with the chosen solvent three times, hence no other organic solvents were used in the synthetic processes.

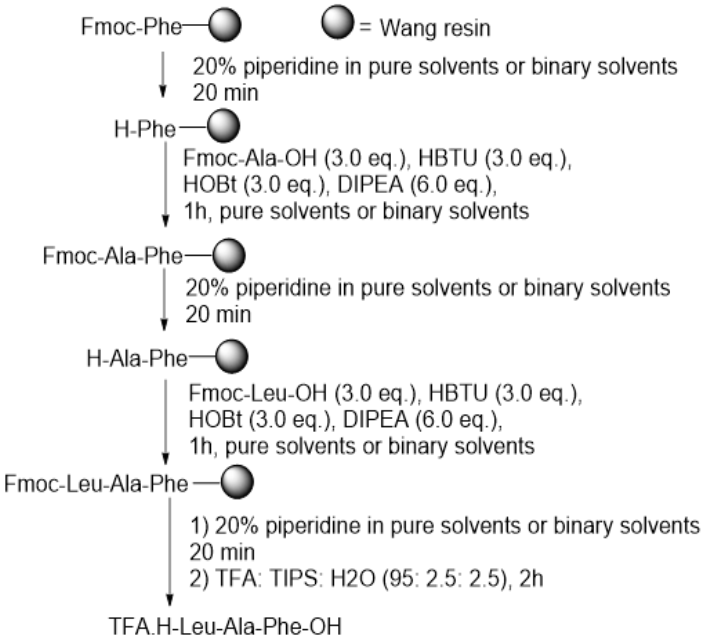


Figure 2-29: The synthetic sequence for the synthesis of the tripeptide (H-Leu-Ala-Phe-OH)

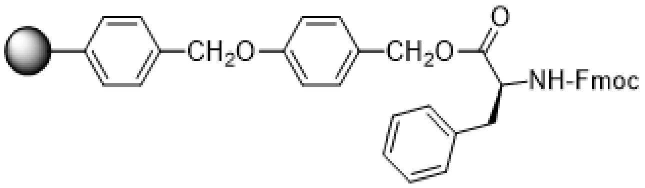


Figure 2-30: Structural formula of Fmoc-Phe-Wang resin; 0.4-0.8 mmol/g loading

2.2.2.1. Tripeptide prepared in pure propylene carbonate

Peptide synthesis in propylene carbonate on Wang resin was tested first. As Chapter 2.1.3.4 discussed, propylene carbonate is a poor solvent for Wang resin as it gives resin swelling below 2 mL g^{-1} (1.80 mL g^{-1}). In theory, it should not be a suitable solvent for successful peptide synthesis. However, in order to prove the correctness of this theory and also to compare with the peptide synthesis in ethyl acetate and their binary solvent, it was still necessary for this control to be carried out. The results of ^{1}H NMR spectroscopy, mass spectroscopy and HPLC chromatography on this sample are shown in Figure 2-31, Figure 2-32 and Figure 2-33. The ^{1}H NMR spectrum shows only that phenylalanine (δ=7.70-7.00) exists in this sample and Figure 2-34 shows that no product precipitated in diethyl ether. However, the mass spectrum shows that there is some H-Leu-Ala-Phe-OH in the sample (m/z: 350.2068 $[M+H]^+$). The HPLC chromatogram also shows product eluting at 14.318 min, but the content of it in the sample is very low (around 3%). According to analysis of these results, although propylene carbonate is a poor solvent for Wang resin, it still has a little swelling ability for this resin and allows a small amount of peptide synthesis to occur.

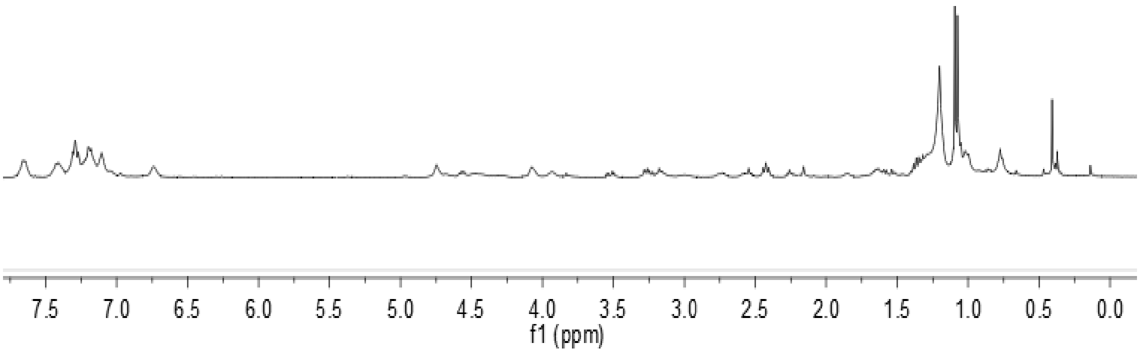
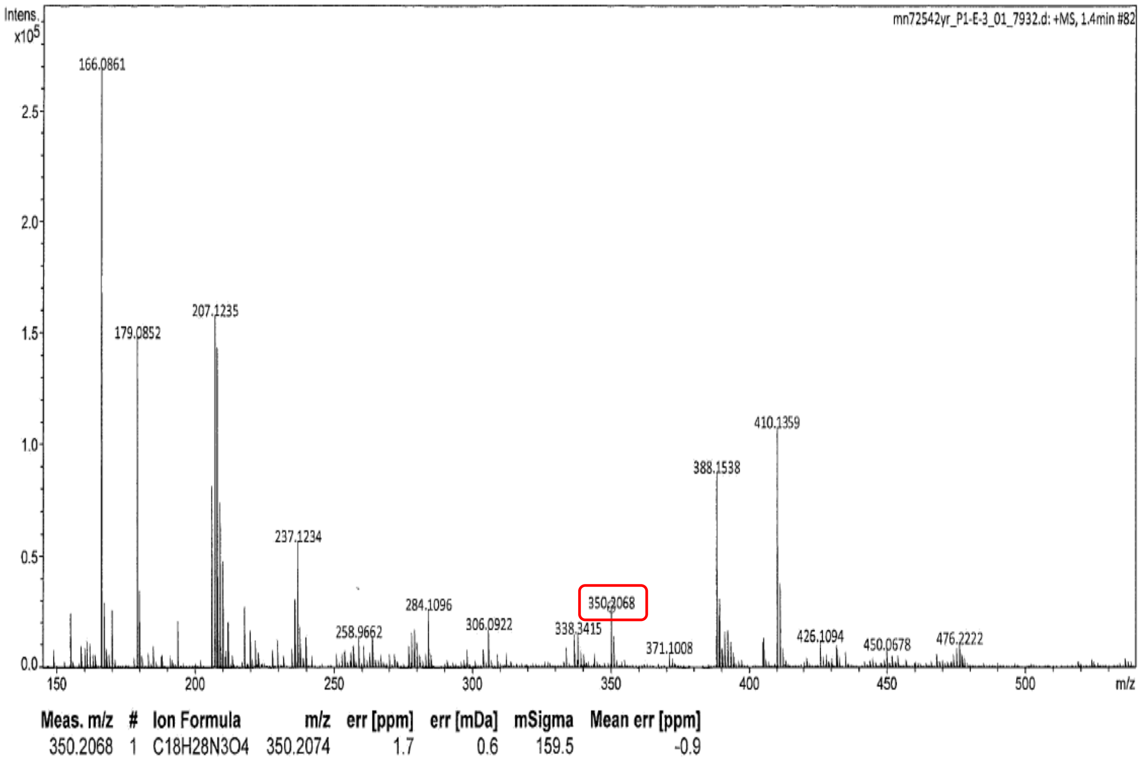
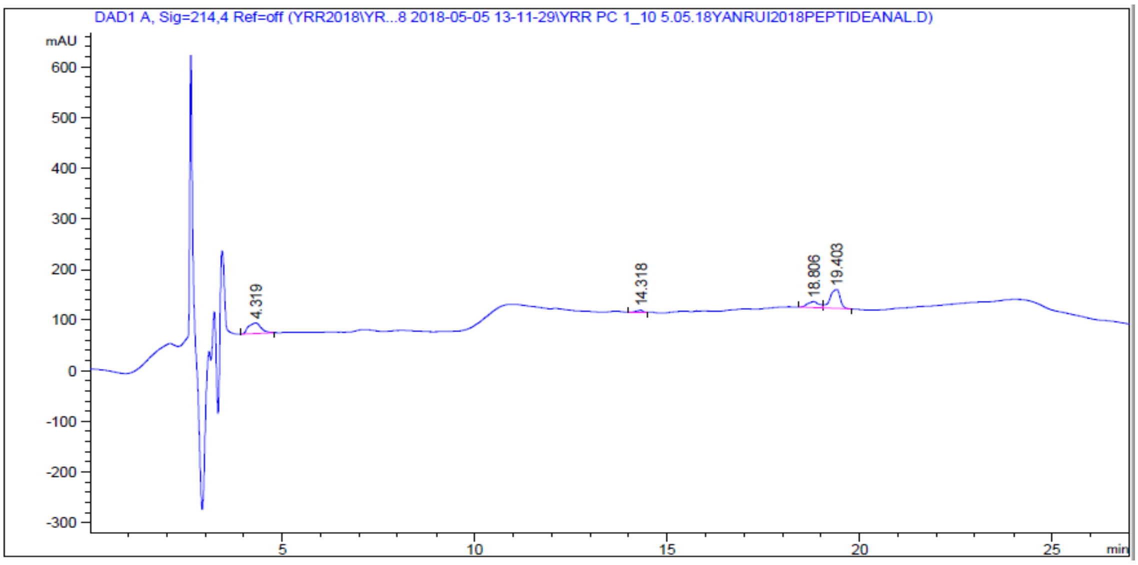


Figure 2-31: ^{1}H NMR spectrum (TFA-d) of TFA·H-Leu-Ala-Phe-OH in synthesized in propylene carbonate on Wang resin



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2068	1	C18H28N3O4	350.2074	1.7	0.6	159.5	-0.9

Figure 2-32: Mass spectrum of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate on Wang resin



HPLC Chromatogram Report						
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.319	BB	0.2882	463.74301	20.79243	32.608
2	14.318	BB	0.1358	44.72331	4.42886	3.1447
3	18.806	BV	0.2444	239.16025	11.75478	16.8165
4	19.403	VB	0.2378	674.54858	37.86259	47.4308

Figure 2-33: HPLC trace of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate on Wang resin

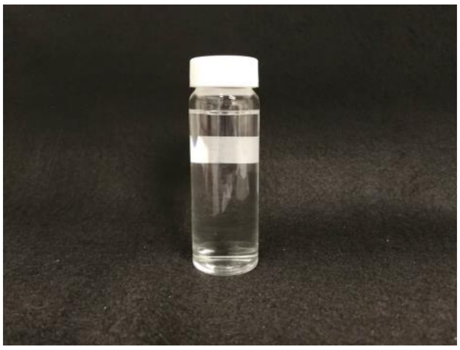


Figure 2-34: Picture of peptide prepared in propylene carbonate on Wang resin, not precipitating in cold diethyl ether

2.2.2.2. Tripeptide prepared in pure ethyl acetate

The resin swelling of Wang resin in ethyl acetate was reported before, it is a moderate solvent (swelling=3.80 mL g^{-1}) for this resin because its swelling was between 2 mL g^{-1} to 4 mL g^{-1}. This means that peptide synthesis should be possible, but not optimal in ethyl acetate. The ^{1}H NMR spectrum of TFA·H-Leu-Ala-Phe-OH prepared in ethyl acetate on Wang resin (Figure 2-35) is similar to the ^{1}H NMR spectrum of it prepared in propylene carbonate on ChemMatrix resin (Figure 2-26). The mass spectrum (Figure 2-36) shows a very high intensity peak at m/z: 350.2073 $[M+H]^+$ and also a peak at m/z: 372.1889 $[M+Na]^+$. HPLC (Figure 2-37) indicates that there is a high purity (96%) of tripeptide in this sample with a peak at 14.119 min. The precipitation in cold diethyl ether (Figure 2-38) gave a white solid.

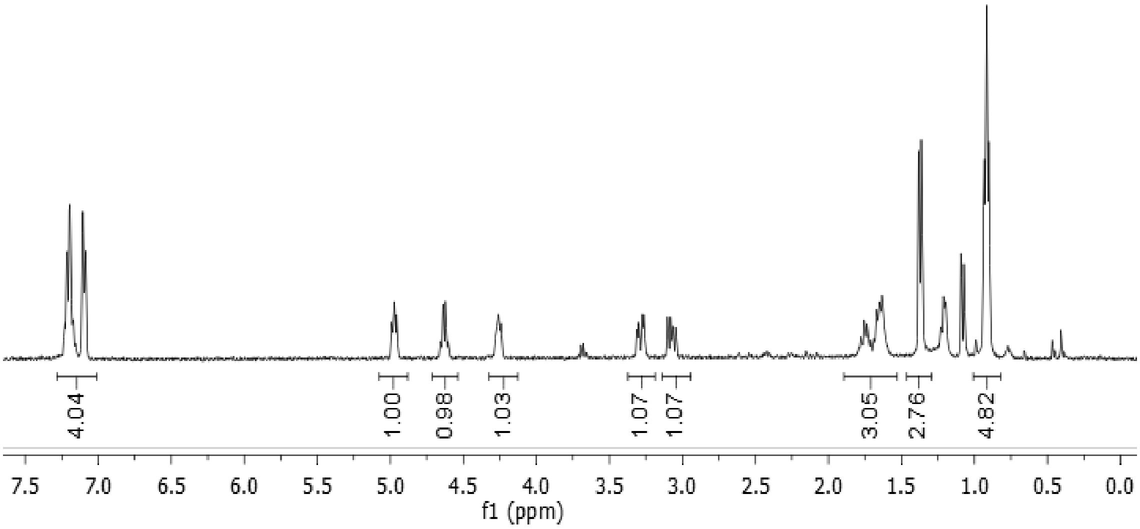
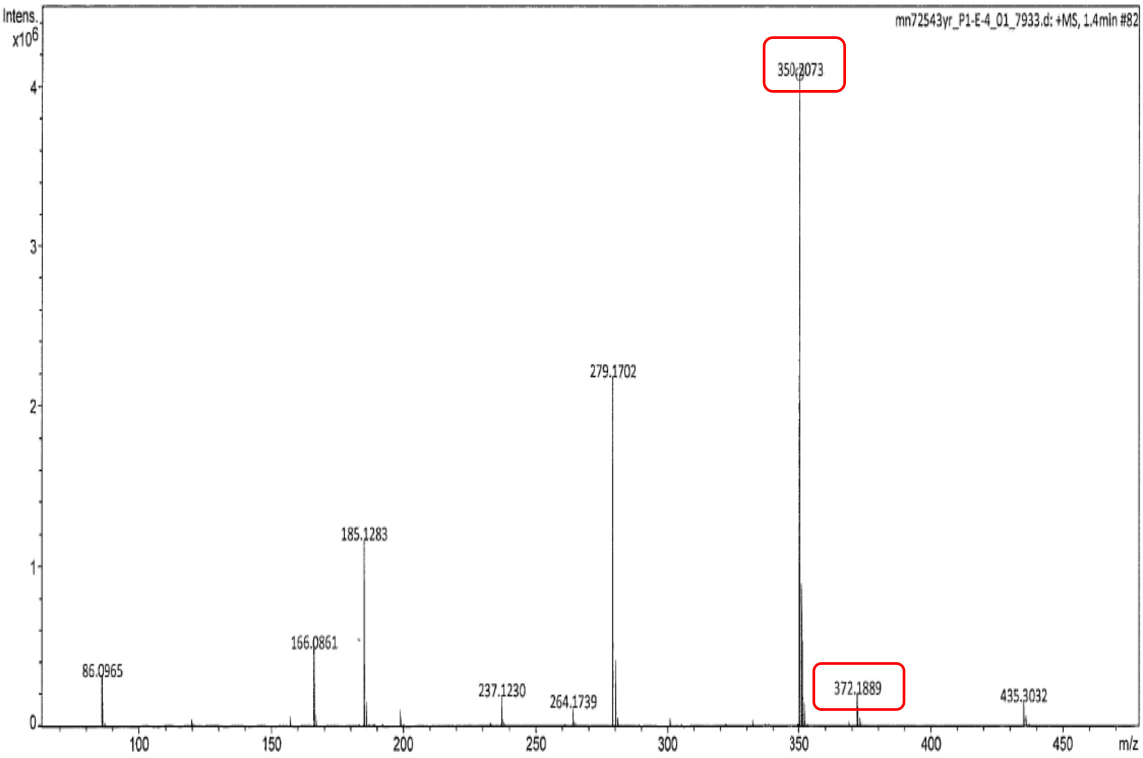
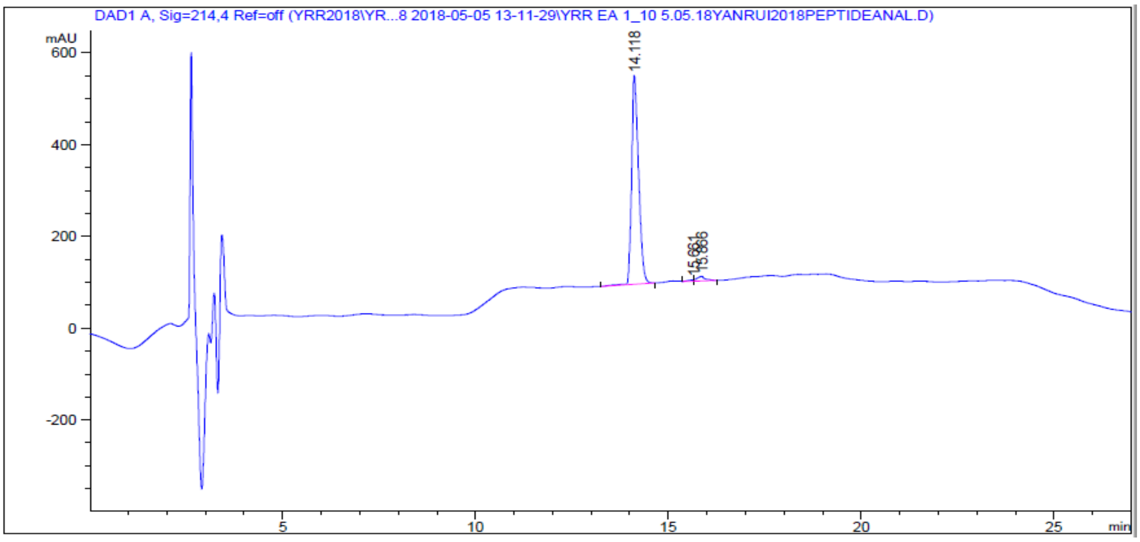


Figure 2-35: ^{1}H NMR spectrum (TFA-d) of TFA·H-Leu-Ala-Phe-OH synthesized in ethyl acetate on Wang resin



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2073	1	C18H28N3O4	350.2074	0.3	0.1	1.9	0.8

Figure 2-36: Mass spectrum of TFA.H-Leu-Ala-Phe-OH synthesized in ethyl acetate on Wang resin



HPLC Chromatogram Report

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.118	VV R	0.1827	5696.5957	455.2377	96.9384
2	15.661	BV	0.1138	28.18783	3.05198	0.4797
3	15.866	VB	0.1814	151.73021	10.45145	2.582

Figure 2-37: HPLC trace of TFA.H-Leu-Ala-Phe-OH synthesized in ethyl acetate on Wang resin

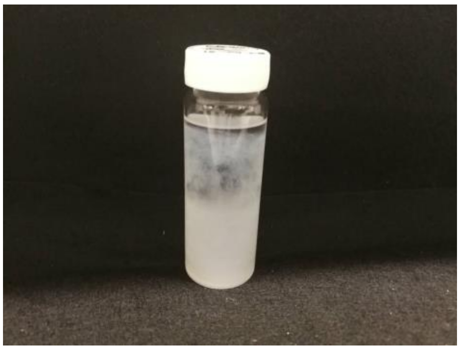


Figure 2-38: Picture of peptide prepared in ethyl acetate on Wang resin and precipitated in cold diethyl ether

2.2.2.3. Tripeptide prepared in the PC:EA=10:90 (v/v)

Finally, the solvent blend (PC:EA=10:90) was chosen to perform the same peptide synthesis. It can swell Wang resin up 4.61 mL g^{-1} and is a good solvent (swelling > 4 mL g^{-1}). As the solvent blend has a considerably higher swelling than each of the pure solvents, theoretically, it would be expected to generate more peptide than synthesis in either pure solvent. The results are displayed from to Figure 2-42. The

^{1}H NMR spectrum of TFA·H-Leu-Ala-Phe-OH (Figure 2-39) prepared in this mixture is the same as the sample prepared in PC on ChemMatrix resin (Figure 2-26) or in EA (Figure 2-35) on Wang resin. The sample also shows high intensity at m/z: 350.2069 $[M+H]^+$ and has m/z: 372.1888 $[M+Na]^+$ (Figure 2-40). HPLC shows its purity is 95% (Figure 2-41). Thus, tripeptide prepared in an EA & PC mixture or in pure ethyl acetate have almost the same purity as each other (95% and 96% respectively). However, the precipitate in cold diethyl ether (Figure 2-42) shows that more sample was prepared in the mixture than was obtained in pure ethyl acetate.

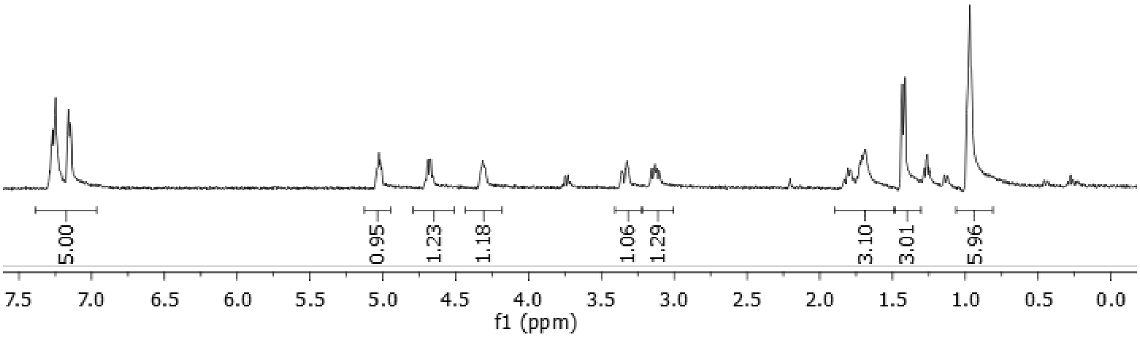
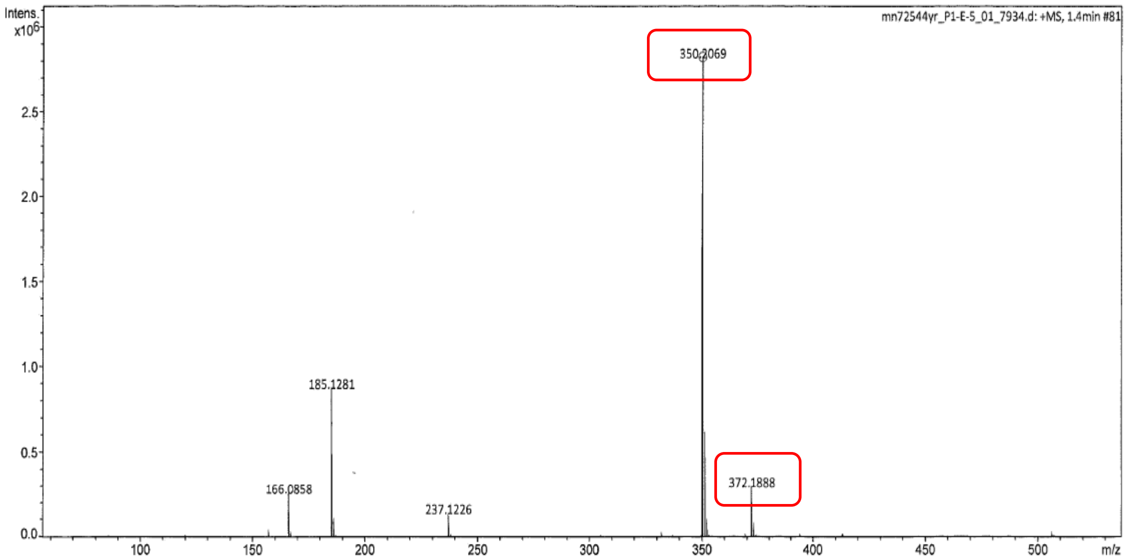
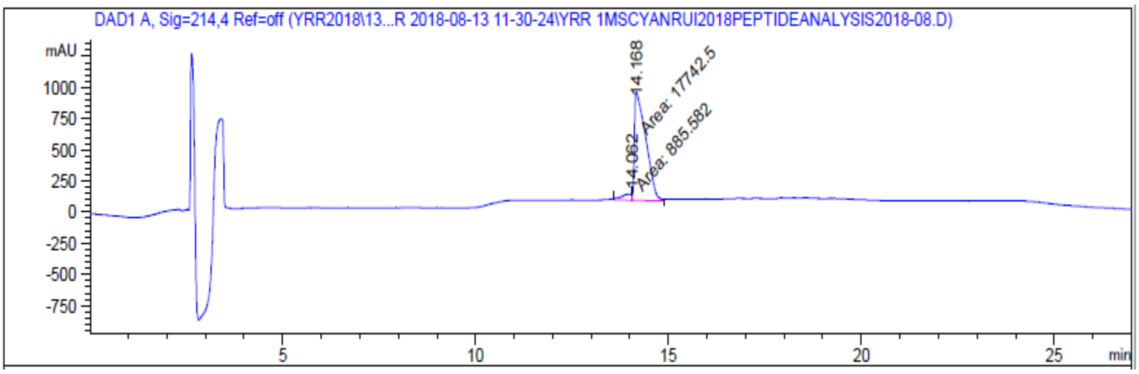


Figure 2-39: ^{1}H NMR spectrum (TFA-d) of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate:ethyl acetate=10:90 (v/v) on Wang resin



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2069	1	$C_{18}H_{28}N_3O_4$	350.2074	1.6	0.6	1.1	1.7

Figure 2-40: Mass spectrum of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate: ethyl acetate =10:90 (v/v) on Wang resin



HPLC Chromatogram Report

| Peak
#
RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.062	MF	0.3112	885.58167	47.42891	4.754
2	14.168	FM	0.3399	1.77E+04	869.89368	95.246

Figure 2-41: HPLC trace of TFA.H-Leu-Ala-Phe-OH synthesized in propylene carbonate: ethyl acetate=10:90 (v/v) on Wang resin

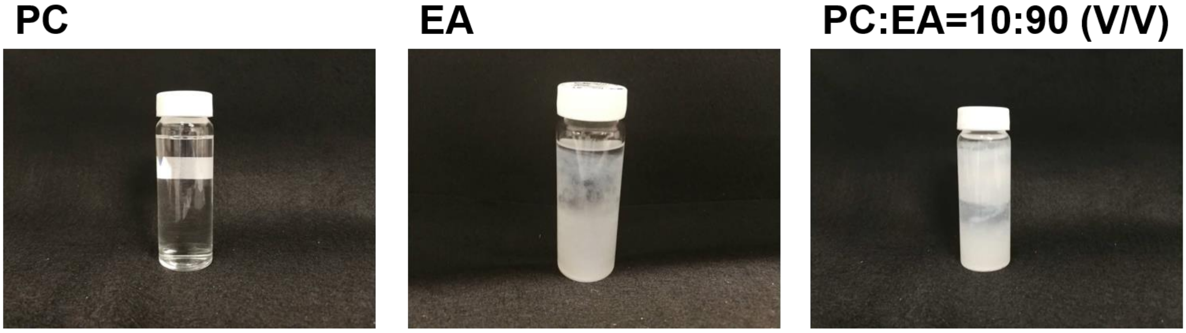


Figure 2-42: Picture of peptide prepared in propylene carbonate, ethyl acetate and propylene carbonate:ethyl acetate=10:90 (v/v) on Wang resin then precipitated in cold diethyl ether

The % yields of these samples cannot be calculated accurately as the loading of Fmoc-Phe-resin was only specified as 0.4-0.8 mmol/g. Thus, yields (mg/g) were used as a substitute shown in Table 2-9. It shows that more peptide is formed in the mixture than in either propylene carbonate or ethyl acetate.

Table 2-9: Yields of peptide synthesized in propylene carbonate & ethyl acetate solvent systems using HBTU/HOBt

Solvent	Yield (mg/g)
propylene carbonate	7.52
ethyl acetate	291.73
PC:EA=10:90	306.86

2.2.2.4. The swelling of Wang resin with attached Fmoc-amino acid or peptide

At the same time that peptide synthesis was carried out in pure solvents and their mixture, the swelling of the Wang resin attached to Fmoc-groups or peptide in the binary solvent mixture was also investigated to see what changes occurred during peptide synthesis. The swelling results are shown in Figure 2-43. Each bar represents a stage of peptide synthesis on Wang resin. In general, the swelling of the resin with no attached protecting group or peptide was above 4 mL g^{-1}, otherwise it was under 4 mL g^{-1} but above 3 mL g^{-1}. These data showed that the attached Fmoc group and attached peptide would slightly negatively influence the resin swelling.

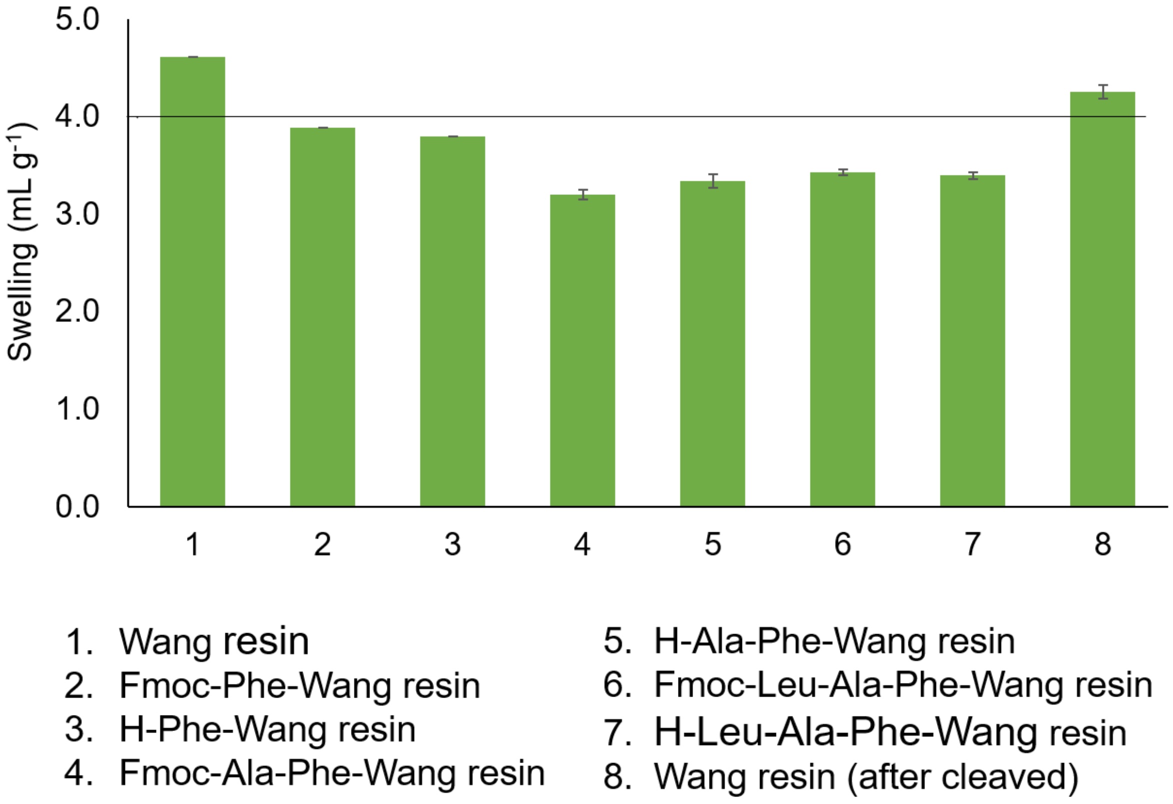


Figure 2-43: Resin swelling attached with peptide, supporting information seen in Appendix E (Table 5-48)

2.2.2.5. Conclusion of PC & EA binary solvent used in SPPS

The experimental results of peptide synthesis in propylene carbonate, ethyl acetate and PC:EA=10:90 (v/v) on Wang resin respectively imply that the binary solvent has better applicability for peptide synthesis than either pure solvent. These results indicate that the HSP-3D space model could be potentially applied to predict the binary solvents to apply in solid-phase peptide synthesis (SPPS). However, the available data show small differences in yields and purities from this solvent pair which are not enough to declare that the 3D model can help to predict the binary solvents potentially useful in SPPS. Thus, another solvent pair which can make the yields and purities from pure solvents and their mixtures fully differentiated should be chosen to apply in the tripeptide synthesis.

2.2.3. Tripeptide synthesis in propylene carbonate & TMO solvent system with Merrifield resin using HBTU/HOBt

Another solvent system (propylene carbonate and TMO) was chosen to do the same peptide synthesis on Wang resin as well. All steps were the same and just solvents changed. Peptide synthesis in propylene carbonate on Wang resin was discussed before so only peptide synthesis carried out in pure TMO and their mixtures (PC:TMO=10:90 (v/v), PC:TMO=70:30 (v/v) and PC:TMO =60:40 (v/v)) are reported. The propylene carbonate & TMO solvent system was discussed in Chapter 2.1.4.4; both PC and TMO are poor solvents for Wang resin as resin swellings are less than 2 mL g^{-1}. Although they are only partially miscible, their mixtures show swelling ability and are moderate solvents for Wang resin. The mixture of PC:TMO=10:90 (v/v) has resin swelling=3.81 mL g^{-1}, but it cannot dissolve the HBTU/HOBt coupling agents. The mixture of PC:TMO=70:30 (v/v) can dissolve the HBTU/HOBt but the resin swelling is only 2.92 mL g^{-1}. The blend of PC:TMO=60:40 (v/v) is immiscible, but it can dissolve the coupling agents and the resin swelling is 3.81 mL g^{-1}. Thus, these three mixtures were chosen for comparison to the two pure solvents for SPPS.

2.2.3.1. Tripeptide synthesised in pure TMO

TMO is a new green solvent (swelling=1.78 mL g^{-1}), first prepared by Fergal Byrne in the GCCE.[73] After finishing the sequence of peptide synthesis, the figures below (Figure 2-44, Figure 2-45 and Figure 2-46) illustrate that there is no H-Leu-Ala-Phe-OH peptide in this sample and there was no precipitate in cold diethyl ether. However, two reasons are possible for this result: one is because TMO is a poor solvent for Wang resin and has no ability to swell Wang resin. As discussed above, propylene carbonate is also a poor solvent for Wang resin, but the mass spectrum and HPLC chromatogram indicated there was still a little tripeptide in the sample prepared in it. Thus, another reason could be due to the insolubility of the coupling agents (HBTU/HOBt) in TMO. Later, another pair of coupling agents which can dissolve in TMO were chosen to do the peptide synthesis to investigate this further (see Chapter 2.2.4).

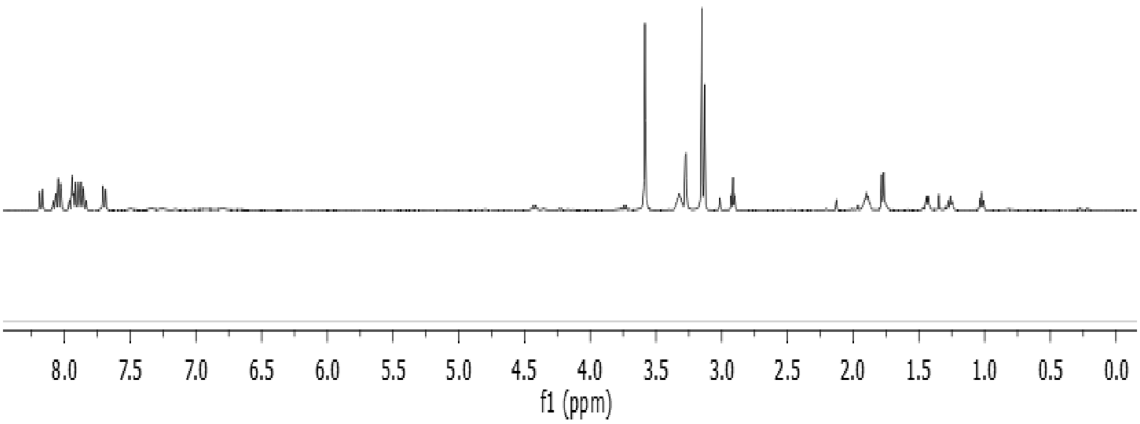


Figure 2-44: ^{1}H NMR spectrum of attempted preparation of TFA·H-Leu-Ala-Phe-OH on Wang resin in TMO

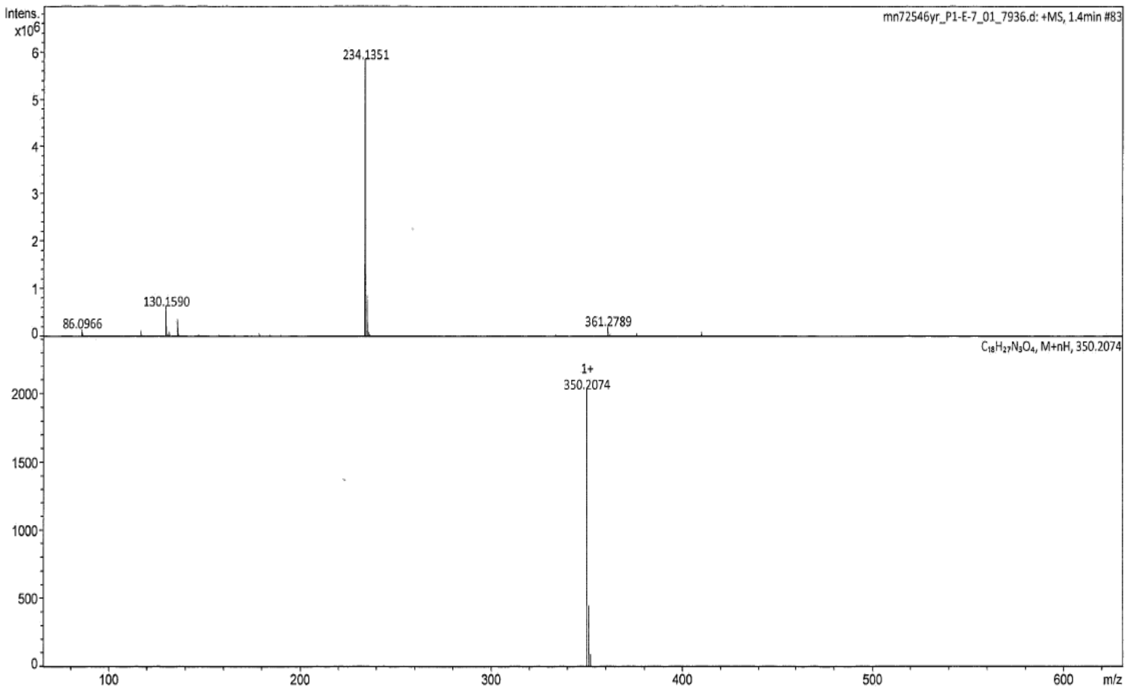
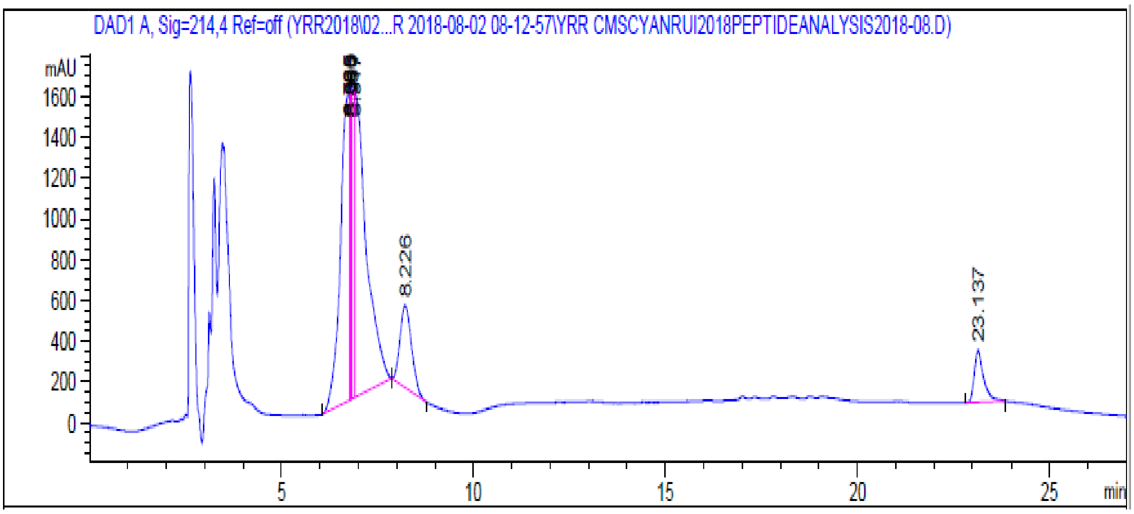


Figure 2-45: Mass spectrum of attempted preparation of TFA·H-Leu-Ala-Phe-OH on Wang resin in TMO.



HPLC Chromatogram Report

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	6.765	BV	0.1887	2.41E+04	1538.38391	29.9242
2	6.8	VV	0.023	2601.34326	1549.18835	3.2321
3	6.815	VV	0.0237	2489	1550.07446	3.0925
4	6.851	VV	0.0608	7323.12158	1557.75269	9.0987
5	6.917	VB	0.3467	3.12E+04	1501.20691	38.8045
6	8.226	BB	0.2768	8456.4707	401.40015	10.5069
7	23.137	BV R	0.2316	4298.79346	255.65021	5.3411

Figure 2-46: HPLC trace of attempted preparation of TFA·H-Leu-Ala-Phe-OH on Wang resin in TMO

2.2.3.2. Tripeptide prepared in PC:TMO=10:90 (v/v), PC:TMO=70:30 (v/v), PC:TMO=60:40 (v/v)

It was reported in Chapter 2.1.4.4 that only some ratios of PC & TMO can mix with each other and these mixtures have better swelling abilities for Merrifield resin than either pure solvents. Therefore, the miscible solvent mixtures: PC:TMO=10:90 (v/v) (resin swelling= 3.82 mL g^{-1}) and PC:TMO=70:30 (v/v) (resin swelling= 2.92 mL g^{-1}); and the immiscible solvent mixture: PC:TMO=60:40 (v/v) (resin swelling= 3.81 mL g^{-1}) were chosen to study if they could be used in this peptide synthesis. The results for the PC:TMO=10:90 (v/v) solvent mixture are shown in Figure 2-47 to Figure 2-50. In the ^{1}H NMR spectrum shown in Figure 2-47, there are peaks belonging to the tripeptide. The picture in Figure 2-50 shows that white solid forms in cold diethyl ether. The mass spectrum (Figure 2-48) and HPLC trace (Figure 2-49) show that there is indeed tripeptide in this sample.

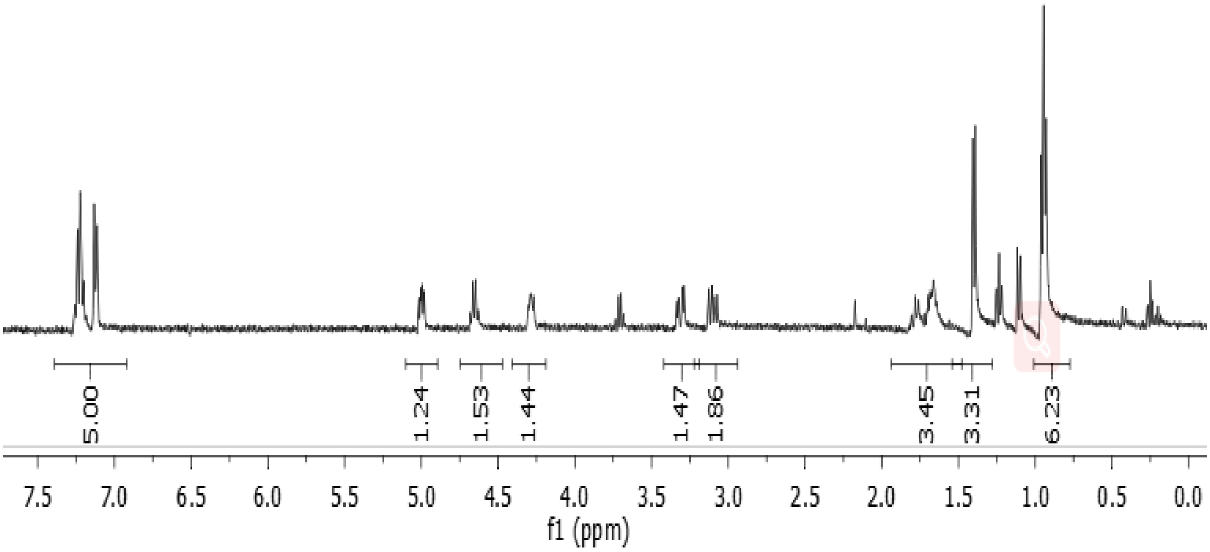
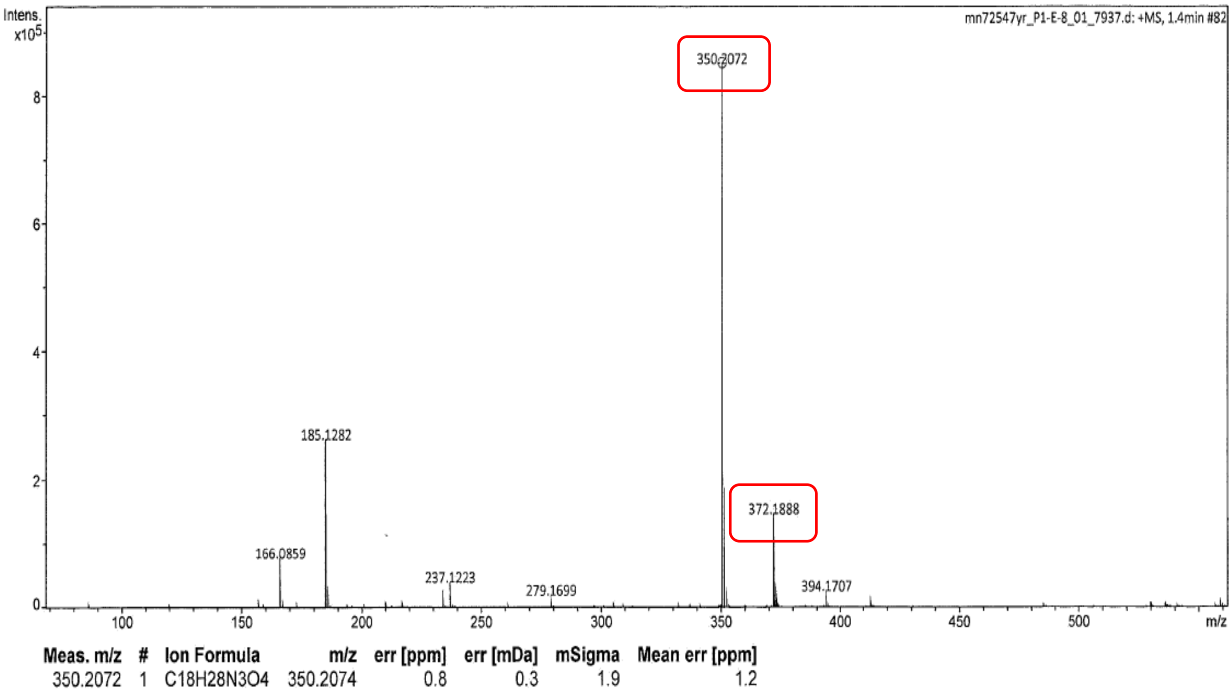
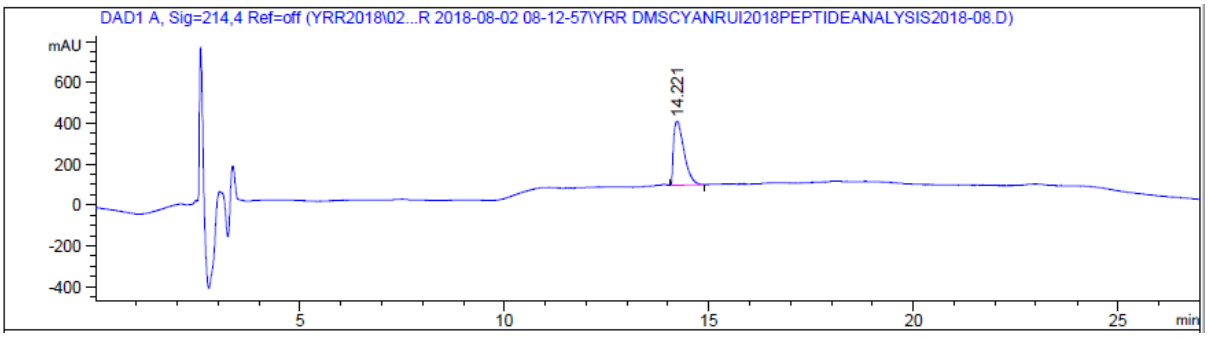


Figure 2-47: ^{1}H NMR spectrum of TFA·H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=10:90 (v/v) on Wang resin; diethyl ether: δ=3.55 (q, 4H, CH_2), δ=1.25 (t, 6H, CH_3)



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2072	1	C18H28N3O4	350.2074	0.8	0.3	1.9	1.2

Figure 2-48: Mass spectrum of TFA·H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=10:90 (v/v) on Wang resin



HPLC Chromatogram Report

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.221	BV R	0.2356	5483.11279	311.19736	100

Figure 2-49: HPLC trace of TFA·H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=10:90 (v/v) on Wang resin

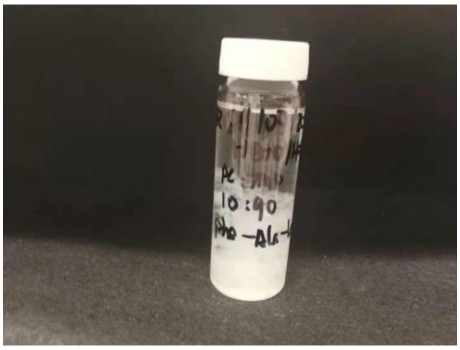


Figure 2-50: Picture of peptide prepared in propylene carbonate:TMO=10:90 (v/v) on Wang resin then precipitated in cold diethyl ether

The experimental result obtained with PC:TMO=10:90 was not perfect as this mixture cannot dissolve all coupling agents. Thus, another two mixtures of this solvent system which can dissolve all coupling agents were chosen to do same kind of peptide synthesis. These were PC:TMO=70:30 (v/v) and PC:TMO=60:40 (v/v). The characterisations of the peptide are displayed from Figure 2-51 to Figure 2-58. As can be seen from Figure 2-51 to Figure 2-54, the end result of peptide synthesis in PC:TMO=70:30 (v/v) is significantly better than that in PC:TMO=10:90 (v/v). The purity is up to 97%. The mixture of PC:TMO=60:40 (v/v) was also employed in this peptide synthesis and gave excellent results which are shown from Figure 2-55 to Figure 2-58.

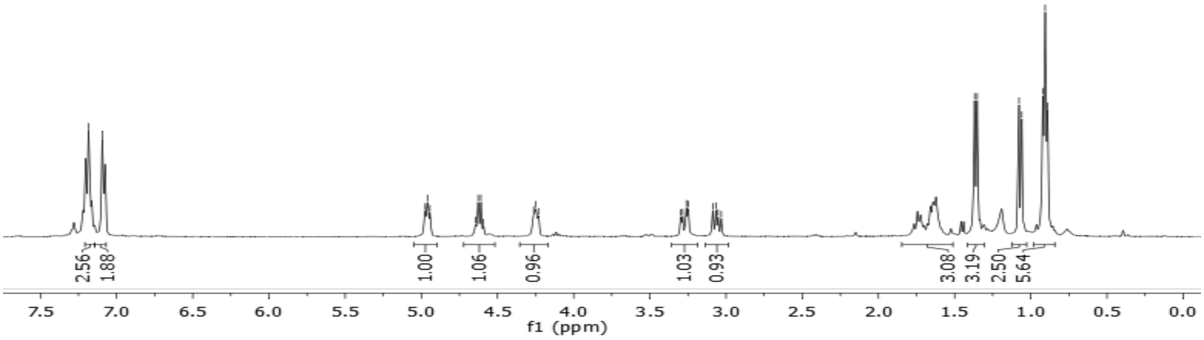
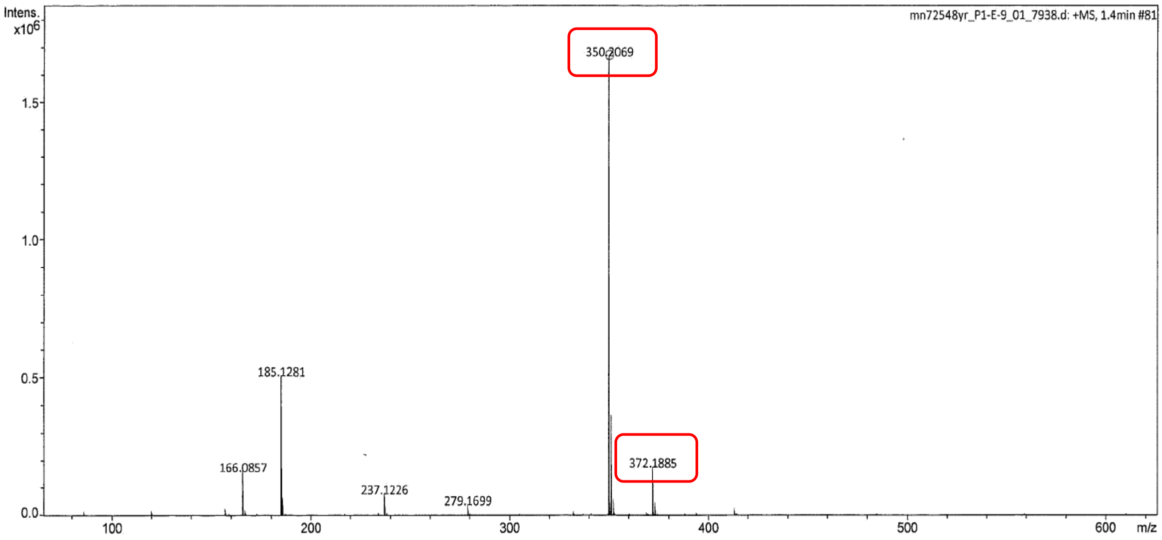
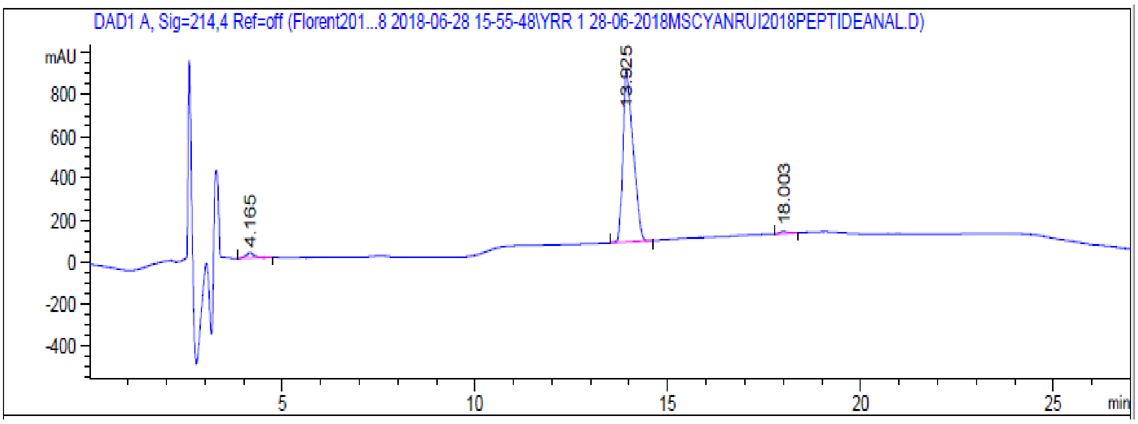


Figure 2-51: ^{1}H NMR spectrum of TFA.H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=70:30 (v/v) on Wang resin



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2069	1	C18H28N3O4	350.2074	1.5	0.5	1.4	1.3

Figure 2-52: Mass spectrum of TFA.H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=70:30 (v/v) on Wang resin



HPLC Chromatogram Report

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.165	BV R	0.1963	379.02905	27.07874	2.4528
2	13.925	BV R	0.2497	1.49E+04	816.17743	96.7402
3	18.003	BV R	0.1647	124.70232	9.85079	0.807

Figure 2-53: HPLC trace of TFA.H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=70:30 (v/v) on Wang resin

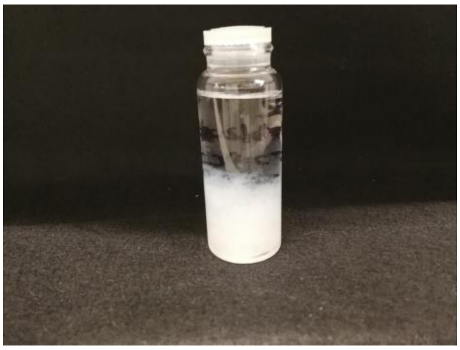


Figure 2-54: Picture of peptide prepared in propylene carbonate:TMO=70:30 (v/v) on Wang resin then precipitated in cold diethyl ether

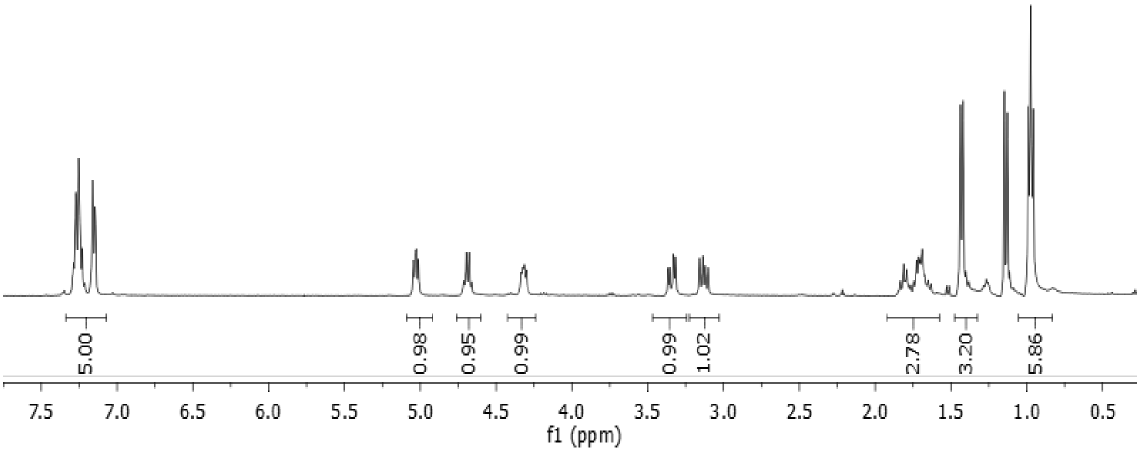
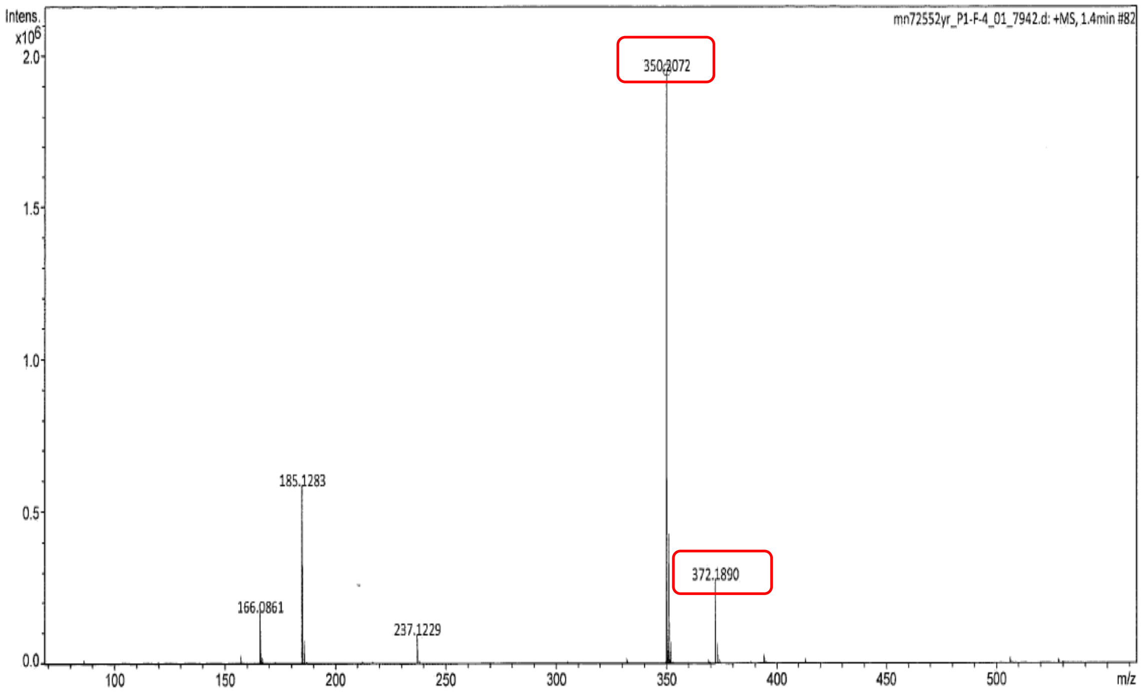
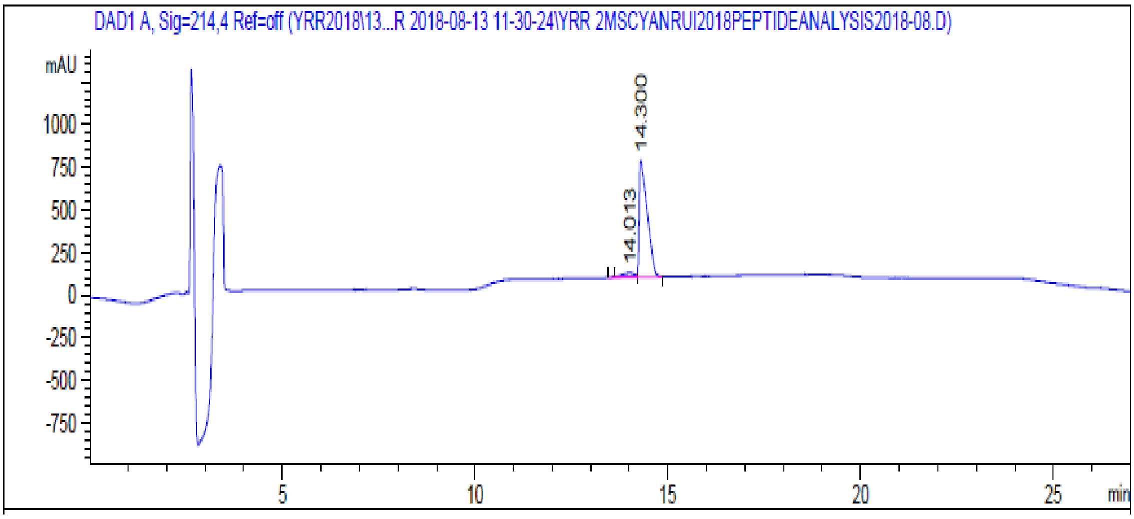


Figure 2-55: ^{1}H NMR spectrum of TFA.H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=60:40 (v/v) on Wang resin



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2072	1	C18H28N3O4	350.2074	0.6	0.2	1.0	1.2

Figure 2-56: Mass spectrum of TFA.H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=60:40 (v/v) on Wang resin



HPLC Chromatogram Report

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.013	VV E	0.2744	617.03644	26.92216	5.8172
2	14.3	VB R	0.194	9989.98535	687.10449	94.1828

Figure 2-57: HPLC trace of TFA.H-Leu-Ala-Phe-OH synthesised in propylene carbonate:TMO=60:40 (v/v) on Wang resin

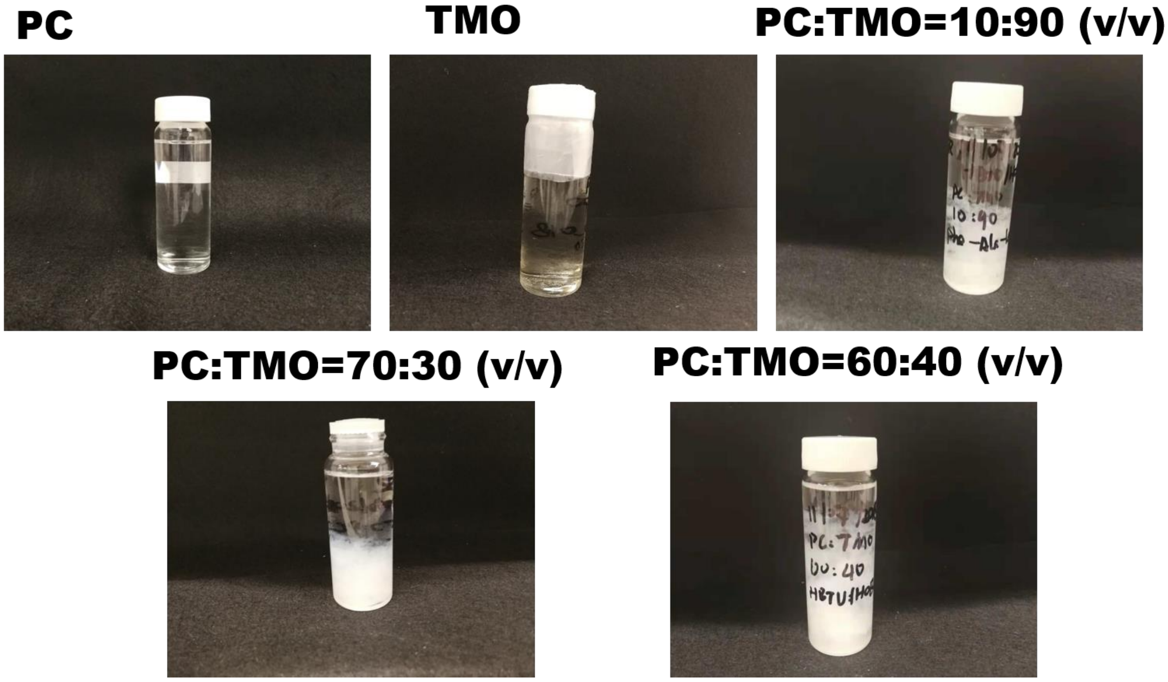


Figure 2-58: Pictures of peptide prepared in propylene carbonate, TMO, propylene carbonate:TMO=10:90 (v/v), propylene carbonate:TMO=70:30 (v/v) and propylene carbonate:TMO=60:40 (v/v) on Wang resin then precipitated in cold diethyl ether

The purity of the tripeptide prepared in PC:TMO=70:30 (v/v) (97%) and PC:TMO=60:40 (v/v) (94%) are similar. However, the PC:TMO=60:40 (v/v) solvent system seems to give more precipitate than the PC:TMO =70:30 (v/v) solvent system (Figure 2-58). As HBTU/HOBt can dissolve in these two mixtures, the swelling ability of the binary solvent influences how much peptide is obtained. The yields are shown in Table 2-10. The immiscible mixture of PC:TMO=60:40 has much better synthetic ability than other two mixtures.

Table 2-10: Yields of peptide synthesized in propylene carbonate & TMO solvent systems using HBTU/HOBt

Solvent	Yield (mg/g)
propylene carbonate	7.52
TMO	0.00
PC:TMO=10:90	124.32
PC:TMO=70:30	132.15
PC:TMO=60:40	199.95

2.2.3.3. Conclusion of PC & TMO binary solvent used in SPPS using HBTU/HOBt

SPPS in mixtures of propylene carbonate and TMO is successful even though both pure solvents are poor solvents for Wang resin. However, their mixtures can achieve good results and their mixtures' synthetic ability is nearly equal to a good solvent.

2.2.4. Tripeptide synthesis in propylene carbonate & TMO solvent system on Wang resin using Oxymapure/EDC

It was mentioned earlier that the coupling agents: HBTU/HOBt cannot dissolve at all in TMO or PC:TMO=10:90 (v/v). To eliminate the interference of insolubility of coupling agents in the peptide synthesis results, another pair of coupling agents needed to be applied in this peptide synthesis. Six coupling reagents were chosen to test their solubility: Oxymapure, K-Oxyma, Oxyma-B, COMU, TOTU and Pyoxim. After testing, only Oxymapure was found to be soluble in TMO, and all could dissolve in propylene carbonate. Thus, Oxymapure/EDC was selected to use in peptide synthesis in the PC/TMO solvent systems.

2.2.4.1. Tripeptide prepared in pure PC

The same sequence of peptide synthesis was carried out in pure propylene carbonate with Oxymapure/EDC on Wang resin. The characterisations are shown in Figure 2-59 to Figure 2-61. Although the mass spectrum (Figure 2-60) illustrates that there is tripeptide [m/z: $[M+H]^+$: 350.2072] in the sample, the intensity is very low. In addition, the ^{1}H NMR spectrum is not clear, and HPLC shows that there are many impurities in this sample. Therefore, propylene carbonate is not a good solvent to use in peptide synthesis with Oxymapure/EDC on Wang resin.

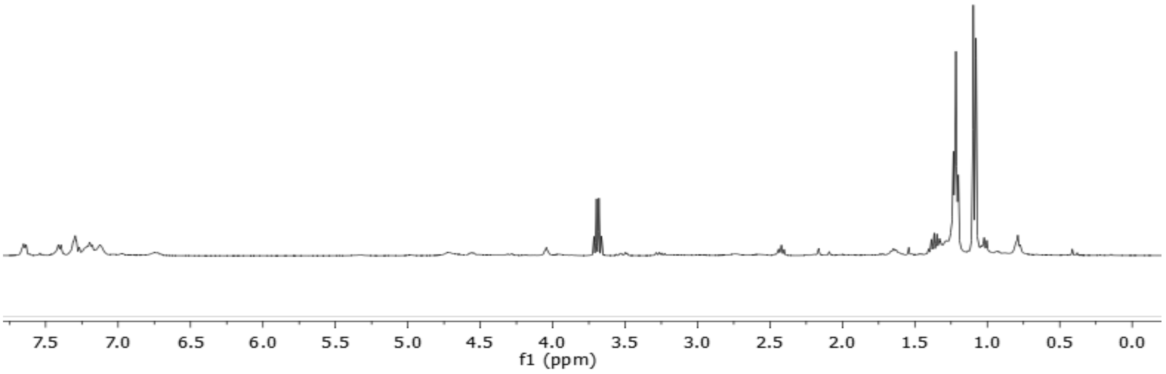
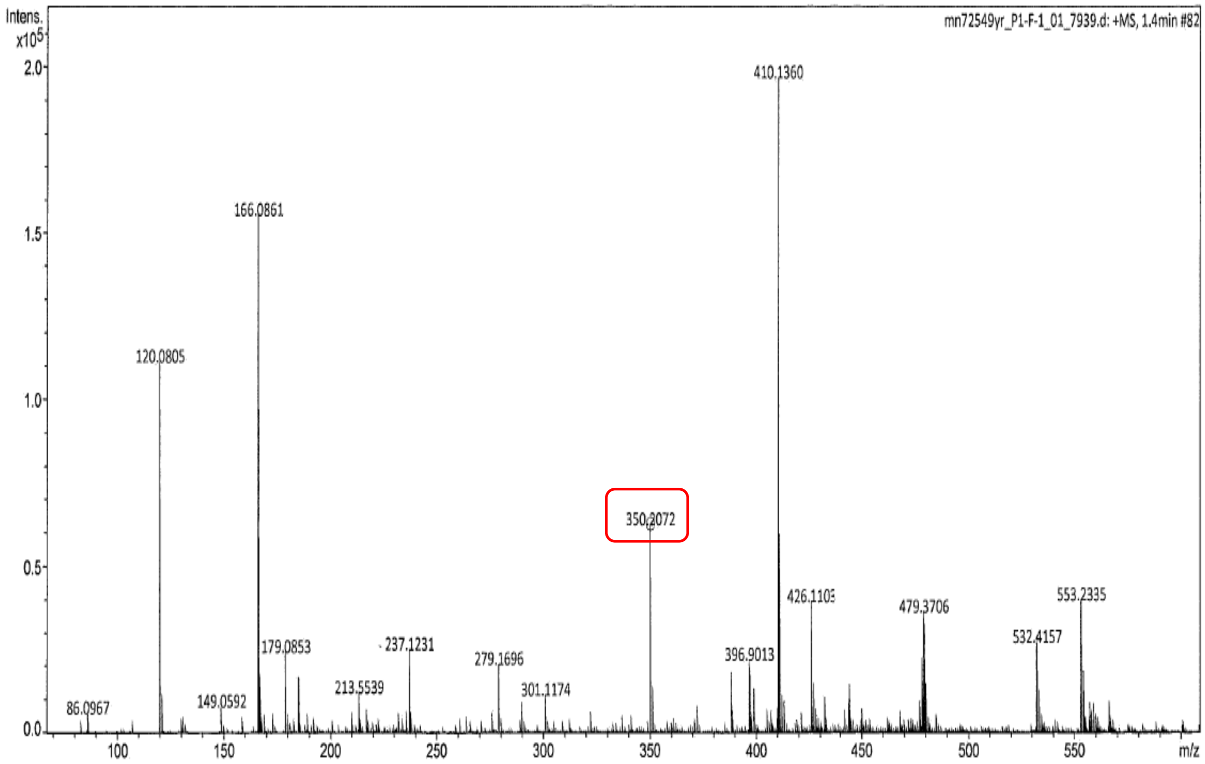
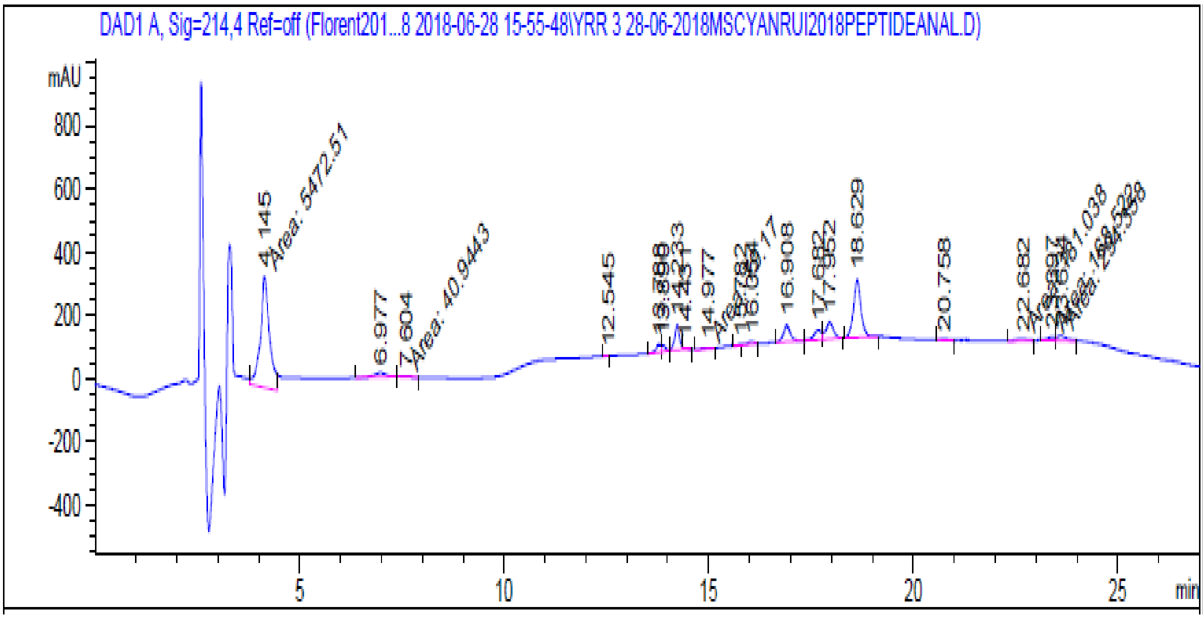


Figure 2-59: ^{1}H NMR spectrum of TFA·H-Leu-Ala-Phe-OH synthesised in propylene carbonate on Wang resin using Oxymapure/EDC.



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2072	1	$C_{18}H_{28}N_3O_4$	350.2074	0.6	0.2	5.8	-0.1

Figure 2-60: Mass spectrum of TFA·H-Leu-Ala-Phe-OH TFA.H-Leu-Ala-Phe-OH synthesised in propylene carbonate on Wang resin using Oxymapure/EDC.



HPLC Chromatogram Report

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	4.145	MM	0.2594	5472.50977	351.63666	46.7813
2	6.977	VVR	0.229	270.37256	14.2068	2.3113
3	7.604	MM	0.2608	40.94433	2.61622	0.35
4	12.545	VVR	0.0786	6.93328	1.08386	0.0593
5	13.788	BV	0.1169	185.24144	22.54499	1.5835
6	13.89	VB	0.0926	113.93326	17.81612	0.9739
7	14.233	BV R	0.1249	671.52484	80.03242	5.7405
8	14.431	VBE	0.0963	33.29334	4.5543	0.2846
9	14.977	MM	0.3459	79.16998	3.81416	0.6768
10	15.782	BV E	0.0931	11.51571	1.49058	0.0984
11	16.054	VVR	0.1423	93.34281	8.29344	0.7979
12	16.908	BVR	0.169	617.3443	52.95773	5.2773
13	17.682	BV	0.1559	377.37726	30.39433	3.226
14	17.952	VB	0.179	700.61804	53.77281	5.9892
15	18.629	BVR	0.1833	2328.10767	184.45279	19.9016
16	19.902	VVR	0.1303	51.91977	4.87132	0.4441
17	22.682	MM	0.3943	181.0383	7.65295	1.5479
18	23.397	MF	0.2277	168.52205	12.33295	1.4409
19	23.634	FM	0.3059	294.35843	16.03775	2.5166

Figure 2-61: HPLC trace of TFA·H-Leu-Ala-Phe-OH TFA.H-Leu-Ala-Phe-OH synthesised in propylene carbonate on Wang resin using Oxymapure/EDC.

2.2.4.2. Tripeptide prepared in pure TMO

The tripeptide synthesis in pure TMO was also carried out. The results of ^{1}H NMR (Figure 2-62), mass spectrum (Figure 2-63) and HPLC (Figure 2-64) indicate that there is no H-Leu-Ala-Phe-OH peptide in this sample. Thus, neat TMO cannot enable solid-phase peptide synthesis on Wang resin.

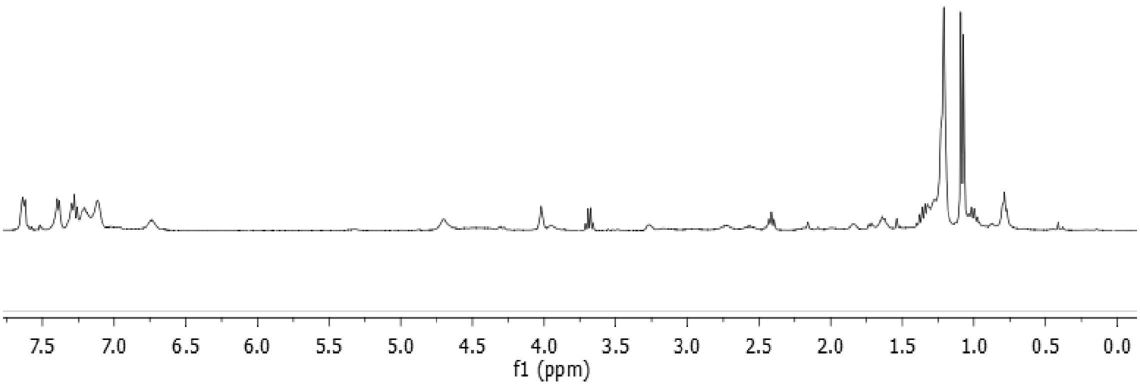


Figure 2-62: ^{1}H NMR spectrum of attempted synthesis of TFA·H-Leu-Ala-Phe-OH in TMO on Wang resin using Oxymapure/EDC

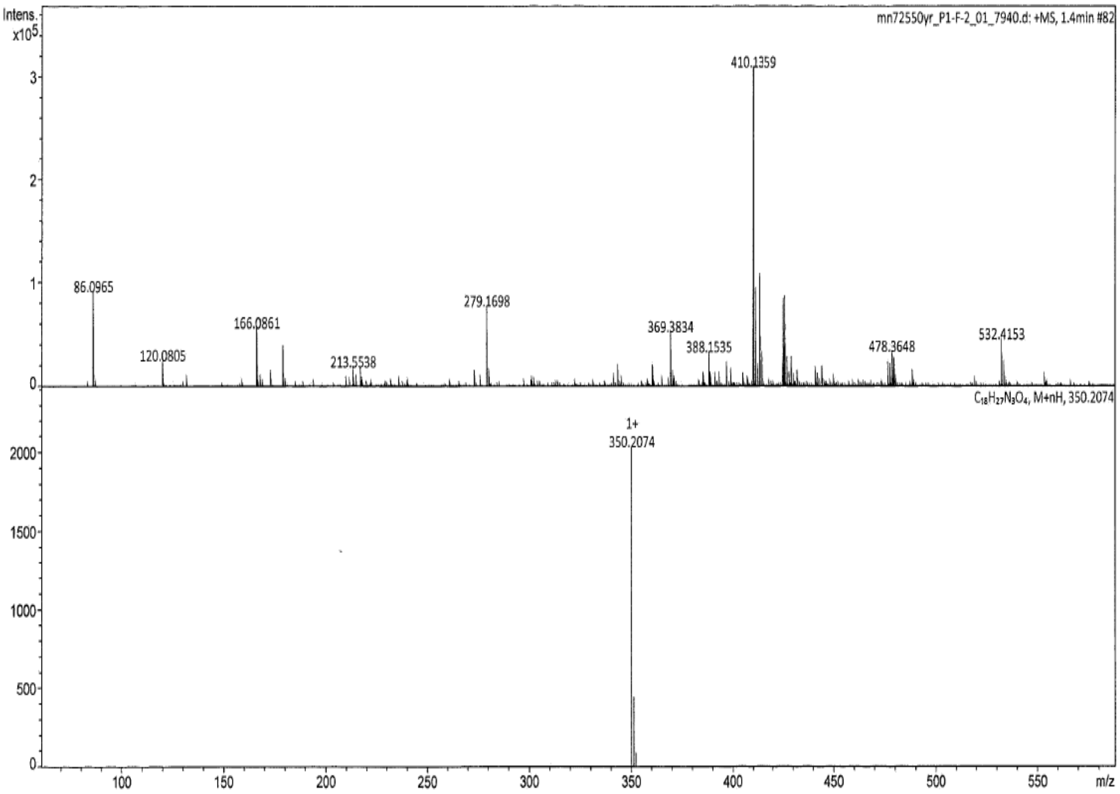
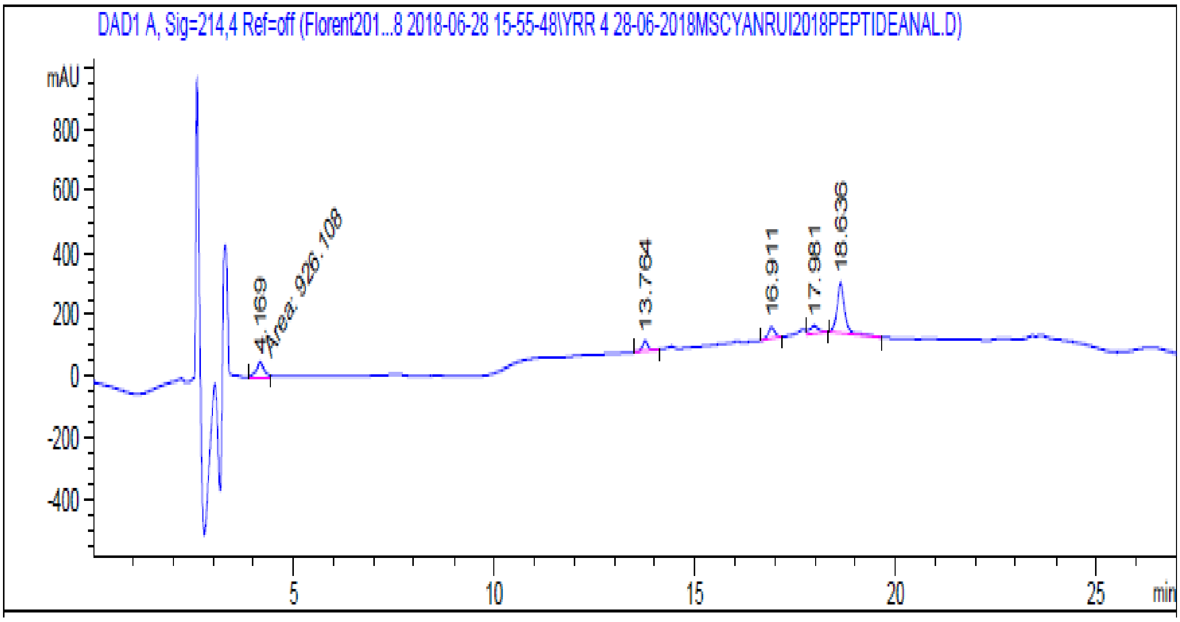


Figure 2-63: Mass spectrum of attempted synthesis of TFA·H-Leu-Ala-Phe-OH in TMO on Wang resin using Oxymapure/EDC



HPLC Chromatogram Report

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.169	MM	0.2696	926.10773	57.25995	21.6513
2	13.764	BV R	0.1301	354.07227	35.56868	8.2781
3	16.911	BB	0.1576	419.85837	37.51313	9.8161
4	17.981	VV R	0.2088	385.04617	25.54818	9.0022
5	18.636	BB	0.1942	2192.38501	163.71407	51.2548

Figure 2-64: HPLC trace of attempted synthesis of TFA·H-Leu-Ala-Phe-OH in TMO on Wang resin using Oxymapure/EDC

2.2.4.3. Tripeptide prepared in PC:TMO =30:70 (v/v)

Although diethyl ether could not be totally removed, the ^{1}H NMR spectrum (Figure 2-65) still has the same peaks as the successful prepared peptide. The mass spectrum (Figure 2-66) and HPLC chromatogram (Figure 2-67) also show that there is H-Leu-Ala-Phe-OH in this sample. However, as it has not precipitated in cold diethyl ether, it has a lot of impurities in it.

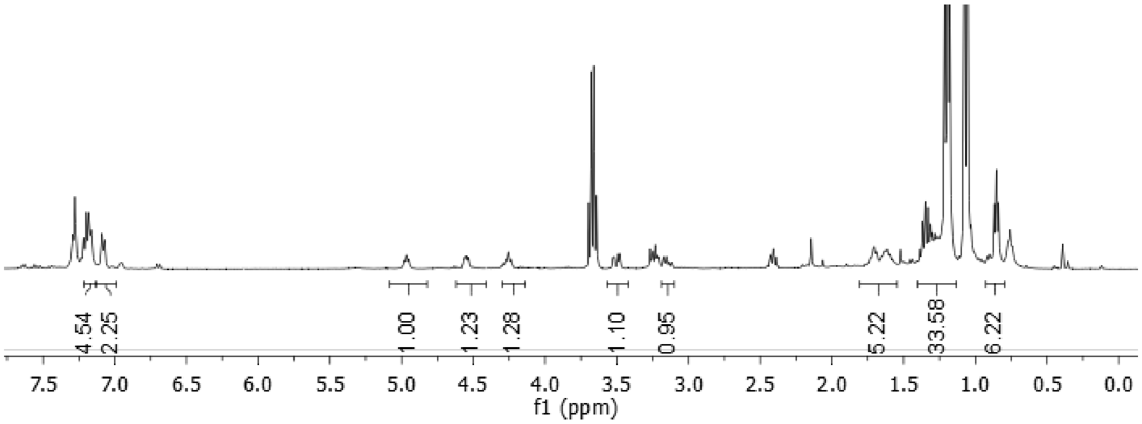
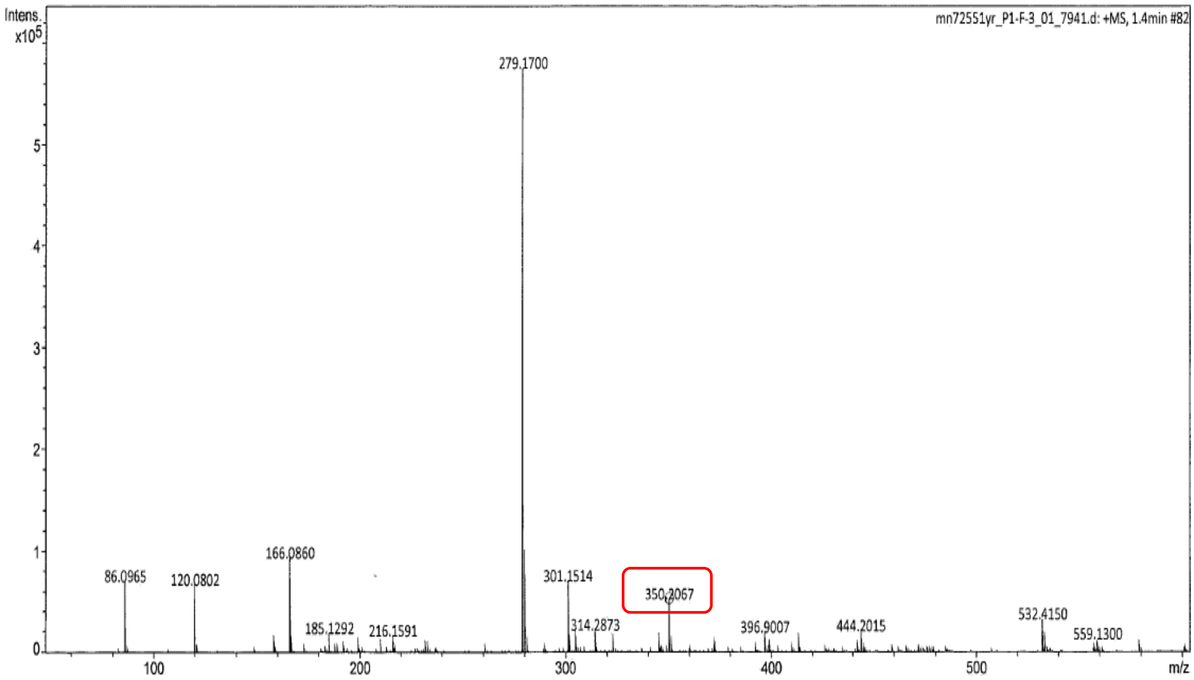
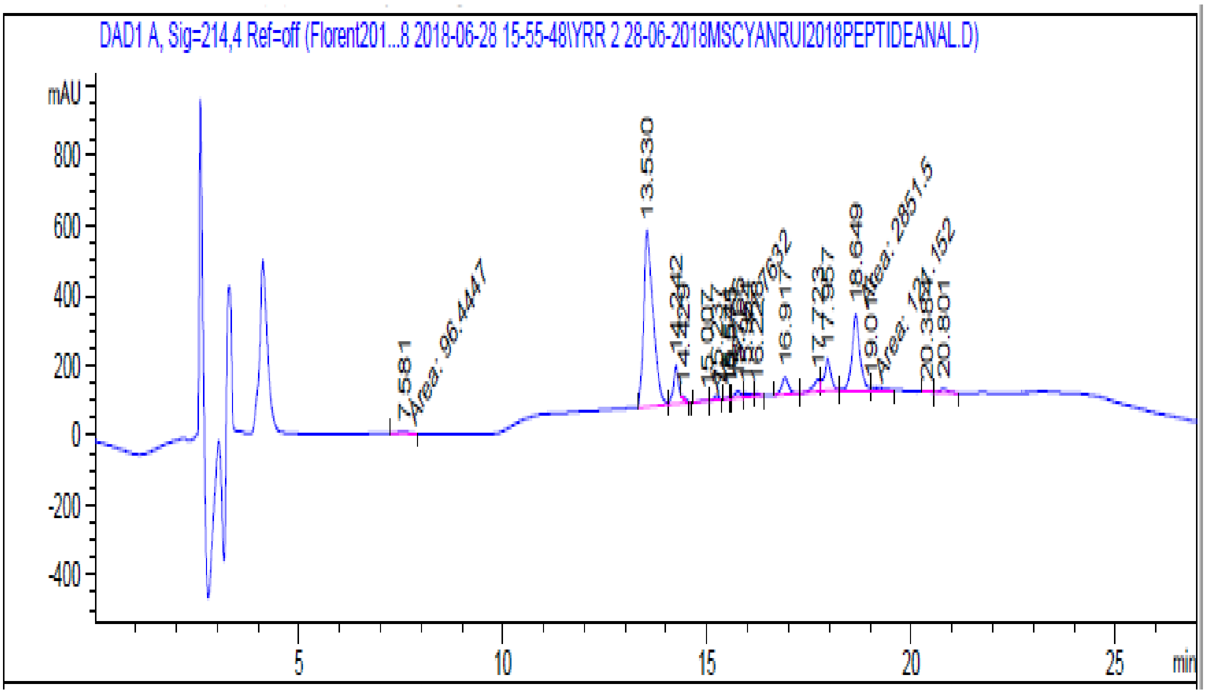


Figure 2-65: ^{1}H NMR spectrum (TFA-d) of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate:TMO=30:70 (v/v) on Wang resin using Oxymapure/EDC



Meas. m/z	#	Ion Formula	m/z	err [ppm]	err [mDa]	mSigma	Mean err [ppm]
350.2067	1	C18H28N3O4	350.2074	2.2	0.8	18.7	2.3

Figure 2-66: Mass spectrum of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate:TMO=30:70 (v/v) on Wang resin using Oxymapure/EDC



HPLC Chromatogram Report

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.581	MM	0.3322	96.44475	4.83916	0.6402
2	13.53	BV	0.2234	8103.23828	504.39413	53.7853
3	14.242	VV R	0.1453	1096.17651	109.06481	7.2759
4	14.429	VB E	0.0988	43.28137	6.33002	0.2873
5	15.007	MM	0.2716	41.76323	1.81983	0.2772
6	15.237	BB	0.1043	96.15948	13.96891	0.6383
7	15.541	BV	0.0764	26.49823	4.95184	0.1759
8	15.575	VV	0.0268	7.02085	4.36579	0.0466
9	15.766	VV	0.1393	202.10127	19.59666	1.3414
10	15.954	VV	0.1687	139.75645	10.74734	0.9276
11	16.228	VB	0.1141	68.84862	68.84862	0.457
12	16.917	BV R	0.1771	589.65283	589.65283	3.9138
13	17.723	BV	0.1566	404.25067	404.25067	2.6832
14	17.957	VB	0.1554	1027.07104	91.90141	6.8172
15	18.649	MF	0.2211	2851.50146	2851.50146	18.9269
16	19.017	FM	0.3817	121.15186	121.15186	0.8041
17	20.384	VB	0.1096	29.34952	29.34952	0.1948
18	20.801	BV R	0.1492	121.62337	121.62337	0.8073

Figure 2-67: HPLC trace of TFA·H-Leu-Ala-Phe-OH synthesized in propylene carbonate:TMO=30:70 (v/v) on Wang resin using Oxymapure/EDC

The yields are shown in Table 2-11. Peptide synthesis carried out in the solvent blend has a slightly higher yield than that obtained in pure propylene carbonate. However, the yield of this mixture is far lower than the yield (132.15 mg/g, Table 2-10) using HBTU/HOBt.

Table 2-11: Yields of peptide synthesized in propylene carbonate & TMO solvent systems using Oxymapure/EDC

Solvent	Yield (mg/g)
propylene carbonate	13.43
TMO	0.00
PC:TMO=70:30	21.44

2.2.5. Conclusions of propylene carbonate & TMO binary solvent used in SPPS

According to this series of experiments, propylene carbonate is not a good solvent to do solid-phase peptide synthesis on Wang resin, and TMO cannot be a solvent for peptide synthesis. However, their mixtures (PC:TMO=30:70 (v/v) and PC:TMO=10:90 (v/v)) are moderate solvents and SPPS can be carried out in them. Additionally, HBTU/HOBt has better coupling ability than Oxymapure/EDC in these solvents.

2.3. Polystyrene dissolution in pure and binary solvents

Since a 3D model of Merrifield resin has been established, the application of it is beginning to be investigated. To start with, we explored using the 3D model to predict binary solvents which could be used in peptide synthesis. Secondly, we investigated its application to predict binary solvents which would dissolve polystyrene. As the literature reported before,[31] resin swelling depends on the backbone of the resins rather than their functionalities. Thus, we could continue the research by comparing the time required to dissolve polystyrene for pure solvents and their optimised binary solvents to identify which solvents had better dissolving ability.

2.3.1. Polystyrene dissolution in poor, moderate and good swelling green solvents

This dissolution experiment was carried out with one pellet of polystyrene (around 0.02 g) in 1 mL of solvent. The data given in Table 2-12 correlate of polystyrene dissolving time and resin swelling ability of solvents. From these data, we can observe that all poor solvents cannot dissolve the polystyrene pellet but TMO can change the shape of it. Most moderate solvents (except acetonitrile and furfuryl alcohol) and good solvents can dissolve the polystyrene pellet totally. But in the main, good solvents are faster than moderate solvents.

Table 2-12: Polystyrene dissolving time in poor, moderate and good solvents for Merrifield resin swelling; the symbols: no dissolving: -; a little dissolving: +; about 1/3 dissolving: ++; about 1/2 dissolving: +++; most part dissolving: ++++; total dissolving: O; shape changed: #.

			Dissolving time					
Solvent	Solvent Type	Swelling (mL g^{-1})	30 min	60 min	90 min	120 min	> 120	> 24h
propylene carbonate	Poor	1.80	-	-	-	-	-	-
EtOH	Poor	1.80	-	-	-	-	-	-
TMO	Poor	1.78	-	-	-	-	-	#
water	Poor	1.80	-	-	-	-	-	-
cyrene	Poor	1.80	-	-	-	-	-	-
isopropanol	Poor	1.80	-	-	-	-	-	-
1-heptanol	Poor	1.80	-	-	-	-	-	-
MeOH	Poor	1.80	-	-	-	-	-	-
heptane	Poor	1.85	-	-	-	-	-	-
acetonitrile	Moderate	2.43	-	-	-	-	-	-
D-limonene	Moderate	2.70	+	+	+++	+++	O	O
furfuryl alcohol	Moderate	2.99	-	-	-	-	-	-
diethyl carbonate	Moderate	3.00	++	+++	O	O	O	O
p-cymene	Moderate	3.21	++	+++	O	O	O	O
acetone	Moderate	3.71	+	++	+++	+++	++++	O
dimethyl carbonate	Moderate	3.77	++	++++	++++	++++	++++	++++
ethyl acetate	Moderate	3.80	+++	O	O	O	O	O
isopropyl acetate	Good	4.24	+++	++++	O	O	O	O
toluene	Good	5.42	O	O	O	O	O	O
cyclopentanone	Good	5.80	+++	O	O	O	O	O

2.3.2. Polystyrene dissolution in green binary solvents

Five solvent systems which have optimised ratios for resin swelling of Merrifield resin were chosen to study for polystyrene dissolution. By comparing the polystyrene dissolution time of pure solvents and their optimised mixtures, we found binary solvent mixtures that have better dissolving ability than pure solvents. The first solvent system is propylene carbonate and ethyl acetate. This system was previously chosen to use for solid-phase peptide synthesis. As can be seen from Table 2-13, although the binary solvent and ethyl acetate dissolve polystyrene totally in the end, the binary solvent dissolves polystyrene slightly faster than pure ethyl acetate.

Table 2-13: Polystyrene dissolving time in propylene carbonate, ethyl acetate and propylene carbonate:ethyl acetate=10:90 (v/v)

		Dissolving time (min)			
Solvent	Swelling (mL g^{-1})	10	20	30	60
propylene carbonate	1.80	-	-	-	-
ethyl acetate	3.80	a little	1/3	1/2	total
PC:EA=10:90	4.61	a little	1/2	2/3	total

Table 2-14: Polystyrene dissolving time in propylene carbonate, TMO, propylene carbonate: TMO=70:30 (miscible), propylene carbonate:TMO=68:32 (miscible) and propylene carbonate:TMO=60:40 (immiscible)

		Dissolving time (h)	
Solvent	Swelling (mL g^{-1})	>5h	>24h
propylene carbonate	1.80	-	-
TMO	1.78	-	-
PC:TMO=70:30 (miscible)	2.77	1/3	2/3
PC:TMO=68:32 (miscible)	3.56	1/3	2/3
PC:TMO=60:40 (immiscible)	3.81	2/3	total

As discussed in the resin swelling section, both propylene carbonate and TMO are poor solvents for Merrifield resin, and their resin swelling performance are approximately equal. However, from solid-phase peptide synthesis research, propylene carbonate has been shown to have a little ability to support the synthesise of the peptide on Merrifield resin while TMO has no ability to do this. The evidence within Table 2-14 shows that each pure solvent cannot dissolve the polystyrene pellet. In contrast, all mixtures can almost dissolve the pellet. In addition, the immiscible mixture has better ability to dissolve the pellet than the miscible mixtures. The details can be seen from the discussion of the special case of propylene carbonate and TMO. ^{1}H NMR spectroscopy was used to test if there was polystyrene dissolved in PC, TMO and their mixtures, details are given in Appendix F.

Table 2-15: Polystyrene dissolving time in propylene carbonate, D-limonene and propylene carbonate:D-limonene=10:90 (v/v) (immiscible)

		Dissolving time (min)					
Solvent	Swelling (mL g^{-1})	10	20	30	60	>120	>300
propylene carbonate	1.80	-	-	-	-	-	-
D-limonene	2.73	a little	a little	1/3	1/2	a little left	total
PC:D-limonene=10:90 (immiscible)	3.81	a little	a little	1/2	2/3	total	total

The solvent system of propylene carbonate and D-limonene is very similar to the solvent system of PC and TMO because their mixtures are also miscible in some ratios, but herein the immiscible solvent mixture: PC:D-limonene=10:90 was used to prove that the phenomenon of the mixture of PC and TMO is not unique. It is very evident from Table 2-15 that the binary solvent has better ability to swell the resin as well as a faster dissolution ofthe polystyrene pellet.

Table 2-16: Polystyrene dissolving time in methanol, cyclopentanone, and cyclopentanone: MeOH=90:10 (v/v)

		Dissolving time (min)			
Solvent	Swelling (mL g^{-1})	10	20	30	60
MeOH	1.80	-	-	-	-
cyclopentanone	5.80	1/3	1/2	2/3	total
cyclopentanone:MeOH=90:10	6.80	1/3	1/2	2/3	total

Table 2-17: Polystyrene dissolving time in isopropanol, cyclopentanone and cyclopentanone:isopropanol=80:20 (v/v)

		Dissolving time (min)			
Solvent	Swelling (mL g-1)	10	20	30	60
isopropanol	1.80	-	-	-	-
cyclopentanone	5.80	1/3	1/2	2/3	total
cyclopentanone:isopropanol=80:20	6.75	1/2	1/2	2/3	total

For the systems of MeOH & cyclopentanone (Table 2-16) and isopropanol & cyclopentanone (Table 2-17), mixtures of each system show better swelling ability than each of their pure solvents. However, as cyclopentanone is a very good solvent for Merrifield resin, the difference of dissolving time of cyclopentanone and these two mixtures is difficult to distinguish by eye. Thus, the dissolving time of cyclopentanone and the mixtures are very close.

2.3.3. Comparing the abilities of solvents to swell crosslinked polystyrene and Merrifield resin

It had been reported in the literature that resin swelling depended on backbone structure rather than functionality.[31] Thus, five solvent systems which have maximum resin swelling for Merrifield resin were used to also swell crosslinked polystyrene. If this is the case, then crosslinked polystyrene and Merrifield resin would have the same trends of resin swelling. Inspection of Figure 2-68 and Figure 2-69 shows that resin swelling of crosslinked polystyrene and Merrifield resin are virtually the same in solvent systems composed of propylene carbonate & ethyl acetate and propylene carbonate & TMO. However, as detailed in Figure 2-70, Figure 2-71 and Figure 2-72 (ethanol & cyclopentanone, MeOH & cyclopentanone and isopropanol & cyclopentanone solvent systems), the crosslinked polystyrene has almost the same resin swelling in cyclopentanone and these three mixtures. The evidence points to the likelihood that even though the resin swelling mainly depends on the backbone, not the functionality, the functionality may possibly impact the optimised ratio in some solvent systems. The supporting information for these figures can be seen in Appendix F (Table 5-49 and Table 5-50).

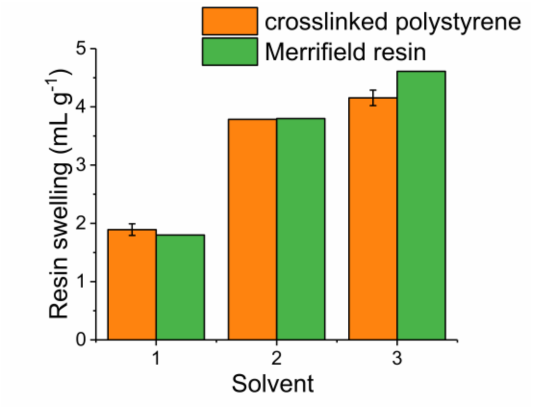


Figure 2-68: Resin swelling of crosslinked polystyrene and Merrifield resin in solvent1: propylene carbonate, solvent 2: ethyl acetate and solvent 3: propylene carbonate ethyl acetate=10:90 (v/v)

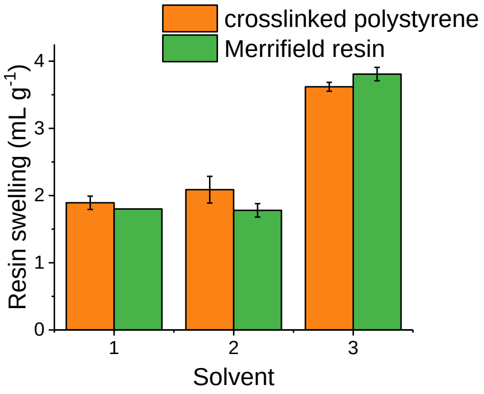


Figure 2-69: Resin swelling of crosslinked polystyrene and Merrifield resin in solvent 1: propylene carbonate, solvent 2: TMO and solvent 3: propylene carbonate:TMO=60:40 (v/v)

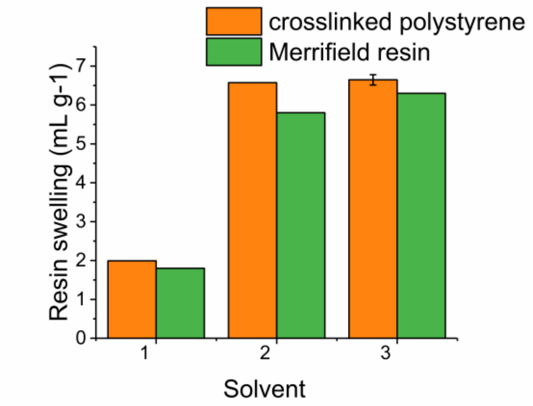


Figure 2-70: Resin swelling of crosslinked polystyrene and Merrifield resin in solvent 1: ethanol, solvent 2: cyclopentanone and solvent 3: ethanol:cyclopentanone=15:85 (v/v)

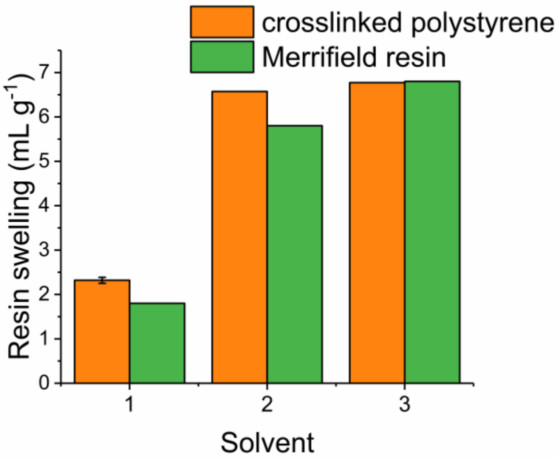


Figure 2-71: Resin swelling of crosslinked polystyrene and Merrifield resin in solvent 1: methanol, solvent 2: cyclopentanone and solvent 3: MeOH:cyclopentanone=10:90 (v/v)

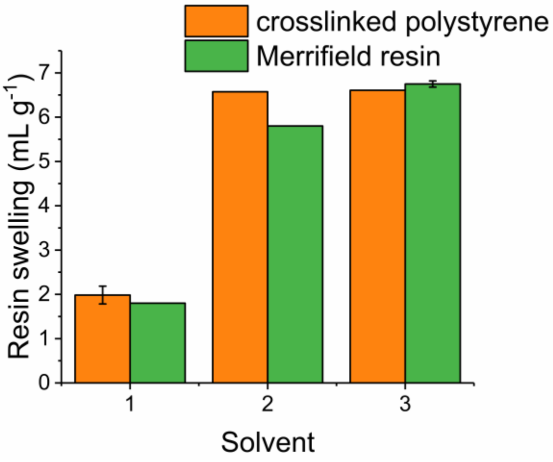


Figure 2-72: Resin swelling of crosslinked polystyrene and Merrifield resin in solvent 1: isopropanol, solvent 2: cyclopentanone and solvent 3: isopropanol:cyclopentanone=20:80 (v/v)

2.3.4. Conclusions for the use of different types of solvents in resin swelling and polystyrene dissolution

The research upon polystyrene dissolution began with the idea to compare the solubilising abilities of pure solvents and solvent blends. The initial method was to add the polystyrene pellets one by one. However, in the end, all pellets became a sticky liquid in the solvent. Thus, it was very difficult to judge when the solvent became a saturated solution. When the polymer dissolves in the solvent, it becomes a polymer solution. Essentially, the polymer solution (also called a macromolecular solution) is a kind of colloidal solution. In the appropriate medium, macromolecular compounds can disperse into a homogeneous solution automatically. A polymer solution is a true solution as it is a homogeneous dispersion. Therefore, the solubility of polystyrene could not be determined in these solvents.

Hence, another method was to study the kinetics of dissolution of single solvents and binary solvents. By comparing the dissolving times of different solvents, the dissolving abilities could be obtained. The dissolving results are divided into four parts as follows: poor solvents for Merrifield resin cannot dissolve polystyrene at all; most moderate solvents can dissolve all or a substantial amount of polystyrene; all good solvents can dissolve polystyrene totally. Generally, the dissolving speed follows: good solvent > moderate solvent > poor solvent. Additionally, resins with the same backbone have the same resin swellings in the same pure solvents, but the functionality may influence the optimised ratio for resin swelling in some binary solvent systems.

3. Materials and experimental methods

3.1. Reagents and materials

2-Methyltetrahydrofuran (≥99%), propylene carbonate (99.7%), d-limonene (97%), cyclopentanone (97%), cyclopen (97%), cyclopentanonean (⩾ 9 (97%), cyclopentanonean (⩾ 99%), propyl (98%), isopropyl acetate (98%), isopropyl acetate(⩾99%) (99%), mesitylene (98%), chloroform-D (99.8 atom% D), carbon disulfide (anhydrous, a99%), furfuryl alcohol (rfuryl alcohol, arbon dis (rfuryl alcohol, arbon (anhydrous, 99.8%), acetone (for HPLC), Merrifield resin with Wang linker (or Wang resin, 0.6-1.0 mmol/g loading, matrix: crosslinked with 1% DVB, mesh: 200-400), ChemMatrix resin (0.5-1.2 mmol/g loading, matrix: crosslinked PEG, mesh: 35-100), H-Phe-HMPB-ChemMatrix® resin (0.30-0.65 mmol/g loading, 35-100 mesh (wet sieved)), Fmoc-Phe-Wang resin (0.4-0.8 mmol/g loading, polystyrene, crosslinked with 1% DVB, 100-200 mesh), piperidine (99%), Fmoc-Ala-OH (95%), Fmoc-Leu-OH (≥97.0%), EDC (N-ethyl-N-(3-dimethylaminopropyl)carbodiimide), ≥97.0%), trifluoroacetic acid-d (99.5 atom%D), and γ-valerolactone (≥99%, FG) were purchased from Sigma-Aldrich and used as supplied.

Cyclopentyl methyl ether was obtained from ZEON corporation. Dimethyl carbonate (99%), isopropanol (99%+, extra pure), and 1,2-dichlorobenzene (99%+, pure) were purchased from Acros Organics. Methanol (ACS), dichloromethane (for HPLC), acetonitrile (for HPLC) and toluene (ACS Reag.) were from VWR. Dimethyl isosorbide (or isosorbide dimethyl ether, 98%), anisole (99%), isobutyl acetate (98%) and gamavalerolactone (98+%) were obtained from Alfa Aesar. Dimethylformamide (laboratory reagent grade), heptane (HPLC grade), trifluoroacetic acid (HPLC grade) and diethyl ether (analytical reagent grade) were from Fisher Chemicals. HypoGel™200-COOH (~0.8 mmol/g loading, mesh: 110-150) was bought from Fluka Chemika. HOBt (monohydrate), HBTU (O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), DIPEA (N, N-diisopropylethylamine) and TIPS (triisopropylsilane) were available from FluoroChem. Oxymapure, K-Oxyma, Oxuma-B, COMU, TOTU and Pyoxim were shipped by Luxembourg Bio Technologies Ltd. Water was deionised water. TMO was distilled three times and dried by molecular sieves (≥99.8%), and made by Dr. Fergal Byrne in the Green Chemistry Centre of Excellence, according to the procedure detailed in the literature.[73]

3.2. Instrumentation

Gas chromatograms were carried out on an Agilent 6890N GC-FID or an Agilent 7890B GC-HP1. On the Agilent 6890N GC-FID, the following parameters were used: Restek Rxi-5HT column (diameter: 250.00 µm, length: 30.0 m, film thickness: 0.25µm, void time: 1.204 min and maximum temperature: 400.0 °C) with initial flow rate: 2 mL min^{-1} and initial pressure: 20.2 psi; the oven: equilibration time: 1 min, initial temperature: 50 °C, initial time: 0.00 min, initial ramp rate at 30 °C min^{-1} until 300 °C and final time: 5 min, post temperature: 50 °C, post time: 0 min, run time: 13.33 min; front inlet: initial temperature: 300 °C , pressure: 20.2 psi, split ratio with 30: 1, split flow: 60.0 mL min^{-1}, saver flow: 20.0 mL min^{-1}, saver time: 2 min, gas type: helium; flow-rate 2.0 mL min^{-1}; front detector: temperature: 340 °C, hydrogen flow: 35 mL min^{-1}, air flow: 350.0 mL min^{-1}, makeup gas type: nitrogen; injection volume: 1 µL. On the Agilent 7890B GC-HP1, the parameters were the same as the Agilent 6890N GC-FID, except that the parameters of the front inlet and front detector were slightly different: heater: 310 °C, split ratio: 50:1, split flow: 100 mL min^{-1}; front detector: heater temperature: 340 °C.

The method for all mass spectra was electrospray Ionisation (ESI) on a Bruker compact® time of flight mass spectrometer coupled to an Agilent 1260 Infinity series LC system.

All ^{1}HNMR spectra were obtained with a JEOL ECS 400MHz instrument. The NMR solvents and were referenced to the residual solvent peak. Coupling constants were analysed by the following nomenclature: d = doublet, dd = double doublet, t = triplet, m = multiplet. The spectrum of H-Leu-Ala-Phe-OH was recorded in TFA-d NMR solvent, TFA-d: δ = 7.26-7.16 (m, 3H, ArH), 7.14-7.08 (m, 2H, ArH), 5.01-4.96 (m, 1H, Phe-NCH), 4.71-4.61 (m, 1H, Ala-NCH), 4.31-4.24 (m, 1H, Leu-NCH), 3.30 (dd *J* 14.3, 4.3 Hz, 1H, CH_2Ph), 3.09 (dd *J* 14.3, 8.5 Hz, 1H, CH_2Ph), 1.80-1.60 (m, 3H, Leu-CH_2CHMe_2), 1.39 (d *J* 6.3 Hz, 3H, $NCHCH_3$), 0.93 (t *J* 6.0 Hz, 6H, $CH(CH_3)_2$).

All peptides prepared in different solvents and with different coupling agents were analysed by HPLC using an Agilent 1260 Infinity Ⅱ fitted with a C18 column (serial: autoID-14, product: 00G-4378-E0, length: 250.0 mm, diameter: 4.6 mm, void volume: 60.0%, particle size: 5.0 µm, maximum pressure: 400.0 bar, maximum pH: 8.0, maximum temperature: 60.0 °C) eluted with a flow rate of 0.4 mL min^{-1} at 40 °C. Injection volume was 10 µL. The eluents were A (water + 0.1% formic acid) and B (acetonitrile + 0.1% formic acid) formic acid. In the initial 5 min, the solvent system was 90% A and 10% B, the 50% A and 50% B in the next 15 minutes. After that, the percentage was gradually changed back to 90% A and 90% B from 20 min to 25 min.

3.3. Typical resin swelling methodology

Resin swelling experiments were carried out using the method developed by Santini *et al*.[32] 0.1 g of resin was weighed into a 2 mL syringe which had been fitted with a polystyrene frit at the bottom (the dead volume of the frit was 0.12 mL). The resin was washed three times with the chosen single solvent or solvent mixture. 2 mL of target solvent was added and the syringe was sealed with a syringe pressure cap and placed on a roller mixer to rotate for one hour at room temperature. Then the plunger of the syringe was compressed to remove excess solvent and fully loosened to allow the resin volume to be read. After recording the volume of the resin, the plunger was taken off and the resin was washed three times with dichloromethane to remove all target solvent. Next, the resin was dried using a vacuum set to pull air through it. This process was repeated three times to get the average resin swelling volume. Swelling times longer than one hour were observed to have no impact on swelling. Solvents were divided into three categories: swelling below 2 mL g^{-1} was deemed a poor solvent, from 2 mL g^{-1} to 4 mL g^{-1} a moderate solvent and higher than 4 mL g^{-1} a good solvent.[32] Resin swelling formula:

$$\text{Swelling (mL g}^{-1}\text{)} = \frac{\text{Measured Volume} - \text{Frit Volume}}{\text{Weight}} \cdots\cdots\cdots\cdots\cdots\cdots \text{ Equation 5}$$

Although some error might arise because visual observation was used to read the scale, an acceptable influence of the swelling changing trend of solvents blends was apparent.

3.4. Solvent mixtures & calculation of Hansen solubility parameters

All ratios of binary solvents used in this project were volume to volume. Preparation of solvent mixtures: using a Gilson pipette to get accurate volumes (total volume=15 mL), two solvents were mixed in a 15 mL screw-topped vial and shaken well. Some mixtures, such as cyclopentanone and water, were also sonicated to promote efficient mixing. Ethylene carbonate was melted in a heating bath at 35 °C before mixing with the appropriate co-solvent and gently heated to promote mixing.

Determination of Hansen solubility parameters for mixed solvent systems: the mixed solvents' HSP calculation principle in the HSPiP software guidebook was followed, the HSP parameters of solvent blends were simply the average (weighted for % contribution) of the individual components".[41] The formula is:

$$\delta\mathrm{HSP}\ (\mathrm{blends})=\sum_{\mathrm{i}}^{\mathrm{n}}\delta\mathrm{HSPi}*\mathrm{PCTi} \cdots\cdots\cdots\cdots\cdots\quad \text{Equation 6}$$

δHSP stands for δD, δP or δH. δD: the value of dispersion forces, δP: the value of polarity forces or δH: the value of hydrogen bonding forces. PCT was percentage of each pure solvent in the binary solvent.

3.5. General method for solid-phase peptide synthesis in green pure and binary mixed solvents

200 mg Fmoc-Phe-Wang resin was weighed into a 6 mL filtration tube which had a 6 mL polyethylene frit fixed so that the resin could be prevented from leaking out.

Before weighing, the filtration tube was wiped with a cloth soaked with distilled water with the purpose of reducing static. The weighed resin was first washed three times with the target solvent (single solvent or solvent blend, 3×5 mL). Then the resin was swollen in 5 mL of this solvent for 1 h. A cap for a 6 mL SPE tube and syringe pressure cap were then used to seal the tube. After that, it was put on a roller mixer to allow it to swell.

For all deprotections, a freshly prepared solution of 5 ml of 20% (v/v) piperidine in target solvent was used for 20 min. For couplings, Fmoc-amino acid (firstly Fmoc-Ala-OH and then Fmoc-Leu-OH) (0.36 mmol, 3.0 eq.), HBTU (137 mg, 0.36 mmol, 3.0 eq.), HOBt (49 mg, 0.36 mmol, 3.0 eq.) and DIPEA (125 µL, 0.72 mmol, 6.0 eq.) were weighed into a 5 mL vial which held 3.6 mL target solvent and stirred for 20 min to pre-activate the amino acid before adding this mixture to the resin. The coupling reactions were allowed to occur at room temperature for 1 h. After each step, the resin was washed three times. For the synthesis using propylene carbonate, the resin was washed with ethyl acetate for three times (5 mL × 3) to ensure removal of all PC. Then the peptide chain could be cleaved from the resin by 5 mL TFA:TIPS:H_2O (95:2.5:2.5) for 2 h. When the cleaving process was finished, the solution could be separated from the resin by filtration, concentrated by rotary evaporation and the peptide precipitated in cold diethyl ether. Finally, the peptide was washed with cold diethyl ether and dried under vacuum. For peptide synthesis using Oxymapure/EDC, all procedures were the same as synthesis using HBTU/HOBt, only the coupling agents were replaced by Oxymapure (51.2 mg, 0.36 mmol, 3.0 eq.) and EDC (63.74 µL, 0.36 mmol, 3.0 eq.).

3.6. Methodology to study the selective interaction of resins with green binary mixed solvents

The NMR internal standard methodology was: a known volume of mesitylene was added to mixed solvent samples taken before and after resin swellings as an internal standard to allow calculation of how the cyclopentanone:water ratio changes. The standard was added to the aliquots taken for NMR only, it was not present for the swelling experiment itself. By comparing the ratio of the integration for mesitylene and the solvent, that solvent was captured by the resin could be proved. The volume for each testing solvent mixture before and after swelling should be kept consistent.

Another way for testing the selectivity was to use GC calibration. One miscible solvent was used to calculate the response factor (Rf). The formula below could be used in calculating the actual value for the immiscible mixture. GC was also used to detect the resin selective ability with binary solvents. The top and bottom layers of immiscible solvent were used to swell the resin separately. GC was used to detect the content variation of the solvents before and after swelling. The formula was:

$$\frac{\mathrm{PC(mol\%)}}{\mathrm{TMO(mol\%)}}=\mathrm{Rf}\frac{\mathrm{PC(Area)}}{\mathrm{TMO(Area)}} \quad \cdots\cdots\cdots\cdots\cdots\cdots \text{ Equation 7}$$

3.7. The method for dissolving polystyrene

Some greener binary solvent systems were chosen on the basis of the previous resin swelling studies. One pellet of standard polystyrene (about 20 mg per pellet, Mw=~19,200), which was bought from Sigma-Aldrich, was dissolved in 1 mL pure or mixed solvent respectively. The dissolving time of each solvent was recorded and compared. According to the comparison of the dissolving time, the dissolving ability of different pure and binary solvents was ranked.

4. Conclusion

4.1. Relationship between the high swelling area and Hansen solubility parameters for Merrifield resin (PS-based resin) and HypoGel™200 resin (PS-PEG-based resin)

To build the HSP-resin swelling model, all available swelling data[31] were plotted as a 3D scatter graph. Therefore, we moved from single solvent to mixed solvent systems chosen to systematically fill in gaps in swelling data and allow the boundaries of the high swelling area in HSP space to be fully mapped for Merrifield and HypoGel™200 resins. In this way, the relationship of resin swelling and HSP was revealed as high resin swelling areas for each resin have been found. As the 3D plots are difficult to visualise on 2D paper, more visualisation methods were adopted such as Teas plots and contour graphs. In the meantime, the poor solvents areas, moderate solvents areas and good solvents areas were investigated. The results show the polystyrene-based resin and PS-PEG-based resin have different high swelling areas in HSP-3D space.

4.2. Swelling trends of different solvent systems

According to this study, four types of resin swelling trends in binary solvent systems for these two resins have been found and they show that the resin swelling does not vary linearly on changing the ratio of two pure solvents. Type 1 and Type 1a are where there is a maximum resin swelling in the solvent system. Type 2 is that the resin swelling trend shows an increase or decrease with no maximum resin swelling in these solvent systems. Type 3 shows the swelling abilities of the two parent solvents are similar and there is no mixture that gives swelling beyond each pure solvent. Type S stands for some special cases of solvent systems. One of the interesting solvent systems: cyclopentanone and water for HypoGel™200 resin was explored using NMR spectroscopy with an internal standard method to prove that only cyclopentanone can swell the resin in this solvent system. 2-MeTHF and cyclopentyl methyl ether have similar Hansen solubility parameters, but there is a minimum resin swelling in this solvent system for Merrifield resin. Dimethylformamide and water can form hydrogen-bonded complexes so that their mixtures cannot swell both these resins until the percentage of dimethyl formamide is more than 80%. In the propylene carbonate and TMO system, both are poor solvents for Merrifield resin and they are partially miscible, but their mixtures show swelling ability and the optimised ratio is PC:TMO=10:90 (v/v).

4.3. The application of the HSP-3D graph: solid-phase peptide synthesis

To prove the significance of the modelling, two solvent systems: propylene carbonate & ethyl acetate and propylene carbonate & TMO were chosen to apply in solid-phase peptide synthesis on Merrifield resin with Wang linker. The tripeptide: H-Leu-Ala-Phe-OH was set as the target peptide chain. The results show that peptide synthesis in binary solvents is superior to synthesis in pure solvents. Additionally, the coupling agent HBTU/HOBt is better than Oxymapure/EDC in this peptide synthesis.

4.4. The application of the HSP-3D graph: dissolving polystyrene

In the study of dissolving polystyrene, generally, the dissolving speed correlated with resin swelling ability: good solvent > moderate solvent > poor solvent. In solvent systems which have a maximum resin swelling, the optimised ratio of binary solvents dissolve polystyrene faster than their parent pure solvents. Resins which have the same backbones have the same resin swelling in pure solvents, but the different functionalities may influence the optimal ratio for mixed solvent systems.

4.5. The significance and applications of this project

In this project, the high swelling areas for these two resins in HSP-3D space were found. Following this methodology, the relevance of swelling and Hansen solubility parameters for more resins with different backbones and functionalities can be studied. Also, these models can be used to predict binary mixtures which may have optimal ratios, and then these binary solvents may be used for solid-phase peptide synthesis and polymer dissolving. The methodology used here should have wide applicability to many other resins and polymers and can provide a general method for developing greener replacements for undesirable conventional solvents, based on the combination of two (or more) green solvents.

4.6. Future work

In this project, only the model of Merrifield resin was investigated for its applications. The established model would likewise reveal other properties for Merrifield resin. Thus, the HSP-3D plot needs to be explored by other visualisations. In the meantime, it is hoped to predict better greener binary solvents as alternatives to traditional organic solvents for peptide synthesis on Merrifield resin, polystyrene dissolution and other chemical processes. For HypoGel™200 resin, only the high swelling area was explored. It is significant to explore the relevant applications for the model of this resin. Furthermore, only the high swelling areas for Merrifield and HypoGel™200 resins were explored in this project. To confirm the feasibility of the methodology established in this project, more resins with different backbones and functionalities need to be fully investigated. Also, the applications of their models can be studied.

5. Appendices

All literature data in all appendices are from reference 31.

5.1. Appendix A

5.1.1. Data supporting Chapter 2.1

Table 5-1: Data to support Figure 2-1

Resin swelling repetitive experiments for Merrifield resin

Number	Solvent	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})	Literatura
1	dimethyl isosorbide	0.80	0.75	0.75	0.0997	0.16	6.08	0.33	5.90
2	2-methyltetrahydrofuran	0.80	0.80	0.80	0.1020	0.15	6.37	0.00	5.80
3	propylene carbonate	0.30	0.30	0.30	0.1017	0.10	1.97	0.00	1.80
4	D-limonene	0.39	0.39	0.39	0.1000	0.16	2.30	0.00	1.80

Table 5-2: Basic swelling data from literature[31] and Hansen solubility parameters of pure solvents

				HypoGel200 resin	Merrifield (Wang) resin
Solvent	δD	δP	δH	Swelling (mL g^{-1})	Swelling (mL g^{-1})
ethylene carbonate	18	21.7	5.1	2.8	1.8
propylene carbonate	20	18	4.1	2.2	1.8
cyrene	18.8	10.5	7	3.2	1.8
acetone	15.5	10.4	7	2.8	2.4
butan-2-one	16	9	5.1	3.2	4.8
4-methylpentan-2-one	15.3	6.1	4.1	2.8	3.5
cyclopentanone	17.9	11.9	5.2	4.8	5.9
ethyl acetate	15.8	5.3	7.2	2.8	3.8
isopropyl acetate	14.9	4.5	8.2	2.2	3.4
isobutyl acetate	15.1	3.7	6.3	2.8	3.8
γ-valerolactone	16.9	11.5	6.3	3.2	3.2
2-methyl-THF	16.9	5	4.3	4	5.8
anisole	17.8	4.4	6.9	4.2	5.9
dimethyl isosorbide	17.6	7.1	7.5	5.2	5.9
cyclopentyl methyl ether	16.7	4.3	4.3	2.8	5.9
dimethyl carbonate	15.5	8.6	9.7	2.8	2.6
diethyl carbonate	15.1	6.3	3.5	2.6	3
D-limonene	17.2	1.8	4.3	2.2	1.8
p-cymene	17.3	2.4	2.4	1.8	1.8
methanol	14.7	12.3	22.3	1.8	1.8
ethanol	15.8	8.8	19.4	1.8	1.8
isopropanol	15.8	6.1	16.4	1.8	1.8
1-heptanol	16	5.3	11.7	1.8	1.8

water	15.5	16	42.3	1.8	1.8
NMP	18	12.3	7.2	4.8	6.2
DMF	17.4	13.7	11.3	4.5	4.8
DCM	17	7.3	7.1	4.9	5.6

Table 5-3: Basic fractional parameters and resin swelling for Merrifield resin and HypoGel™200 resin

				Merrifield resin	HypoGel™200 resin
Solvent	fd	fp	fh	Swelling (mL g^{-1})	Swelling (mL g^{-1})
ethylene carbonate	40.18	48.44	11.38	1.80	2.80
propylene carbonate	47.51	42.76	9.74	1.80	2.20
cyrene	51.79	28.93	19.28	1.80	3.20
acetone	47.11	31.61	21.28	3.71	2.80
butan-2-one	53.16	29.90	16.94	4.80	3.20
4-methylpentan-2-one	60.00	23.92	16.08	3.50	2.80
cyclopentanone	51.14	34.00	14.86	5.80	4.80
ethyl acetate	55.83	18.73	25.44	3.80	2.80
isopropyl acetate	53.99	16.30	29.71	4.24	2.20
isobutyl acetate	60.16	14.74	25.10	3.80	2.80
γ-valerolactone	48.70	33.14	18.16	5.73	3.20
2-methyl-THF	64.50	19.08	16.41	5.80	4.00
anisole	61.17	15.12	23.71	5.90	4.20
dimethyl isosorbide	54.66	22.05	23.29	5.90	5.20
cyclopentyl methyl ether	66.01	17.00	17.00	5.90	2.80
dimethyl carbonate	45.86	25.44	28.70	3.77	2.80
diethyl carbonate	60.64	25.30	14.06	3.00	2.60
D-limonene	73.82	7.73	18.45	2.70	2.20
p-cymene	78.28	10.86	10.86	3.21	1.80
methanol	29.82	24.95	45.23	1.80	1.80
ethanol	35.91	20.00	44.09	1.80	1.80
isopropanol	41.25	15.93	42.82	1.80	1.80
1-heptanol	48.48	16.06	35.45	1.80	1.80
water	21.00	21.68	57.32	1.80	1.80
NMP	48.00	32.80	19.20	6.20	4.80
DMF	41.04	32.31	26.65	4.80	4.50
DCM	54.14	23.25	22.61	5.60	4.90

Table 5-4: Different types of solvent systems for Merrifield resin and values of each solvent's Hansen solubility parameters and their corresponding fractional parameters

Type	Solvent A (%)	Solvent B (%)	δD	δP	δH	fd	fp	fh	Swelling (mL g^{-1})
S	2-MeTHF (100)	CPME (0)	16.9	5	4.3	64.50	19.08	16.41	6.27
	90	10	16.88	4.93	4.3	64.65	18.88	16.47	6.23
	80	20	16.86	4.86	4.3	64.80	18.68	16.53	6.18
	70	30	16.84	4.79	4.3	64.94	18.47	16.58	6.25
	60	40	16.82	4.72	4.3	65.09	18.27	16.64	5.78
	55	45	16.81	4.685	4.3	65.17	18.16	16.67	5.83

	52	48	16.804	4.664	4.3	65.21	18.10	16.69	5.33
	35	65	16.77	4.545	4.3	65.47	17.74	16.79	5.42
	30	70	16.76	4.51	4.3	65.55	17.64	16.82	5.33
	10	90	16.72	4.37	4.3	65.85	17.21	16.94	5.46
	0	100	16.7	4.3	4.3	66.01	17.00	17.00	5.67
1	ethanol (100)	cyclopentanone (0)	15.8	8.8	19.4	35.91	20.00	44.09	1.80
	75	25	16.325	9.575	15.85	39.10	22.93	37.96	2.33
	50	50	16.85	10.35	12.3	42.66	26.20	31.14	4.40
	35	65	17.165	10.815	10.17	44.99	28.35	26.66	5.39
	25	75	17.375	11.125	8.75	46.64	29.87	23.49	5.97
	20	80	17.48	11.28	8.04	47.50	30.65	21.85	5.90
	15	85	17.585	11.435	7.33	48.38	31.46	20.17	6.31
	10	90	17.69	11.59	6.62	49.28	32.28	18.44	6.11
	0	100	17.9	11.9	5.2	51.14	34.00	14.86	5.80
1	propylene carbonate (100)	dimethyl carbonate (0)	20	18	4.1	47.51	42.76	9.74	1.80
	85	15	19.325	16.59	4.94	47.30	40.61	12.09	1.80
	75	25	18.875	15.65	5.5	47.16	39.10	13.74	2.00
	70	30	18.65	15.18	5.78	47.08	38.32	14.59	2.37
	60	40	18.2	14.24	6.34	46.93	36.72	16.35	2.41
	50	50	17.75	13.3	6.9	46.77	35.05	18.18	2.39
	35	65	17.075	11.89	7.74	46.52	32.39	21.09	3.17
	25	75	16.625	10.95	8.3	46.34	30.52	23.14	2.60
	20	80	16.4	10.48	8.58	46.25	29.55	24.20	3.30
	10	90	15.95	9.54	9.14	46.06	27.55	26.39	3.57
	0	100	15.5	8.6	9.7	45.86	25.44	28.70	2.60
1	propylene carbonate (100)	ethyl acetate (0)	20	18	4.1	47.51	42.76	9.74	1.80
	90	10	19.58	16.73	4.41	48.08	41.09	10.83	1.73
	70	30	18.74	14.19	5.03	49.37	37.38	13.25	2.79
	50	50	17.9	11.65	5.65	50.85	33.10	16.05	3.23
	30	70	17.06	9.11	6.27	52.59	28.08	19.33	3.45
	20	80	16.64	7.84	6.58	53.57	25.24	21.18	4.17
	10	90	16.22	6.57	6.89	54.65	22.14	23.21	4.61
	5	95	16.01	5.935	7.045	55.23	20.47	24.30	4.04
	0	100	15.8	5.3	7.2	55.83	18.73	25.44	3.80
1	cyclopentanone (100)	methanol (0)	17.9	11.9	5.2	51.14	34.00	14.86	5.80
	95	5	17.74	11.92	6.055	49.67	33.38	16.95	5.77
	90	10	17.58	11.94	6.91	48.26	32.78	18.97	6.80
	85	15	17.42	11.96	7.765	46.90	32.20	20.90	6.76
	80	20	17.26	11.98	8.62	45.59	31.64	22.77	5.30
	70	30	16.94	12.02	10.33	43.12	30.59	26.29	5.41
	60	40	16.62	12.06	12.04	40.82	29.62	29.57	5.04
	40	60	15.98	12.14	15.46	36.67	27.86	35.47	3.02
	20	80	15.34	12.22	18.88	33.03	26.31	40.65	2.04
	0	100	14.7	12.3	22.3	29.82	24.95	45.23	1.80

1	cyclopentanone (100)	isopropanol (0)	17.9	11.9	5.2	51.14	34.00	14.86	5.80
	95	5	17.795	11.61	5.76	50.60	33.02	16.38	5.83
	90	10	17.69	11.32	6.32	50.07	32.04	17.89	6.56
	80	20	17.48	10.74	7.44	49.02	30.12	20.86	6.75
	70	30	17.27	10.16	8.56	47.99	28.23	23.78	5.81
	50	50	16.85	9	10.8	45.98	24.56	29.47	4.78
	30	70	16.43	7.84	13.04	44.04	21.01	34.95	2.98
	0	100	15.8	6.1	16.4	41.25	15.93	42.82	1.80
2	DCM (100)	1,2-dichlorobenz-ene (0)	17	7.3	7.1	54.14	23.25	22.61	5.91
	75	25	17.55	7.05	6.15	57.07	22.93	20.00	5.84
	50	50	18.1	6.8	5.2	60.13	22.59	17.28	5.75
	25	75	18.65	6.55	4.25	63.33	22.24	14.43	5.58
	0	100	19.2	6.3	3.3	66.67	21.88	11.46	5.49
3	DMF (100)	1,2-dichlorobenz-ene (0)	17.4	13.7	11.3	41.04	32.31	26.65	5.65
	75	25	17.85	11.85	9.3	45.77	30.38	23.85	5.72
	50	50	18.3	10	7.3	51.40	28.09	20.51	5.73
	25	75	18.75	8.15	5.3	58.23	25.31	16.46	5.70
	0	100	19.2	6.3	3.3	66.67	21.88	11.46	5.49
1	acetonitrile （100）	toluene （0）	15.3	18	6.1	38.83	45.69	15.48	2.43
	80	20	15.84	14.68	5.28	44.25	41.01	14.75	2.69
	60	40	16.38	11.36	4.46	50.87	35.28	13.85	4.12
	40	60	16.92	8.04	3.64	59.16	28.11	12.73	5.33
	20	80	17.46	4.72	2.82	69.84	18.88	11.28	5.64
	0	100	18	1.4	2	84.11	6.54	9.35	5.42
2	PC （100）	1,2-dichlorobenz-ene (0)	20	18	4.1	47.51	42.76	9.74	1.80
	75	25	19.8	15.075	3.9	51.06	38.88	10.06	3.24
	50	50	19.6	12.15	3.7	55.29	34.27	10.44	3.94
	25	75	19.4	9.225	3.5	60.39	28.72	10.89	4.97
	0	100	19.2	6.3	3.3	66.67	21.88	11.46	5.49
2	1,2-dichloroben-zene (100)	heptane (0)	19.2	6.3	3.3	66.67	21.88	11.46	5.49
	75	25	18.225	4.725	2.475	71.68	18.58	9.73	5.21
	59	41	17.25	3.15	1.65	78.23	14.29	7.48	4.13
	25	75	16.275	1.575	0.825	87.15	8.43	4.42	3.26
	0	100	15.3	0	0	100.00	0.00	0.00	1.85
1	PC (100)	acetonitrile (0)	20	18	4.1	47.51	42.76	9.74	1.80
	75	25	18.825	18	4.6	45.44	43.45	11.10	2.27
	50	50	17.65	18	5.1	43.31	44.17	12.52	3.11
	25	75	16.475	18	5.6	41.11	44.92	13.97	2.95
	0	100	15.3	18	6.1	38.83	45.69	15.48	2.43
1	isopropyl acetate	acetonitrile (0)	14.9	4.5	8.2	53.99	16.30	29.71	4.24

	(100)								
	90	10	14.94	5.85	7.99	51.91	20.33	27.76	3.91
	80	20	14.98	7.2	7.78	50.00	24.03	25.97	3.84
	75	25	15	7.875	7.675	49.10	25.78	25.12	3.83
	70	30	15.02	8.55	7.57	48.23	27.46	24.31	3.61
	50	50	15.1	11.25	7.15	45.07	33.58	21.34	2.82
	25	75	15.2	14.625	6.625	41.70	40.12	18.18	2.86
	0	100	15.3	18	6.1	38.83	45.69	15.48	2.43
1	furfuryl alcohol (100)	cyclopentane-one (0)	17.4	7.6	15.1	43.39	18.95	37.66	2.99
	70	30	17.55	8.89	12.13	45.50	23.05	31.45	4.49
	50	50	17.65	9.75	10.15	47.00	25.97	27.03	5.22
	30	70	17.75	10.61	8.17	48.59	29.04	22.37	6.09
	0	100	17.9	11.9	5.2	51.14	34.00	14.86	5.80
S	water (100)	DMF (0)	15.5	16	42.3	21.00	21.68	57.32	1.80
	80	20	15.88	15.54	36.1	23.52	23.02	53.47	1.63
	60	40	16.26	15.08	29.9	26.55	24.62	48.82	1.75
	50	50	16.45	14.85	26.8	28.31	25.56	46.13	1.87
	40	60	16.64	14.62	23.7	30.28	26.60	43.12	1.76
	20	80	17.02	14.16	17.5	34.96	29.09	35.95	1.97
	10	90	17.21	13.93	14.4	37.79	30.59	31.62	1.97
	0	100	17.4	13.7	11.3	41.04	32.31	26.65	5.65
1	TMO (100)	cyclopentane-one (0)	15.4	2.4	2.1	77.39	12.06	10.55	1.78
	90	10	15.65	3.35	2.41	73.10	15.65	11.26	3.95
	80	20	15.9	4.3	2.72	69.37	18.76	11.87	4.21
	70	30	16.15	5.25	3.03	66.11	21.49	12.40	5.02
	50	50	16.65	7.15	3.65	60.66	26.05	13.30	5.60
	40	60	16.9	8.1	3.96	58.36	27.97	13.67	5.71
	30	70	17.15	9.05	4.27	56.28	29.70	14.01	6.10
	20	80	17.4	10	4.58	54.41	31.27	14.32	6.12
	15	85	17.525	10.475	4.735	53.54	32.00	14.46	6.19
	10	90	17.65	10.95	4.89	52.70	32.70	14.60	6.25
	5	95	17.775	11.425	5.045	51.91	33.36	14.73	6.35
	0	100	17.9	11.9	5.2	51.14	34.00	14.86	5.80
1	propylene carbonate (100)	TMO (0)	20	18	4.1	47.51	42.76	9.74	1.80
	90	10	19.54	16.44	3.9	49.00	41.22	9.78	2.14
	80	20	19.08	14.88	3.7	50.66	39.51	9.82	2.31
	70	30	18.62	13.32	3.5	52.54	37.58	9.88	2.92
	60	40	18.16	11.76	3.3	54.67	35.40	9.93	3.81
	50	50	17.7	10.2	3.1	57.10	32.90	10.00	3.74
	40	60	17.24	8.64	2.9	59.90	30.02	10.08	3.70
	30	70	16.78	7.08	2.7	63.18	26.66	10.17	3.77
	20	80	16.32	5.52	2.5	67.05	22.68	10.27	3.74
	10	90	15.86	3.96	2.3	71.70	17.90	10.40	3.82
	0	100	15.4	2.4	2.1	77.39	12.06	10.55	1.78

1	propylene carbonate (100)	D-limonene (0)	20	18	4.1	47.51	42.76	9.74	1.80
	90	10	19.72	16.38	4.12	49.03	40.73	10.24	2.65
	80	20	19.44	14.76	4.14	50.70	38.50	10.80	2.72
	70	30	19.16	13.14	4.16	52.55	36.04	11.41	2.77
	60	40	18.88	11.52	4.18	54.60	33.31	12.09	3.13
	50	50	18.6	9.9	4.2	56.88	30.28	12.84	2.92
	40	60	18.32	8.28	4.22	59.44	26.87	13.69	3.21
	30	70	18.04	6.66	4.24	62.34	23.01	14.65	3.63
	20	80	17.76	5.04	4.26	65.63	18.63	15.74	3.61
	10	90	17.48	3.42	4.28	69.42	13.58	17.00	3.81
	0	100	17.2	1.8	4.3	73.82	7.73	18.45	2.73
2	propylene carbonate (100)	acetone (0)	20	18	4.1	47.51	42.76	9.74	1.80
	70	30	18.65	15.72	4.97	47.41	39.96	12.63	2.71
	50	50	17.75	14.2	5.55	47.33	37.87	14.80	3.14
	30	70	16.85	12.68	6.13	47.25	35.56	17.19	3.53
	0	100	15.5	10.4	7	47.11	31.61	21.28	3.71
1	propylene carbonate (100)	isopropyl acetate (0)	20	18	4.1	47.51	42.76	9.74	1.80
	70	30	18.47	13.95	5.33	48.93	36.95	14.12	3.03
	50	50	17.45	11.25	6.15	50.07	32.28	17.65	3.71
	30	70	16.43	8.55	6.97	51.42	26.76	21.82	3.92
	20	80	15.92	7.2	7.38	52.20	23.61	24.20	4.40
	10	90	15.41	5.85	7.79	53.05	20.14	26.82	4.51
	0	100	14.9	4.5	8.2	53.99	16.30	29.71	4.24

Table 5-5: Different types of solvent systems for HypoGel™200 resin and values of each solvent's Hansen solubility parameters and their corresponding fractional parameters

Type	Solvent A (%)	Solvent B (%)	δD	δP	δH	fd	fp	fh	Swelling (mL g^{-1})
S	cyclopenta-none (100)	water (0)	17.9	11.9	5.2	51.14	34.00	14.86	5.02
	95	5	17.78	12.105	7.055	48.13	32.77	19.10	5.05
	86	14	17.564	12.474	10.394	43.44	30.85	25.71	5.13
	31	69	16.244	14.729	30.799	26.30	23.84	49.86	4.45
	25	75	16.1	14.975	33.025	25.12	23.36	51.52	3.82
	20	80	15.98	15.18	34.88	24.20	22.99	52.82	2.91
	15	85	15.86	15.385	36.735	23.33	22.63	54.04	2.51
	10	90	15.74	15.59	38.59	22.51	22.30	55.19	2.09
	5	95	15.62	15.795	40.445	21.74	21.98	56.28	2.04
	0	100	15.5	16	42.3	21.00	21.68	57.32	2.01
1	propylene carbonate (100)	EtOH (0)	20	18	4.1	47.51	42.76	9.74	2.20
	90	10	19.58	17.08	5.63	46.30	40.39	13.31	3.30
	75	25	18.95	15.7	7.925	44.51	36.88	18.61	3.68

	60	40	18.32	14.32	10.22	42.74	33.41	23.85	3.78
	50	50	17.9	13.4	11.75	41.58	31.13	27.29	3.60
	40	60	17.48	12.48	13.28	40.43	28.86	30.71	3.76
	25	75	16.85	11.1	15.575	38.71	25.50	35.78	3.04
	10	90	16.22	9.72	17.87	37.02	22.19	40.79	2.27
	0	100	15.8	8.8	19.4	35.91	20.00	44.09	1.80
1	propylene carbonate (100)	diethyl carbonate (0)	20	18	4.1	47.51	42.76	9.74	2.20
	90	10	19.51	16.83	4.04	48.32	41.68	10.00	2.51
	75	25	18.775	15.075	3.95	49.67	39.88	10.45	2.99
	60	40	18.04	13.32	3.86	51.22	37.82	10.96	3.38
	50	50	17.55	12.15	3.8	52.39	36.27	11.34	3.69
	40	60	17.06	10.98	3.74	53.68	34.55	11.77	3.72
	25	75	16.325	9.225	3.65	55.91	31.59	12.50	3.78
	10	90	15.59	7.47	3.56	58.56	28.06	13.37	3.25
	0	100	15.1	6.3	3.5	60.64	25.30	14.06	2.60
1	dimethyl carbonate (100)	propylene carbonate (0)	15.5	8.6	9.7	45.86	25.44	28.70	2.80
	75	25	16.625	10.95	8.3	46.34	30.52	23.14	3.21
	60	40	17.3	12.36	7.46	46.61	33.30	20.10	3.28
	50	50	17.75	13.3	6.9	46.77	35.05	18.18	3.09
	40	60	18.2	14.24	6.34	46.93	36.72	16.35	3.23
	25	75	18.875	15.65	5.5	47.16	39.10	13.74	3.01
	0	100	20	18	4.1	47.51	42.76	9.74	2.20
1	Isopropanol (100)	propylene carbonate (0)	15.8	6.1	16.4	41.25	15.93	42.82	1.80
	90	10	16.22	7.29	15.17	41.93	18.85	39.22	2.31
	80	20	16.64	8.48	13.94	42.60	21.71	35.69	2.94
	75	25	16.85	9.075	13.325	42.93	23.12	33.95	3.24
	50	50	17.9	12.05	10.25	44.53	29.98	25.50	3.79
	25	75	18.95	15.025	7.175	46.05	36.51	17.44	3.44
	20	80	19.16	15.62	6.56	46.35	37.78	15.87	3.41
	10	90	19.58	16.81	5.33	46.93	40.29	12.78	3.01
	0	100	20	18	4.1	47.51	42.76	9.74	2.20
1	methanol (100)	propylene carbonate (0)	14.7	12.3	22.3	29.82	24.95	45.23	1.80
	90	10	15.23	12.87	20.48	31.35	26.49	42.16	2.91
	75	25	16.025	13.725	17.75	33.74	28.89	37.37	2.97
	60	40	16.82	14.58	15.02	36.23	31.41	32.36	3.41
	50	50	17.35	15.15	13.2	37.96	33.15	28.88	3.60
	40	60	17.88	15.72	11.38	39.75	34.95	25.30	3.87
	25	75	18.675	16.575	8.65	42.54	37.76	19.70	3.65
	10	90	19.47	17.43	5.92	45.47	40.71	13.83	3.23
	0	100	20	18	4.1	47.51	42.76	9.74	2.20
1	propylene carbonate (100)	ethyl acetate (0)	20	18	4.1	47.51	42.76	9.74	2.20

	80	20	19.16	15.46	4.72	48.70	39.30	12.00	3.00
	60	40	18.32	12.92	5.34	50.08	35.32	14.60	3.41
	40	60	17.48	10.38	5.96	51.69	30.69	17.62	3.98
	30	70	17.06	9.11	6.27	52.59	28.08	19.33	3.92
	20	80	16.64	7.84	6.58	53.57	25.24	21.18	3.64
	10	90	16.22	6.57	6.89	54.65	22.14	23.21	3.88
	0	100	15.8	5.3	7.2	55.83	18.73	25.44	2.80
1	propylene carbonate (100)	isobutyl acetate (0)	20	18	4.1	47.51	42.76	9.74	2.20
	80	20	19.02	15.14	4.54	49.15	39.12	11.73	3.23
	60	40	18.04	12.28	4.98	51.10	34.79	14.11	3.61
	50	50	17.55	10.85	5.2	52.23	32.29	15.48	3.57
	40	60	17.06	9.42	5.42	53.48	29.53	16.99	3.74
	30	70	16.57	7.99	5.64	54.87	26.46	18.68	3.88
	20	80	16.08	6.56	5.86	56.42	23.02	20.56	3.38
	0	100	15.1	3.7	6.3	60.16	14.74	25.10	2.80
1	propylene carbonate (100)	cyclopenyl methyl ether (0)	20	18	4.1	47.51	42.76	9.74	2.20
	80	20	19.34	15.26	4.14	49.92	39.39	10.69	3.40
	60	40	18.68	12.52	4.18	52.80	35.39	11.81	4.05
	40	60	18.02	9.78	4.22	56.28	30.54	13.18	4.71
	20	80	17.36	7.04	4.26	60.57	24.56	14.86	4.47
	10	90	17.03	5.67	4.28	63.12	21.02	15.86	3.81
	5	95	16.865	4.985	4.29	64.52	19.07	16.41	3.76
	0	100	16.7	4.3	4.3	66.01	17.00	17.00	2.80
1	methanol (100)	isobutyl acetate (0)	14.7	12.3	22.3	29.82	24.95	45.23	1.80
	70	30	14.82	9.72	17.5	35.25	23.12	41.63	2.84
	50	50	14.9	8	14.3	40.05	21.51	38.44	2.81
	30	70	14.98	6.28	11.1	46.29	19.41	34.30	3.41
	10	90	15.06	4.56	7.9	54.72	16.57	28.71	3.38
	0	100	14.9	4.5	8.2	53.99	16.30	29.71	2.80
3	DCM (100)	1,2-dichlorobenzene (0)	17	7.3	7.1	54.14	23.25	22.61	5.78
	75	25	17.55	7.05	6.15	57.07	22.93	20.00	5.77
	50	50	18.1	6.8	5.2	60.13	22.59	17.28	5.54
	25	75	18.65	6.55	4.25	63.33	22.24	14.43	5.36
	0	100	19.2	6.3	3.3	66.67	21.88	11.46	5.36
1	DMF (100)	1,2-dichlorobenzene (0)	17.4	13.7	11.3	41.04	32.31	26.65	4.85
	75	25	17.85	11.85	9.3	45.77	30.38	23.85	5.07
	50	50	18.3	10	7.3	51.40	28.09	20.51	5.66
	25	75	18.75	8.15	5.3	58.23	25.31	16.46	5.30
	0	100	19.2	6.3	3.3	66.67	21.88	11.46	5.36
1	acetonitrile (100)	toluene (0)	15.3	18	6.1	38.83	45.69	15.48	2.94
	80	20	15.84	14.68	5.28	44.25	41.01	14.75	3.89

	60	40	16.38	11.36	4.46	50.87	35.28	13.85	4.76
	40	60	16.92	8.04	3.64	59.16	28.11	12.73	5.01
	20	80	17.46	4.72	2.82	69.84	18.88	11.28	4.81
	0	100	18	1.4	2	84.11	6.54	9.35	3.87
2	propylene carbonate (100)	1,2-dichlorobenzene (0)	20	18	4.1	47.51	42.76	9.74	2.68
	75	25	19.8	15.075	3.9	51.06	38.88	10.06	3.45
	50	50	19.6	12.15	3.7	55.29	34.27	10.44	4.12
	25	75	19.4	9.225	3.5	60.39	28.72	10.89	4.94
	0	100	19.2	6.3	3.3	66.67	21.88	11.46	5.36
2	1,2-dichlorobenzene (100)	heptane (0)	19.2	6.3	3.3	66.67	21.88	11.46	5.36
	75	25	18.225	4.725	2.475	71.68	18.58	9.73	4.87
	50	50	17.25	3.15	1.65	78.23	14.29	7.48	3.87
	25	75	16.275	1.575	0.825	87.15	8.43	4.42	3.03
	0	100	15.3	0	0	100.00	0.00	0.00	1.97
1	propylene carbonate (100)	acetonitrile (0)	20	18	4.1	47.51	42.76	9.74	2.20
	75	25	18.825	18	4.6	45.44	43.45	11.10	2.85
	50	50	17.65	18	5.1	43.31	44.17	12.52	3.04
	25	75	16.475	18	5.6	41.11	44.92	13.97	2.97
	0	100	15.3	18	6.1	38.83	45.69	15.48	2.94
1	isopropyl acetate (100)	acetonitrile (0)	14.9	4.5	8.2	53.99	16.30	29.71	2.20
	75	25	15	7.875	7.675	49.10	25.78	25.12	3.26
	50	50	15.1	11.25	7.15	45.07	33.58	21.34	3.59
	25	75	15.2	14.625	6.625	41.70	40.12	18.18	2.63
	0	100	15.3	18	6.1	38.83	45.69	15.48	2.94
2	furfuryl alcohol (100)	cyclopentanone (0)	17.4	7.6	15.1	43.39	18.95	37.66	5.69
	70	30	17.55	8.89	12.13	45.50	23.05	31.45	5.33
	50	50	17.65	9.75	10.15	47.00	25.97	27.03	5.28
	30	70	17.75	10.61	8.17	48.59	29.04	22.37	5.34
	0	100	17.9	11.9	5.2	51.14	34.00	14.86	5.02
S	water (100)	DMF (0)	15.5	16	42.3	21.00	21.68	57.32	2.01
	80	20	15.88	15.54	36.1	23.52	23.02	53.47	1.90
	60	40	16.26	15.08	29.9	26.55	24.62	48.82	1.86
	50	50	16.45	14.85	26.8	28.31	25.56	46.13	1.88
	40	60	16.64	14.62	23.7	30.28	26.60	43.12	1.93
	20	80	17.02	14.16	17.5	34.96	29.09	35.95	2.09
	10	90	17.21	13.93	14.4	37.79	30.59	31.62	2.86
	0	100	17.4	13.7	11.3	41.04	32.31	26.65	4.85
2	TMO (100)	cyclopentanone (0)	15.4	2.4	2.1	77.39	12.06	10.55	2.12
	70	30	16.15	5.25	3.03	66.11	21.49	12.40	3.16
	50	50	16.65	7.15	3.65	60.66	26.05	13.30	4.15

	30	70	17.15	9.05	4.27	56.28	29.70	14.01	4.74
	0	100	17.9	11.9	5.2	51.14	34.00	14.86	5.02
2	methanol (100)	dimethyl isosorbide (0)	14.7	12.3	22.3	29.82	24.95	45.23	1.80
	70	30	15.57	10.74	17.86	35.25	24.32	40.43	3.46
	50	50	16.15	9.7	14.9	39.63	23.80	36.56	3.98
	30	70	16.73	8.66	11.94	44.82	23.20	31.98	4.45
	10	90	17.31	7.62	8.98	51.05	22.47	26.48	4.60
	0	100	17.6	7.1	7.5	54.66	22.05	23.29	5.20

Table 5-6: Resin swelling results of pure solvents (carbon disulphide and chlorobenzene) and their Hansen solubility parameters

Resin	Solvent	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
Merrifield resin	CS_2	0.50	0.50	0.50	0.1016	0.10	3.94	0.00
	chlorobenzene	0.71	0.70	0.70	0.1040	0.12	5.61	0.06
HypoGel™ 200 resin	CS_2	0.40	0.42	0.40	0.1020	0.11	2.91	0.13
	chlorobenzene	0.59	0.59	0.60	0.1019	0.11	4.74	0.07

Solvent	dD	dP	dH	fd	fp	fh
CS_2	20.2	0.00	0.60	97.12	0.00	2.88
chlorobenzene	19	4.30	2.00	43.39	18.95	37.66

5.2. Appendix B

5.2.1. All line graphs of solvent systems for Merrifield resin

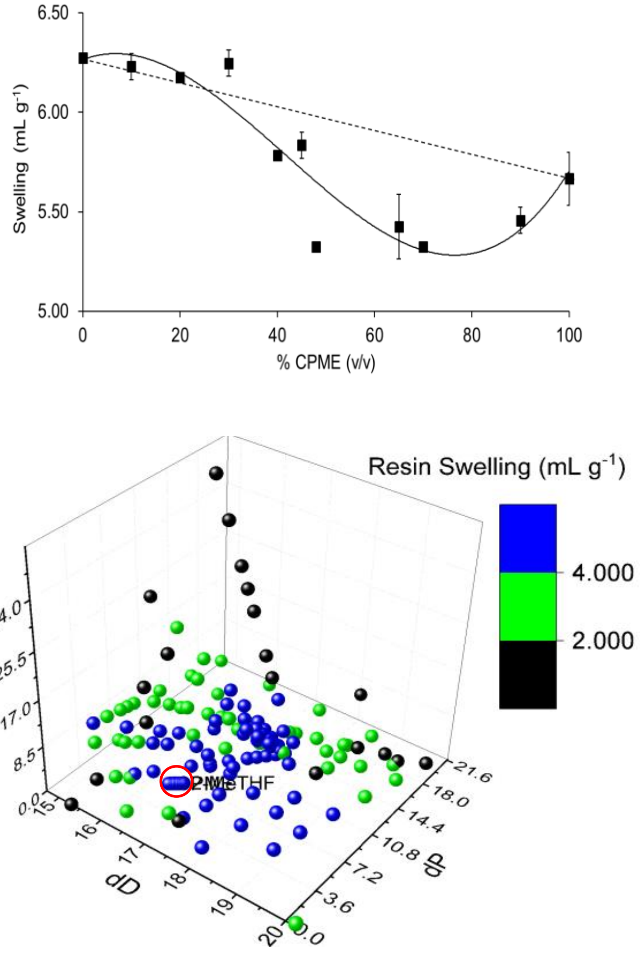


Figure 5-1: Line graph showing the resin swelling changes by changing the 2-MeTHF and cyclopentyl methyl ether (CPME) (v/v) ratio

Table 5-7: Resin swelling data used to construct Figure 5-1

Merrifield resin in 2MeTHF and CPME							
%CPME	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.80	0.80	0.80	0.1020	0.16	6.27	0.00
10	0.80	0.80	0.79	0.1022	0.16	6.23	0.07
20	0.79	0.79	0.79	0.1020	0.16	6.18	0.00
30	0.79	0.80	0.79	0.1014	0.16	6.25	0.07
40	0.75	0.75	0.75	0.1020	0.16	5.78	0.00
45	0.70	0.69	0.69	0.1017	0.10	5.83	0.07
48	0.70	0.70	0.70	0.1014	0.16	5.33	0.00
65	0.73	0.70	0.71	0.1020	0.16	5.42	0.16
70	0.70	0.70	0.70	0.1014	0.16	5.33	0.00
90	0.72	0.71	0.71	0.1014	0.16	5.46	0.07
100	0.70	0.68	0.68	0.1000	0.12	5.67	0.13

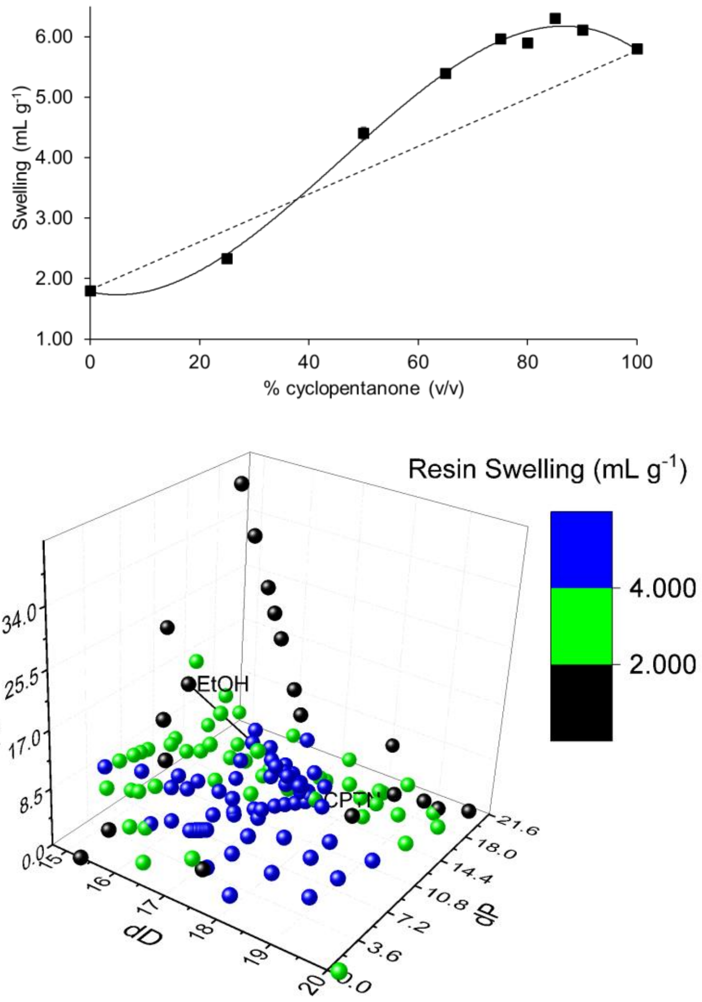


Figure 5-2 Line graph showing the resin swelling changes by changing the ethanol (EtOH) and cyclopentanone (CPTN) (v/v) ratio

Table 5-8: Resin swelling data used to construct Figure 5-2

			Merrifield resin in EtOH and cyclopentanone				
%cyclopentanone	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
25	0.40	0.39	0.40	0.1014	0.16	2.33	0.07
50	0.60	0.62	0.61	0.1022	0.16	4.40	0.10
65	0.71	0.71	0.71	0.1020	0.16	5.39	0.00
75	0.71	0.72	0.72	0.1000	0.12	5.97	0.07
80	0.70	0.70	0.70	0.1017	0.10	5.90	0.00
85	0.80	0.80	0.80	0.1014	0.16	6.31	0.00
90	0.78	0.79	0.78	0.1020	0.16	6.11	0.07
100			Literature data			5.80	0.00

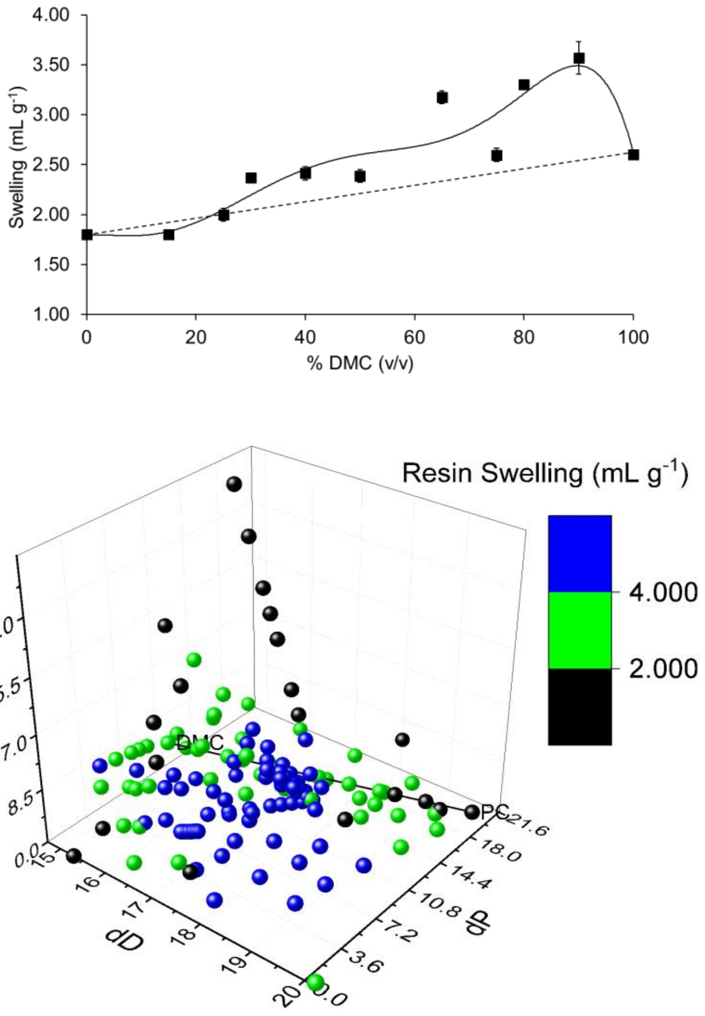


Figure 5-3: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and dimethyl carbonate (DMC) (v/v) ratio

Table 5-9: Resin swelling data used to construct Figure 5-3

			Merrifield resin in PC and DMC				
%DMC	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
15	0.30	0.30	0.30	0.1000	0.12	1.80	0.00
25	0.30	0.31	0.30	0.1017	0.10	2.00	0.07
30	0.40	0.40	0.40	0.1014	0.16	2.37	0.00
40	0.41	0.40	0.41	0.1022	0.16	2.41	0.07
50	0.40	0.41	0.40	0.1020	0.16	2.39	0.07
65	0.43	0.42	0.43	0.1022	0.10	3.17	0.07
75	0.43	0.42	0.42	0.1014	0.16	2.60	0.07
80	0.45	0.45	0.45	0.1000	0.12	3.30	0.00
90	0.45	0.48	0.46	0.1018	0.10	3.57	0.16
100			Literature data			2.60	0.00

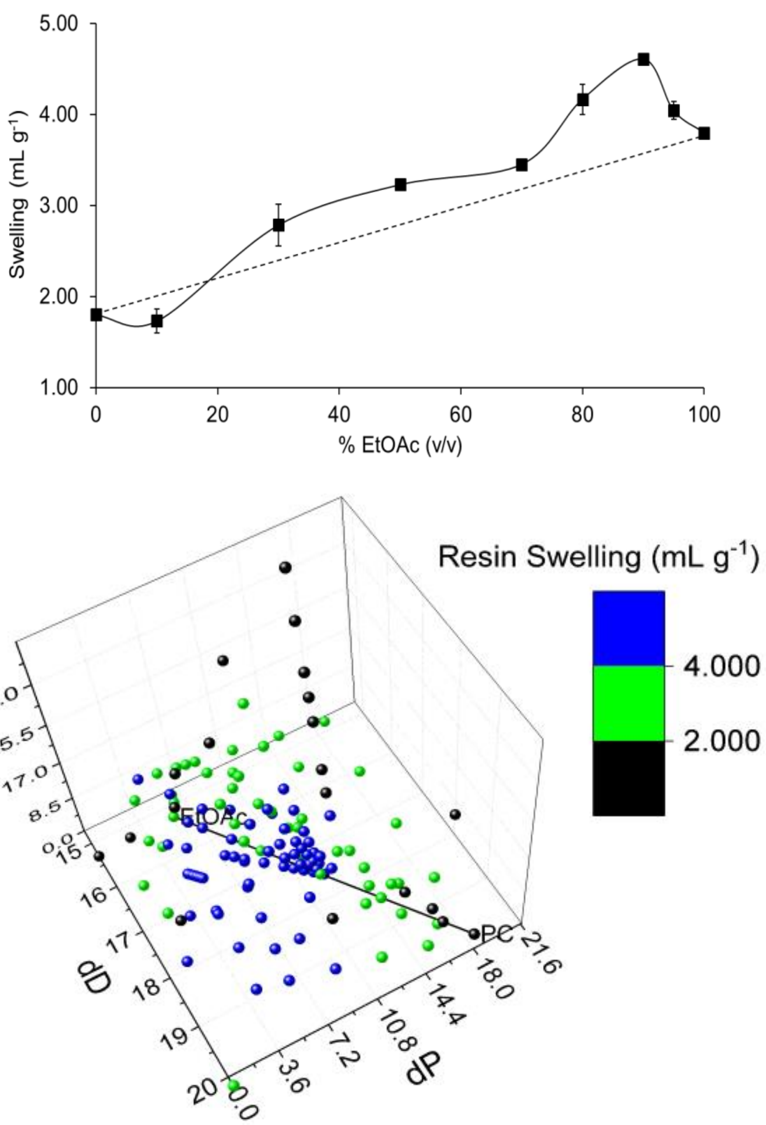


Figure 5-4: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and ethyl acetate (EtOAc) (v/v) ratio

Table 5-10: Resin swelling data used to construct Figure 5-4

			Merrifield resin in PC and EtOAc				
%EtOAc	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
10	0.33	0.35	0.33	0.1020	0.16	1.73	0.13
30	0.40	0.39	0.36	0.1017	0.10	2.79	0.23
50	0.49	0.49	0.49	0.1022	0.16	3.23	0.00
70	0.51	0.51	0.51	0.1014	0.16	3.45	0.00
80	0.55	0.54	0.52	0.1000	0.12	4.17	0.17
90	0.58	0.58	0.58	0.0998	0.12	4.61	0.00
95	0.58	0.56	0.57	0.1014	0.16	4.04	0.10
100			Literature data			3.80	0.00

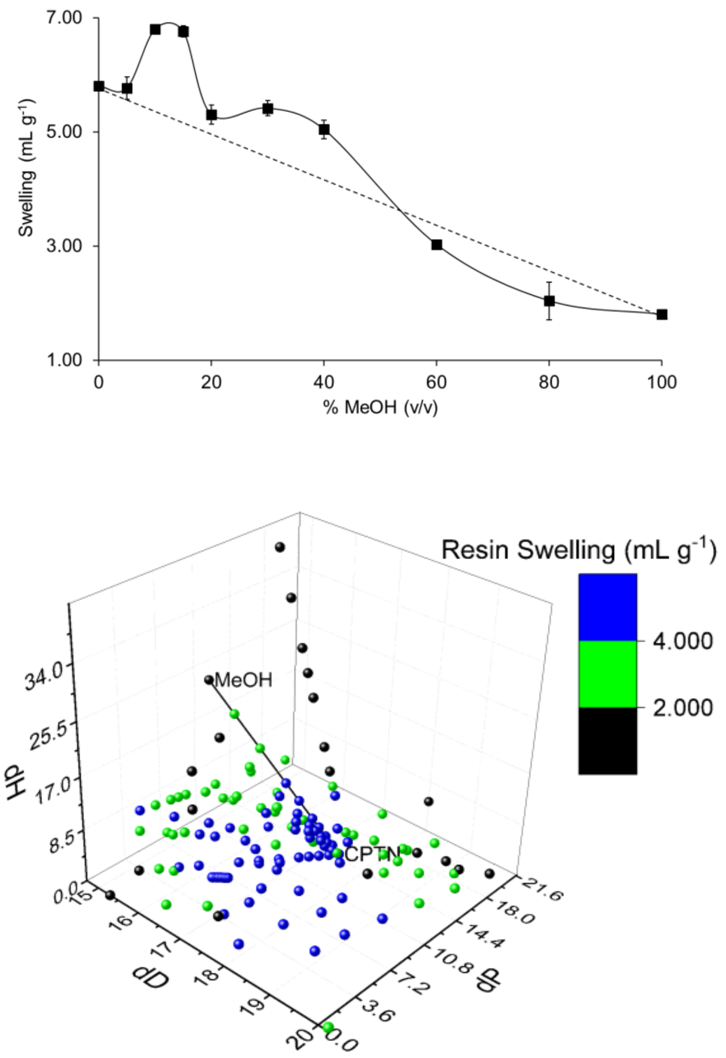


Figure 5-5: Line graph showing the resin swelling changes by changing the cyclopentanone (CPTN) and methanol (MeOH) (v/v) ratio

Table 5-11: Resin swelling data used to construct Figure 5-5

Merrifield resin in cyclopentanone and MeOH							
%MeOH	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			5.80	0.00
5	0.69	0.69	0.66	0.1006	0.10	5.77	0.20
10	0.80	0.80	0.80	0.1000	0.12	6.80	0.00
15	0.81	0.80	0.79	0.1021	0.11	6.76	0.10
20	0.65	0.63	0.62	0.1006	0.10	5.30	0.17
30	0.72	0.72	0.70	0.1022	0.16	5.41	0.13
40	0.60	0.61	0.63	0.1018	0.10	5.04	0.16
60	0.42	0.43	0.43	0.1014	0.12	3.02	0.07
80	0.35	0.35	0.40	0.1014	0.16	2.04	0.33
100			Literature data			1.80	0.00

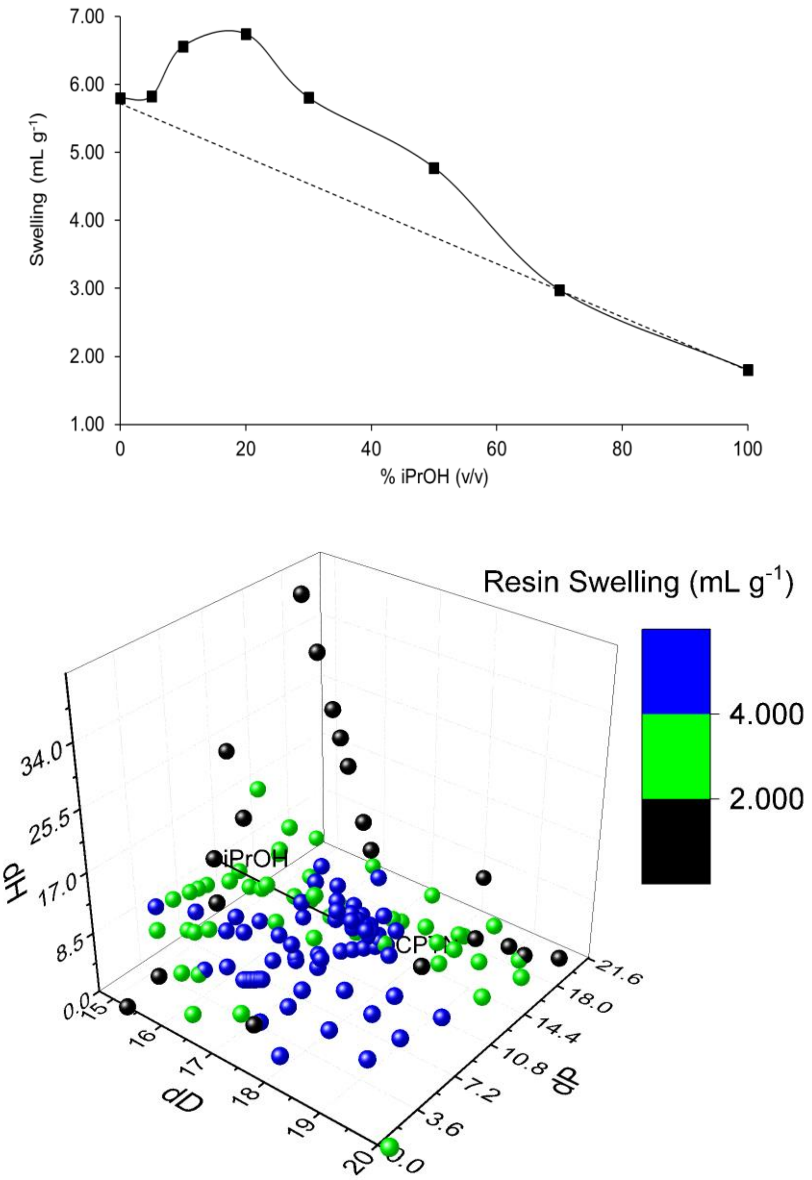


Figure 5-6: Line graph showing the resin swelling changes by changing the cyclopentanone (CPTN) and isopropanol (iPrOH) (v/v) ratio

Table 5-12: Resin swelling data used to construct Figure 5-6

			Merrifield resin in cyclopentanone and iPrOH				
%iPrOH	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			5.80	0.00
5	0.68	0.69	0.69	0.1006	0.10	5.83	0.07
10	0.78	0.78	0.78	0.1021	0.11	6.56	0.00
20	0.79	0.79	0.78	0.1018	0.10	6.75	0.07
30	0.70	0.70	0.70	0.1016	0.11	5.81	0.00
50	0.59	0.60	0.60	0.1019	0.11	4.78	0.07
70	0.41	0.42	0.41	0.1019	0.11	2.98	0.07
100			Literature data			1.80	0.00

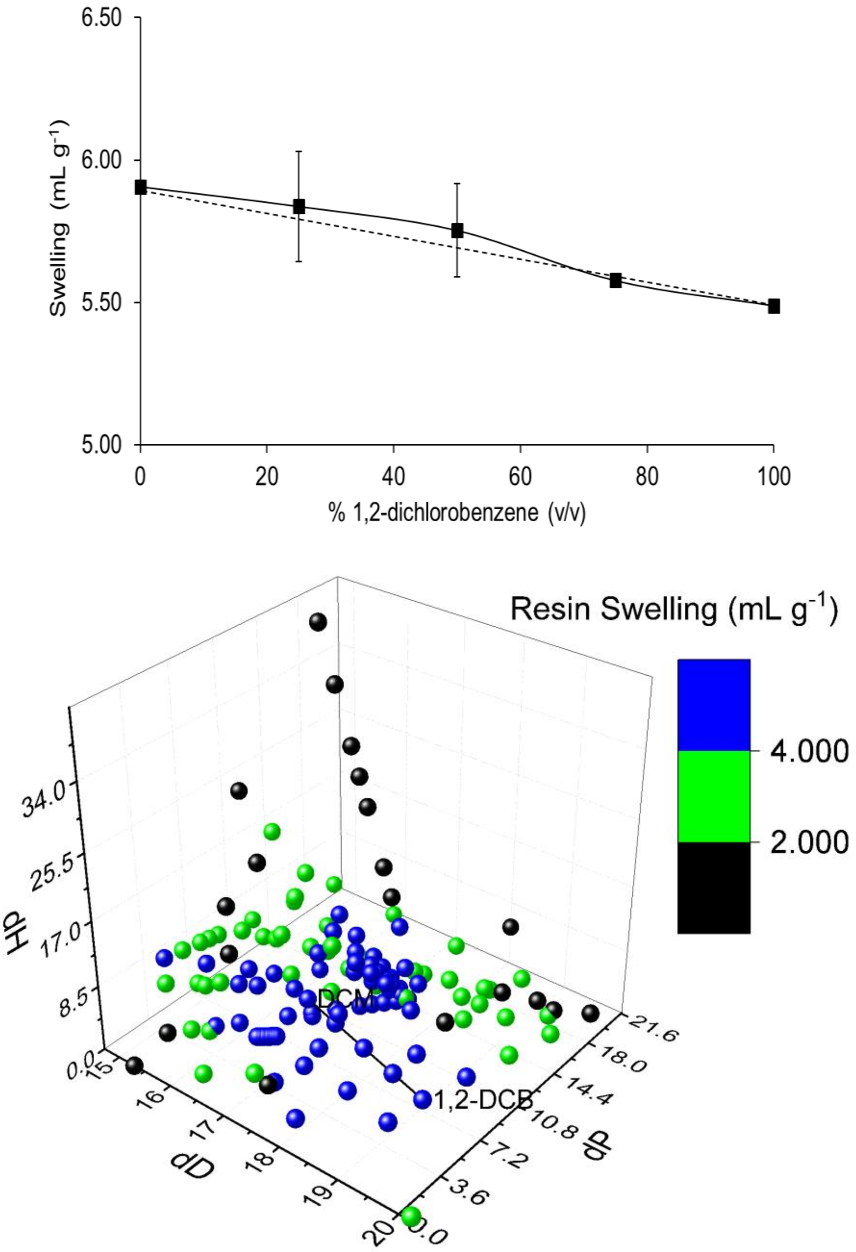


Figure 5-7: Line graph showing the resin swelling changes by changing the dichloromethane (DCM) and 1,2-dichlorobenzene (1,2-DCB) (v/v) ratio

Table 5-13: Resin swelling data used to construct Figure 5-7

Merrifield resin in dichloromethane and 1,2-dichlorobenzene							
%1,2-dichlorobenzene	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.70	0.70	0.70	0.1016	0.10	5.91	0.00
25	0.74	0.71	0.71	0.1028	0.12	5.84	0.19
50	0.71	0.69	0.68	0.1014	0.11	5.75	0.16
75	0.70	0.70	0.70	0.1040	0.12	5.58	0.00
100	0.70	0.70	0.70	0.1002	0.15	5.49	0.00

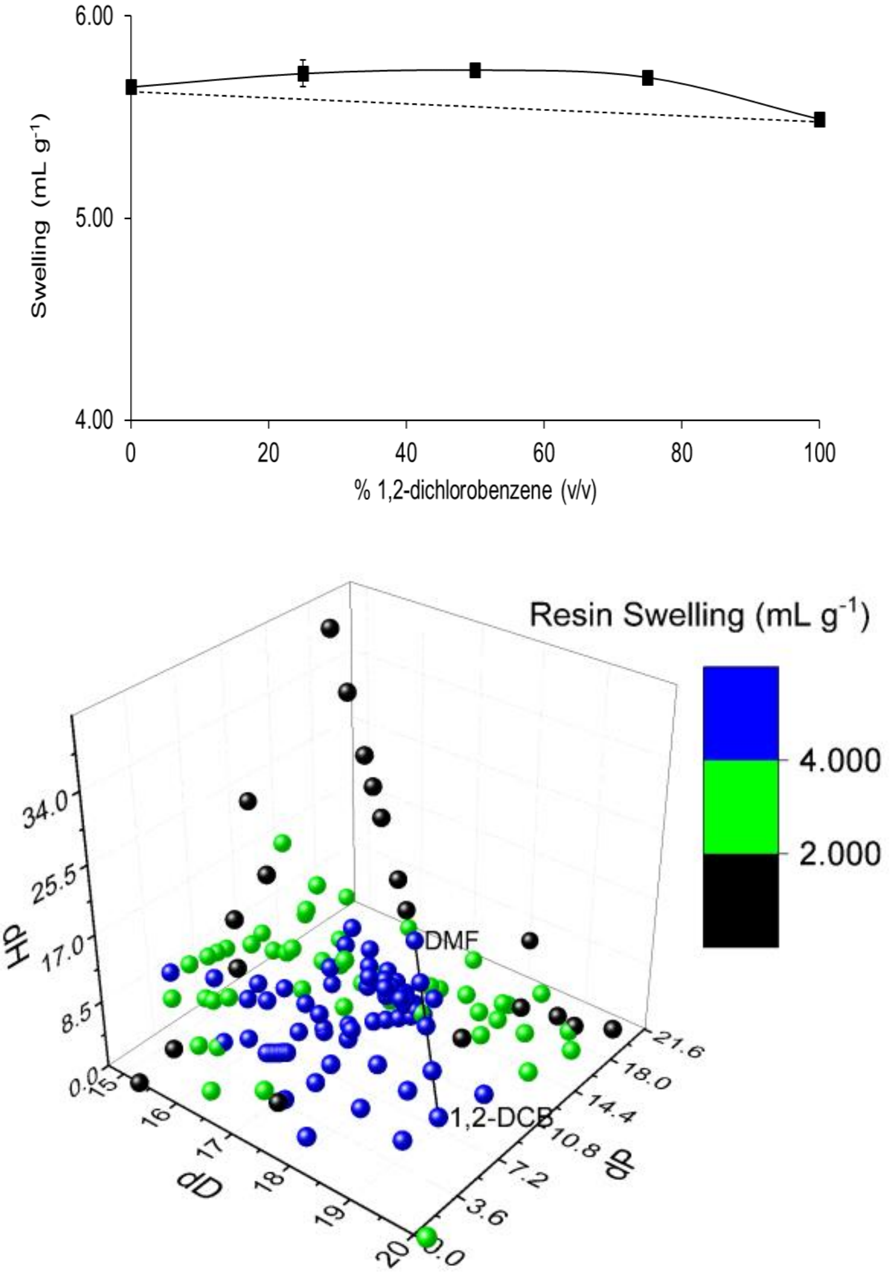


Figure 5-8: Line graph showing the resin swelling changes by changing the dimethylformamide (DMF) and 1,2-dichlorobenzene (1,2-DCB) (v/v) ratio

Table 5-14: Resin swelling data used to construct Figure 5-8

Merrifield resin in DMF and 1,2-dichlorobenzene							
%1,2-dichlorobenzene	Run1 (mL)	Run2 (mL)	Run 3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.70	0.70	0.70	0.1009	0.13	5.65	0.00
25	0.68	0.69	0.68	0.1003	0.11	5.72	0.07
50	0.71	0.71	0.71	0.1029	0.12	5.73	0.00
75	0.70	0.70	0.70	0.1018	0.12	5.70	0.00
100	0.70	0.70	0.70	0.1002	0.15	5.49	0.00

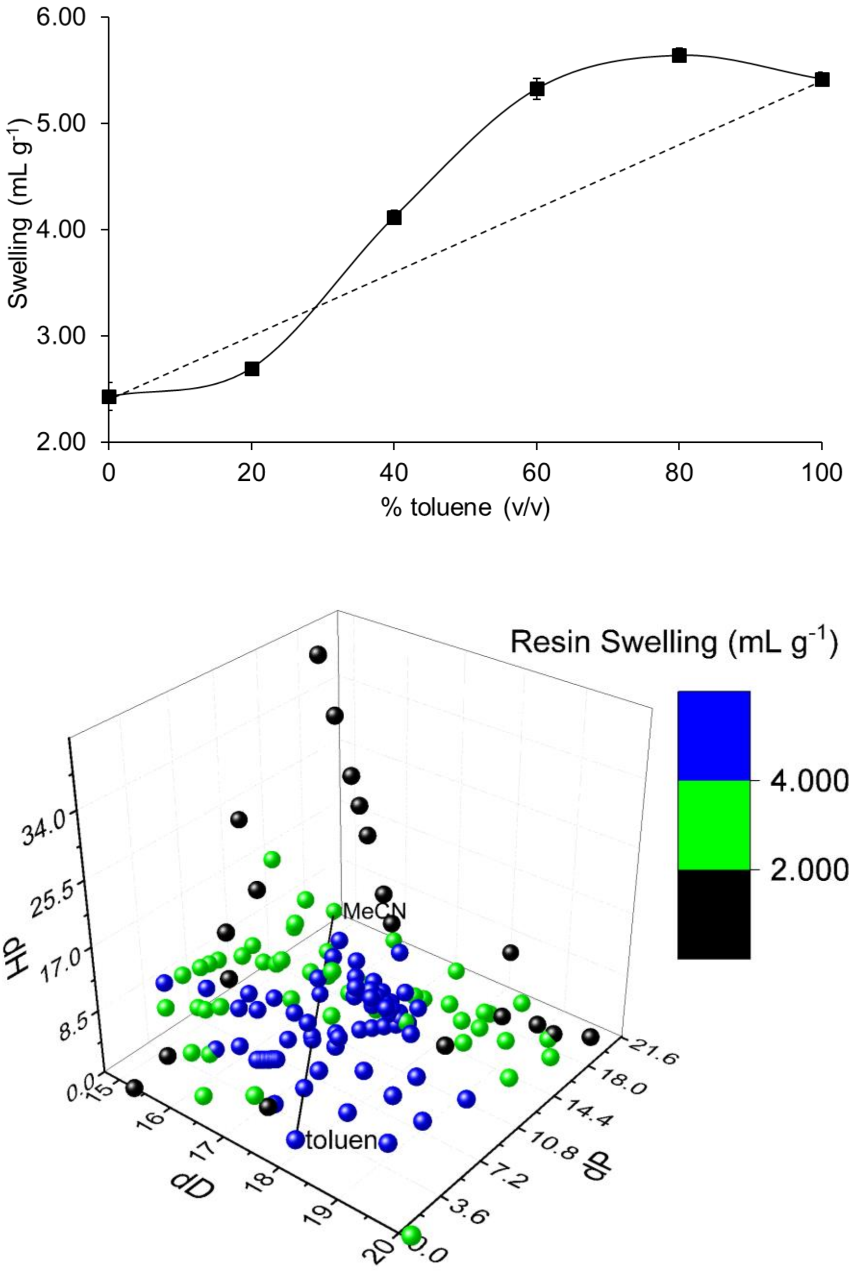


Figure 5-9: Line graph showing the resin swelling changes by changing the acetonitrile (MeCN) and toluene (v/v) ratio

Table 5-15: Resin swelling data used to construct Figure 5-9

				Merrifield resin in acetonitrile and toluene			
%toluene	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.34	0.36	0.34	0.1016	0.10	2.43	0.13
20	0.42	0.42	0.42	0.1002	0.15	2.69	0.00
40	0.54	0.54	0.55	0.1028	0.12	4.12	0.06
60	0.65	0.64	0.66	0.1014	0.11	5.33	0.10
80	0.71	0.70	0.71	0.1040	0.12	5.64	0.06
100	0.68	0.68	0.67	0.1009	0.13	5.42	0.07

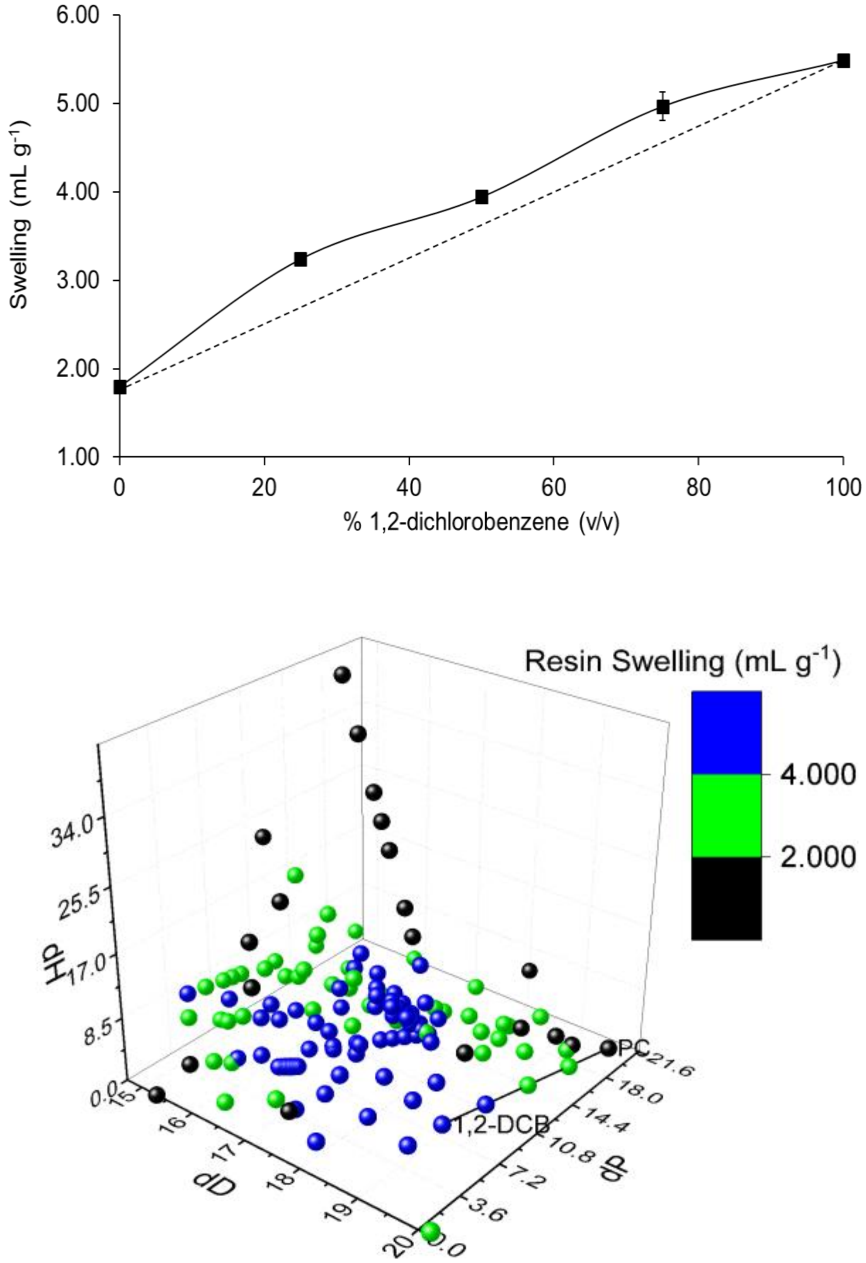


Figure 5-10: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and 1,2-dichlorobenzene (1,2-DCB) (v/v) ratio

Table 5-16: Resin swelling data used to construct Figure 5-10

Merrifield resin in PC and 1,2-dichlorobenzene							
%1,2-dichlorobenzene	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
25	0.46	0.45	0.45	0.1028	0.12	3.24	0.06
50	0.51	0.51	0.51	0.1014	0.11	3.94	0.00
75	0.65	0.62	0.64	0.1040	0.12	4.97	0.16
100	0.70	0.70	0.70	0.1002	0.15	5.49	0.00

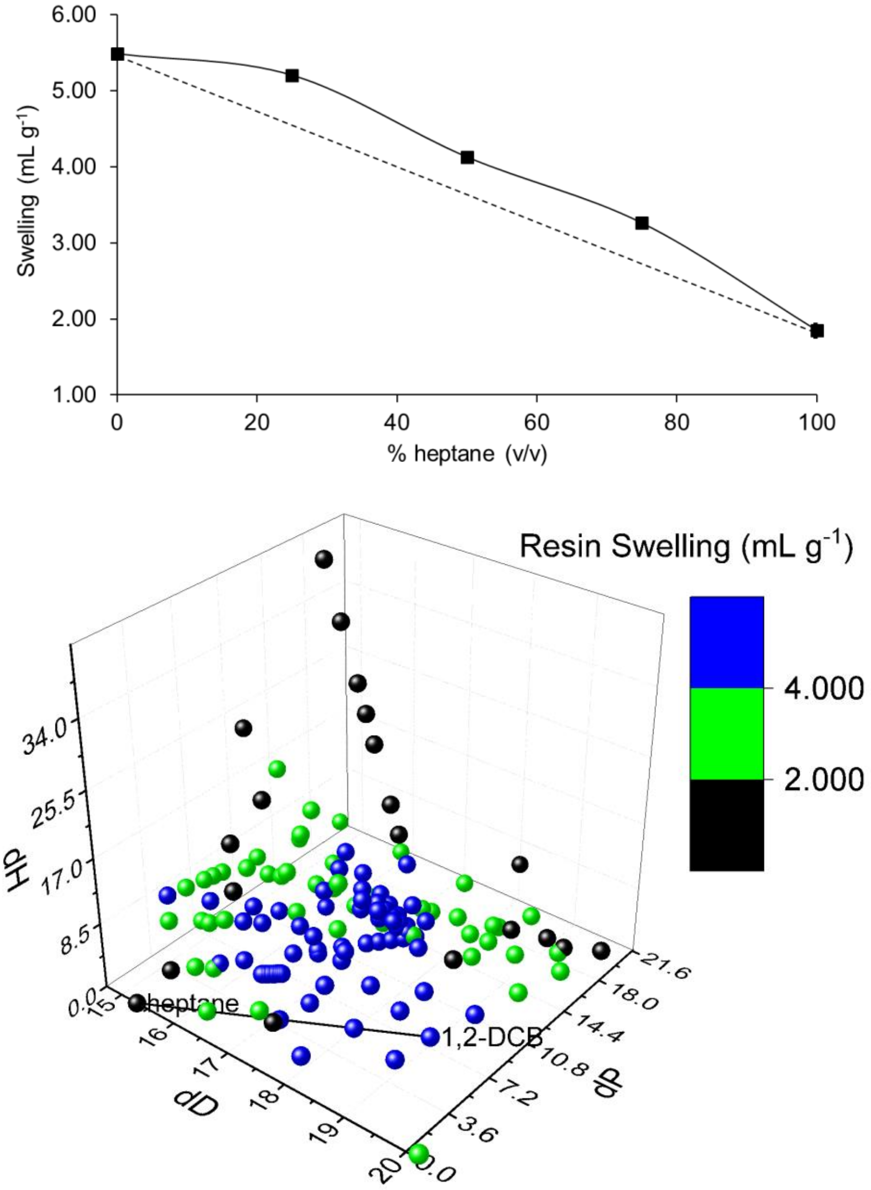


Figure 5-11: Line graph showing the resin swelling changes by changing the 1,2-dichlorobenzene (1,2-DCB) and heptane (v/v) ratio

Table 5-17: Resin swelling data used to construct Figure 5-11

Merrifield resin in 1,2-dichlorobenzene and heptane							
%heptane	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.70	0.70	0.70	0.1002	0.15	5.49	0.00
25	0.65	0.65	0.65	0.1018	0.12	5.21	0.00
50	0.55	0.55	0.54	0.1009	0.13	4.13	0.07
75	0.47	0.48	0.48	0.1002	0.15	3.26	0.07
100	0.31	0.32	0.30	0.1029	0.12	1.85	0.10

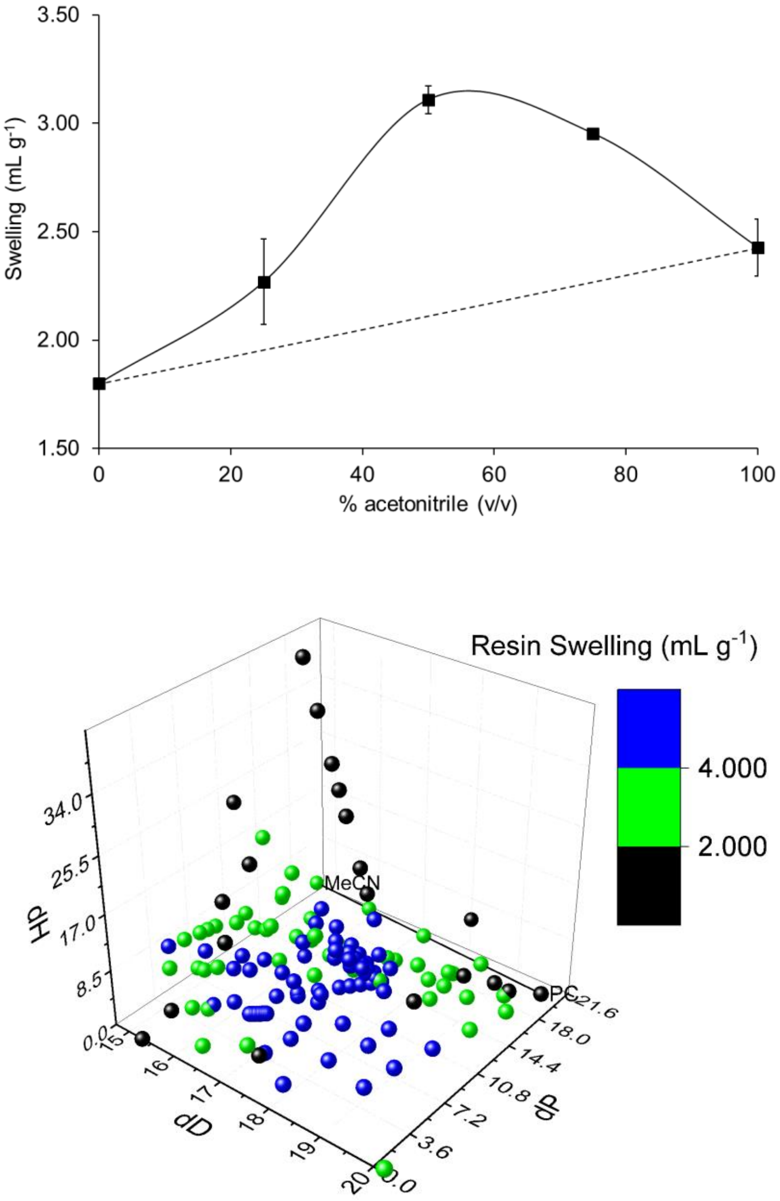


Figure 5-12: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and acetonitrile (MeCN) (v/v) ratio

Table 5-18: Resin swelling data used to construct Figure 5-12

			Merrifield resin in PC and MeCN				
%MeCN	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
25	0.32	0.36	0.34	0.10	0.11	2.27	0.20
50	0.44	0.44	0.45	0.10	0.12	3.11	0.06
75	0.40	0.40	0.40	0.10	0.10	2.95	0.00
100	0.34	0.36	0.34	0.10	0.10	2.43	0.13

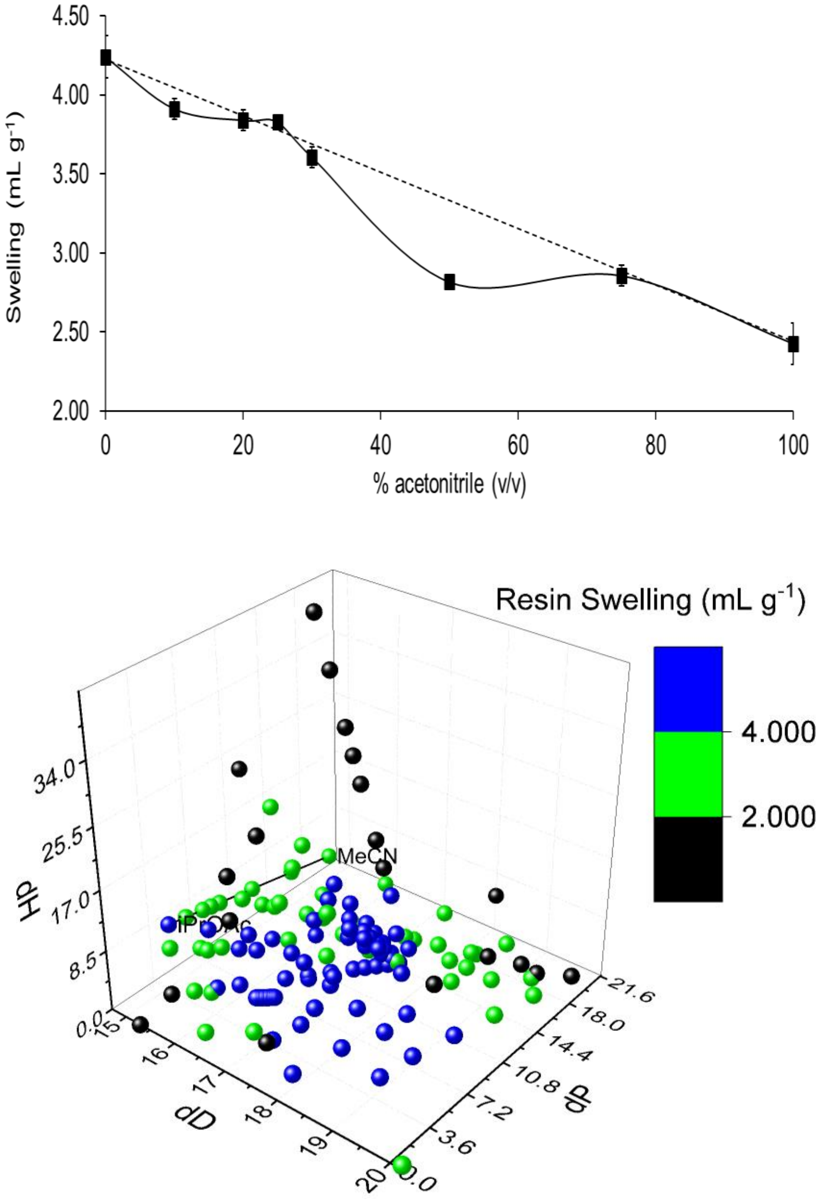


Figure 5-13 Line graph showing the resin swelling changes by changing the isopropyl acetate (iPrOAc) and acetonitrile (MeCN) (v/v) ratio

Table 5-19: Resin swelling data used to construct Figure 5-13

			Merrifield resin in iPrOAc and MeCN				
%MeCN	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.55	0.53	0.55	0.0998	0.12	4.24	0.13
10	0.51	0.51	0.52	0.1005	0.12	3.91	0.07
20	0.50	0.51	0.50	0.0998	0.12	3.84	0.07
25	0.51	0.51	0.51	0.1018	0.12	3.83	0.00
30	0.48	0.49	0.48	0.1007	0.12	3.61	0.07
50	0.41	0.41	0.41	0.1029	0.12	2.82	0.00
75	0.39	0.40	0.40	0.1003	0.11	2.86	0.07
100	0.34	0.36	0.34	0.1016	0.10	2.43	0.13

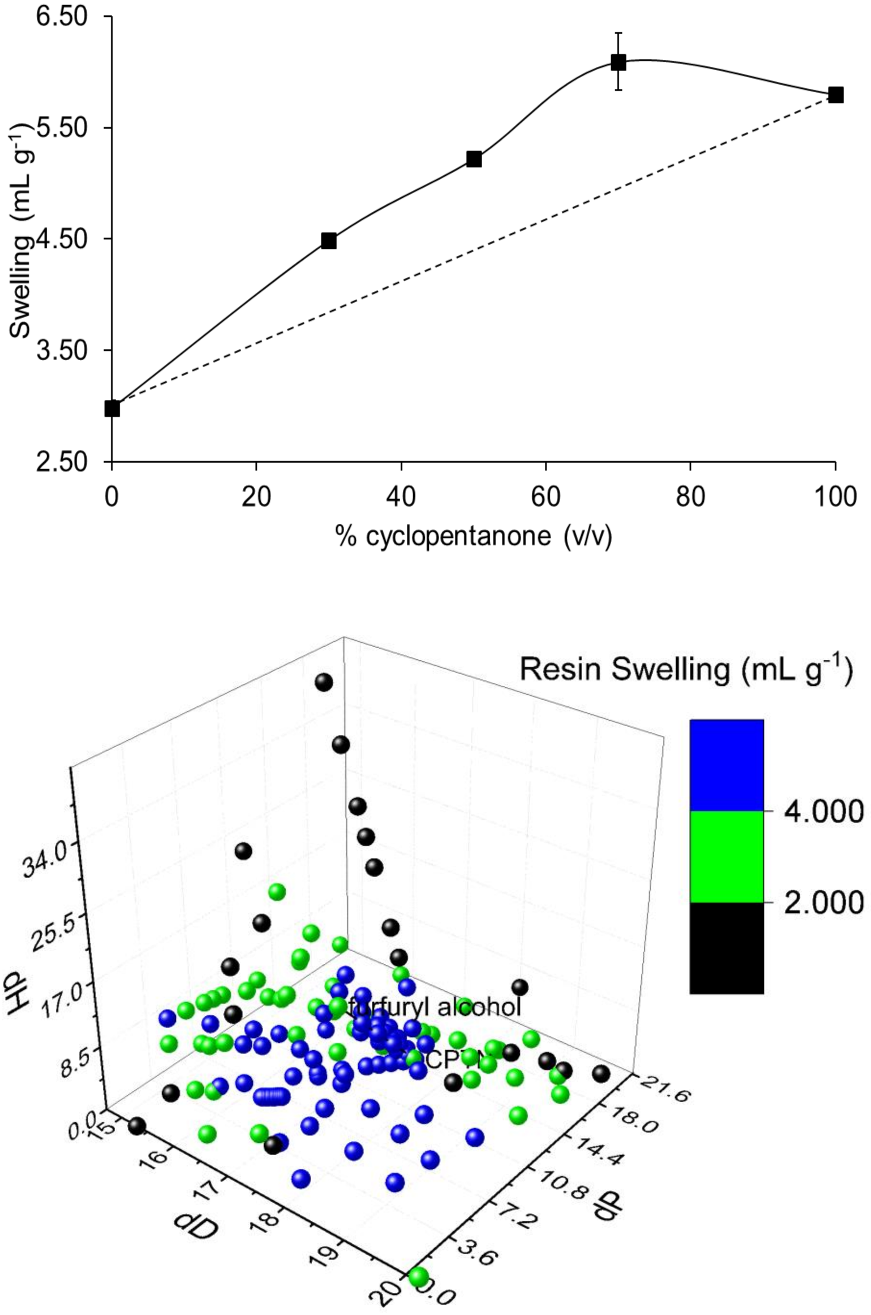


Figure 5-14: Line graph showing the resin swelling changes by changing the furfuryl alcohol and cyclopentanone (CPTN) (v/v) ratio

Table 5-20: Resin swelling data used to construct Figure 5-14

	Merrifield resin in furfurylOH and cyclopentanone						
%cyclopentanone	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.41	0.40	0.40	0.1016	0.10	2.99	0.07
30	0.60	0.60	0.60	0.1002	0.15	4.49	0.00
50	0.65	0.66	0.66	0.1028	0.12	5.22	0.06
70	0.74	0.78	0.74	0.1040	0.12	6.09	0.26
100	Literature data					5.80	0.00

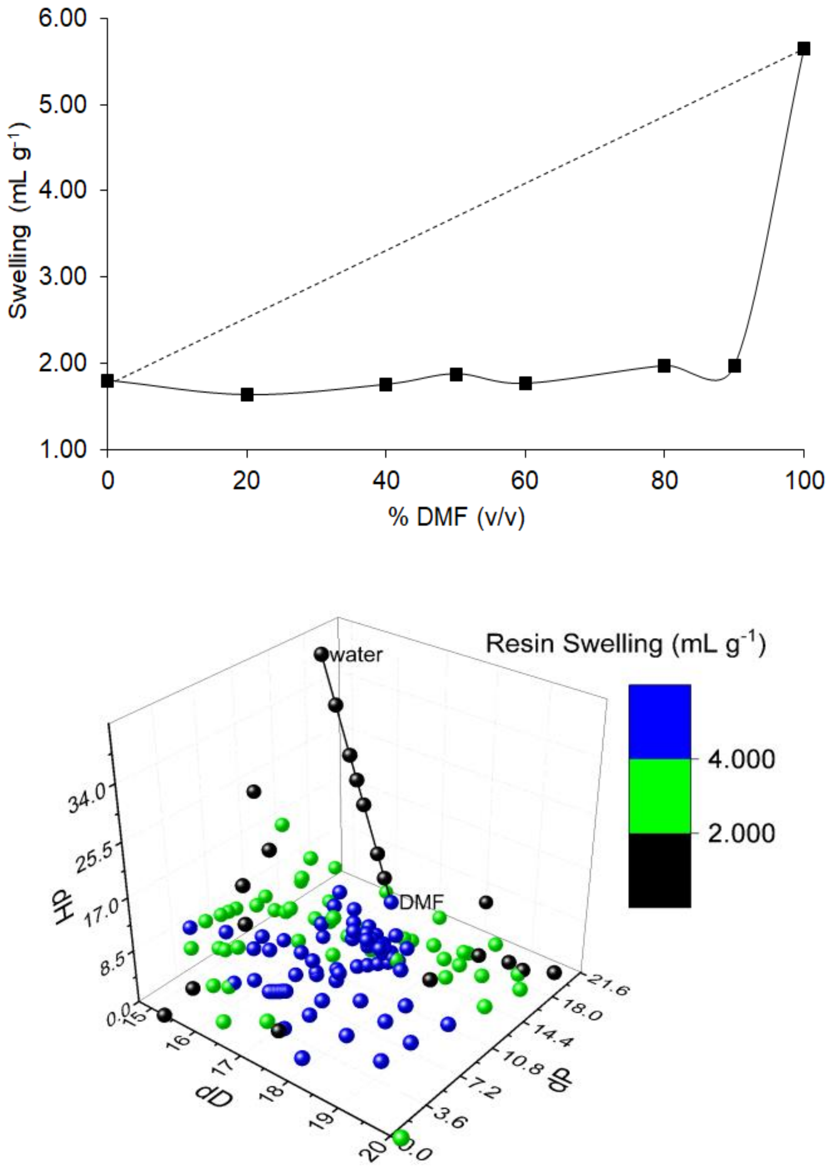


Figure 5-15: Line graph showing the resin swelling changes by changing the water and dimethylformamide (DMF) (v/v) ratio

Table 5-21: Resin swelling data used to construct Figure 5-15

			Merrifield resin in water and DMF				
%DMF	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
20	0.32	0.31	0.31	0.1002	0.15	1.63	0.07
40	0.30	0.30	0.30	0.1028	0.12	1.75	0.00
50	0.30	0.30	0.30	0.1014	0.11	1.87	0.00
60	0.31	0.30	0.30	0.1040	0.12	1.76	0.06
80	0.30	0.30	0.30	0.1016	0.10	1.97	0.00
90	0.32	0.32	0.32	0.1017	0.12	1.97	0.00
100	0.70	0.70	0.70	0.1009	0.13	5.65	0.00

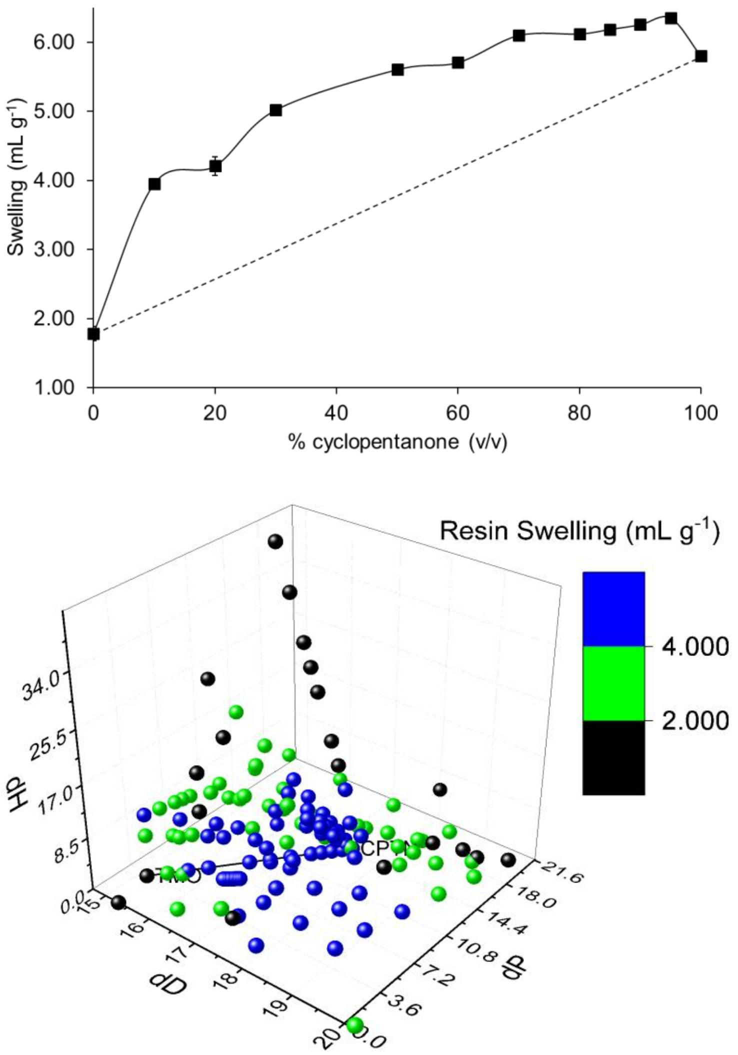


Figure 5-16: Line graph showing the resin swelling changes by changing the TMO and cyclopentanone (CPTN) (v/v) ratio

Table 5-22: Resin swelling data used to construct Figure 5-16

		Merrifield resin in TMO and cyclopentanone					
%cyclopentanone	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.32	0.30	0.31	0.1009	0.13	1.78	0.10
10	0.52	0.52	0.52	0.1012	0.12	3.95	0.00
20	0.55	0.53	0.55	0.1006	0.12	4.21	0.13
30	0.62	0.62	0.62	0.0996	0.12	5.02	0.00
50	0.70	0.69	0.70	0.1029	0.12	5.60	0.06
60	0.69	0.72	0.71	0.1028	0.12	5.71	0.16
70	0.72	0.71	0.75	0.1011	0.11	6.10	0.23
80	0.76	0.76	0.75	0.1040	0.12	6.12	0.06
85	0.75	0.76	0.76	0.1029	0.12	6.19	0.06
90	0.73	0.76	0.72	0.1002	0.11	6.25	0.23
95	0.76	0.76	0.78	0.1018	0.12	6.35	0.13
100			Literature data			5.80	0.00

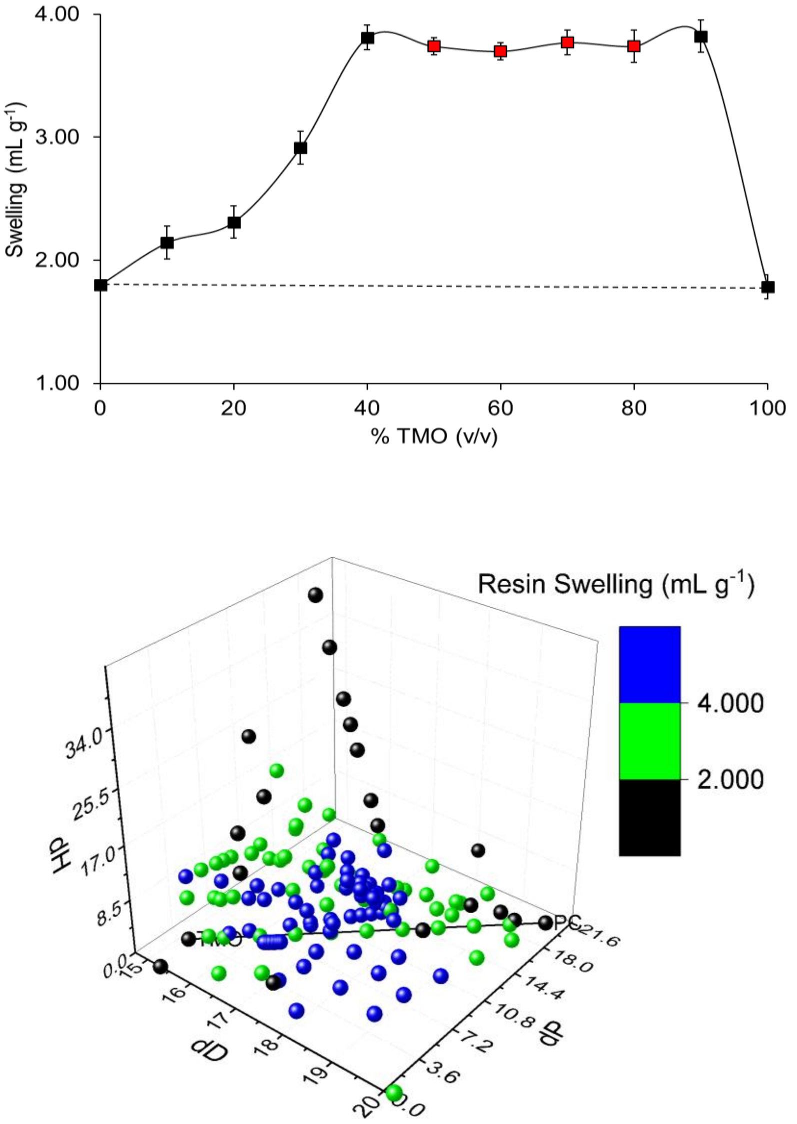


Figure 5-17: Line graph showing the resin swelling changes by changing the TMO and propylene carbonate (PC) (v/v) ratio

Table 5-23: Resin swelling data used to construct Figure 5-17

				Merrifield resin in propylene carbonate and TMO				
Miscibility	%TMO	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
	0	Literature data					1.80	0.00
	10	0.32	0.34	0.34	0.0996	0.12	2.14	0.13
	20	0.34	0.36	0.36	0.1010	0.12	2.31	0.13
	30	0.42	0.42	0.40	0.1006	0.12	2.92	0.13
immiscible	40	0.49	0.50	0.51	0.0998	0.12	3.81	0.10
	50	0.49	0.49	0.50	0.0998	0.12	3.74	0.07
	60	0.49	0.49	0.50	0.1008	0.12	3.70	0.07
	70	0.49	0.50	0.51	0.1007	0.12	3.77	0.10
	80	0.51	0.49	0.49	0.1006	0.12	3.74	0.13
	90	0.52	0.50	0.50	0.1012	0.12	3.82	0.13
	100	0.32	0.30	0.31	0.1009	0.13	1.78	0.10

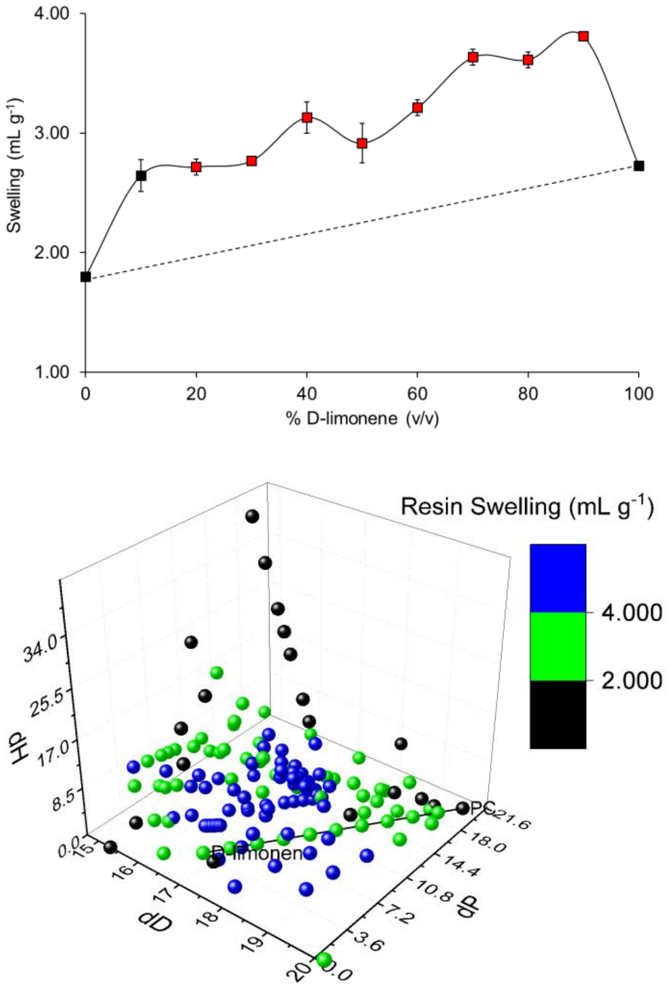


Figure 5-18: Line graph showing the resin swelling changes by changing the D-limonene and propylene carbonate (PC) (v/v) ratio

Table 5-24: Resin swelling data used to construct Figure 5-18

Merrifield resin in D-limonene and propylene carbonate								
Miscibility	%D-limonene	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
	0	Literature data					1.80	0.00
immiscible	10	0.40	0.38	0.38	0.1008	0.12	2.65	0.13
	20	0.39	0.39	0.40	0.1006	0.12	2.72	0.07
	30	0.40	0.40	0.40	0.1012	0.12	2.77	0.00
	40	0.45	0.43	0.43	0.1012	0.12	3.13	0.13
	50	0.40	0.43	0.41	0.1006	0.12	2.92	0.17
	60	0.44	0.44	0.45	0.1007	0.12	3.21	0.07
	70	0.48	0.49	0.48	0.1000	0.12	3.63	0.07
	80	0.48	0.49	0.48	0.1006	0.12	3.61	0.07
	90	0.50	0.50	0.50	0.0998	0.12	3.81	0.00
	100	0.39	0.39	0.39	0.1200	0.12	2.73	0.00

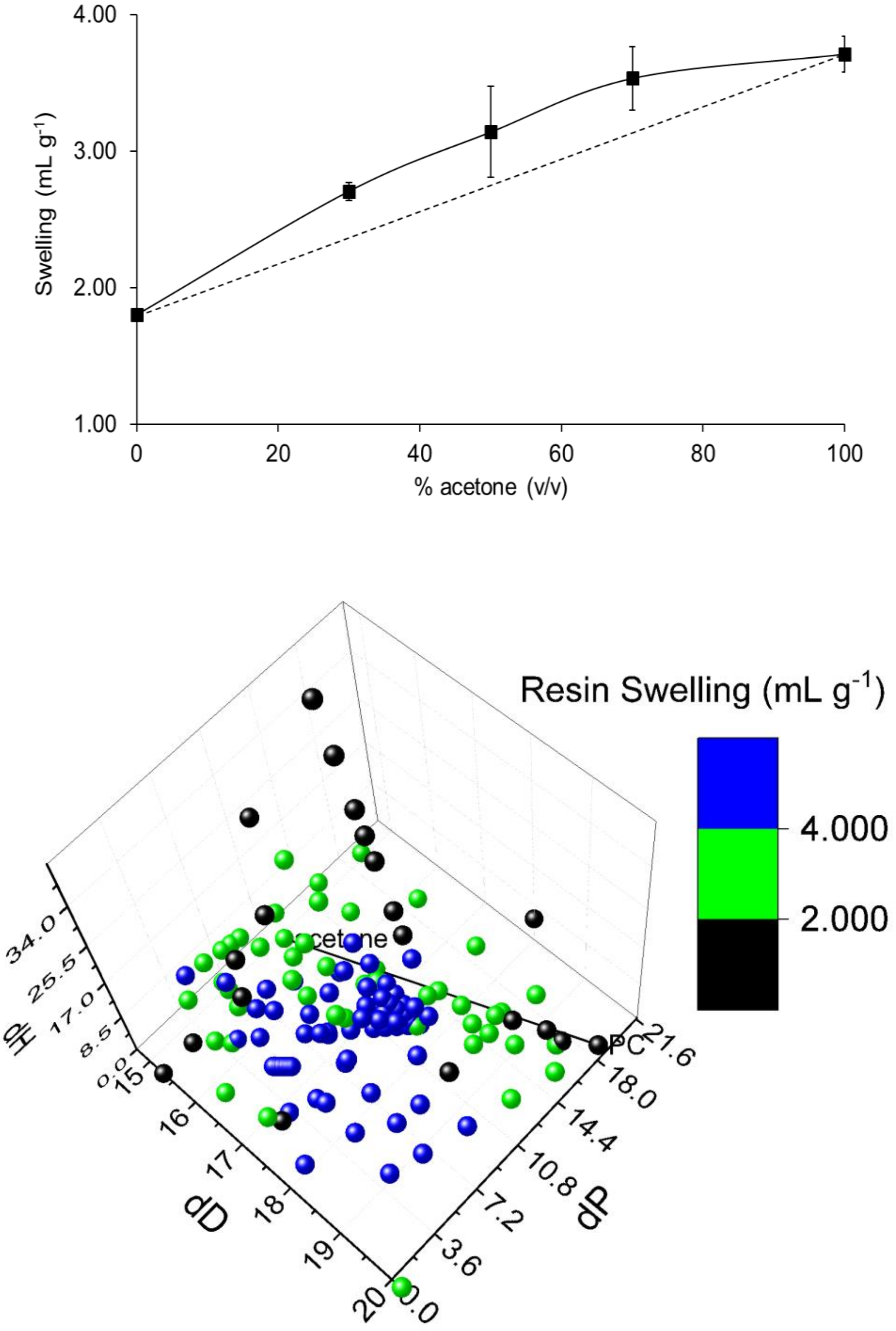


Figure 5-19: Line graph showing the resin swelling changes by changing the acetone and propylene carbonate (PC) (v/v) ratio

Table 5-25: Resin swelling data used to construct Figure 5-19

			Merrifield resin in PC and acetone				
%acetone	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
30	0.4	0.39	0.39	0.101	0.12	2.71	0.07
50	0.4	0.45	0.45	0.0998	0.12	3.14	0.33
70	0.45	0.48	0.49	0.1	0.12	3.53	0.23
100	0.5	0.5	0.48	0.1006	0.12	3.71	0.13

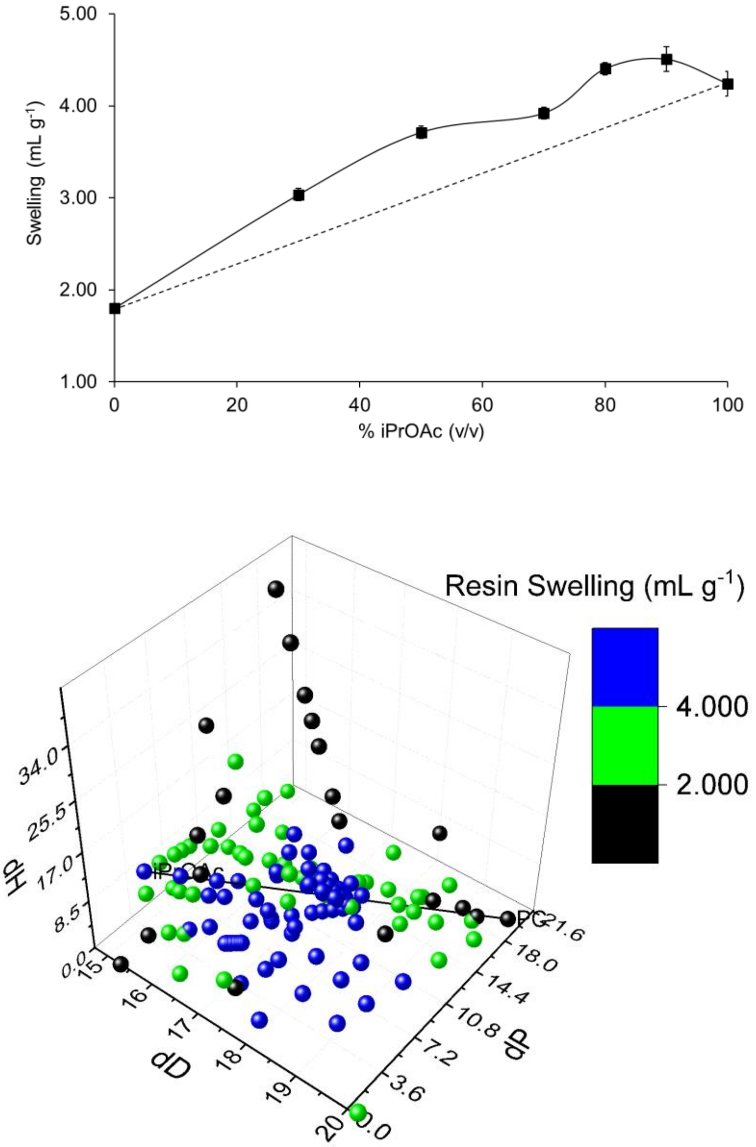


Figure 5-20: Line graph showing the resin swelling changes by changing the isopropyl acetate (iPrOAc) and propylene carbonate (PC) (v/v) ratio

Table 5-26: Resin swelling data used to construct Figure 5-20

			Merrifield resin in PC and iPrOAc				
%iPrOAc	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
30	0.42	0.42	0.43	0.1000	0.12	3.03	0.07
50	0.49	0.49	0.50	0.1006	0.12	3.71	0.07
70	0.52	0.51	0.52	0.1012	0.12	3.92	0.07
80	0.56	0.57	0.56	0.1007	0.12	4.40	0.07
90	0.58	0.58	0.56	0.1006	0.12	4.51	0.13
100	0.55	0.53	0.55	0.0998	0.12	4.24	0.13

5.2.2. All line graphs of solvent systems for HypoGel™200 resin

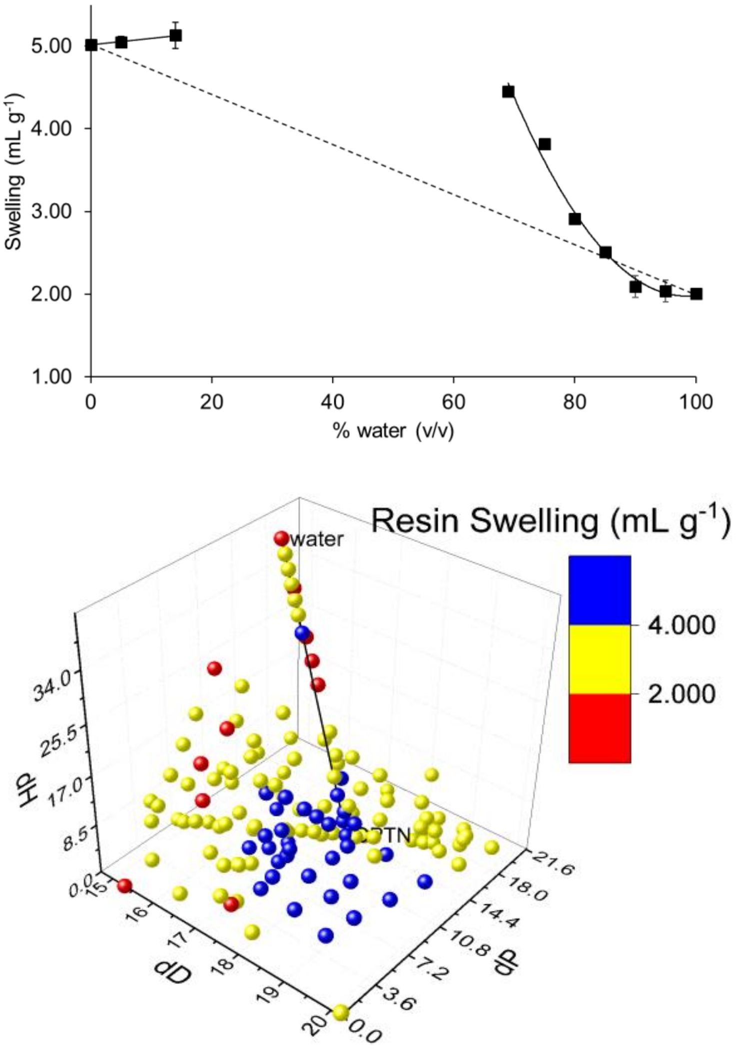


Figure 5-21: Line graph showing the resin swelling changes by changing the cyclopentanone (CPTN) and water (v/v) ratio

Table 5-27: Resin swelling data used to construct Figure 5-21

		HypoGel™200 resin in cyclopentanone and water					
%water (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.60	0.60	0.60	0.0996	0.10	5.02	0.00
5	0.61	0.60	0.60	0.0996	0.10	5.05	0.07
14	0.61	0.64	0.62	0.1021	0.10	5.13	0.16
69	0.61	0.60	0.60	0.0997	0.16	4.45	0.06
75	0.48	0.48	0.48	0.0996	0.10	3.82	0.00
80	0.45	0.45	0.45	0.0997	0.16	2.91	0.00
85	0.36	0.36	0.35	0.1021	0.10	2.51	0.06
90	0.38	0.36	0.36	0.1037	0.15	2.09	0.13
95	0.34	0.32	0.32	0.1015	0.12	2.04	0.13
100	0.30	0.30	0.30	0.0996	0.10	2.01	0.00

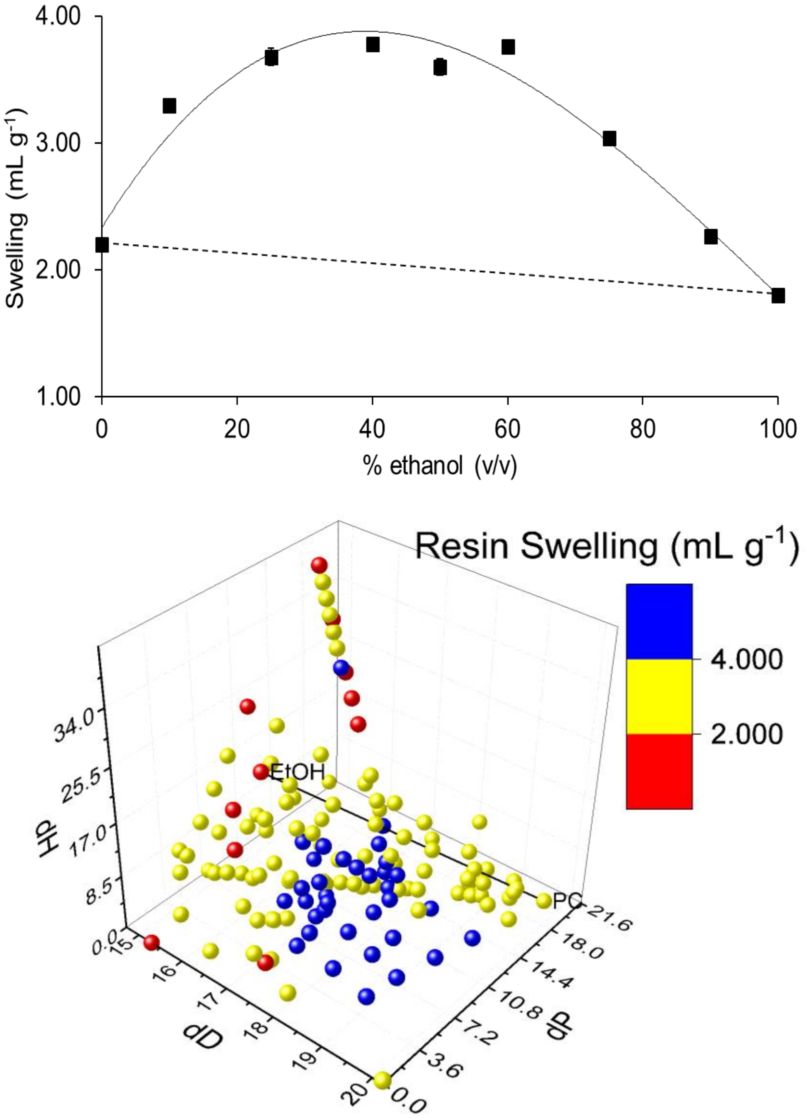


Figure 5-22: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and ethanol (EtOH) (v/v) ratio

Table 5-28: Resin swelling data used to construct Figure 5-22

			HypoGel™200 resin in propylene carbonate and ethanol				
%ethanol (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			2.20	0.00
10	0.44	0.44	0.44	0.1031	0.10	3.30	0.00
25	0.50	0.49	0.49	0.1015	0.12	3.68	0.07
40	0.50	0.50	0.50	0.1005	0.12	3.78	0.00
50	0.53	0.52	0.52	0.1037	0.15	3.60	0.06
60	0.48	0.48	0.48	0.1011	0.10	3.76	0.00
75	0.41	0.41	0.41	0.1021	0.10	3.04	0.00
90	0.35	0.35	0.35	0.1015	0.12	2.27	0.00
100			Literature data			1.80	0.00

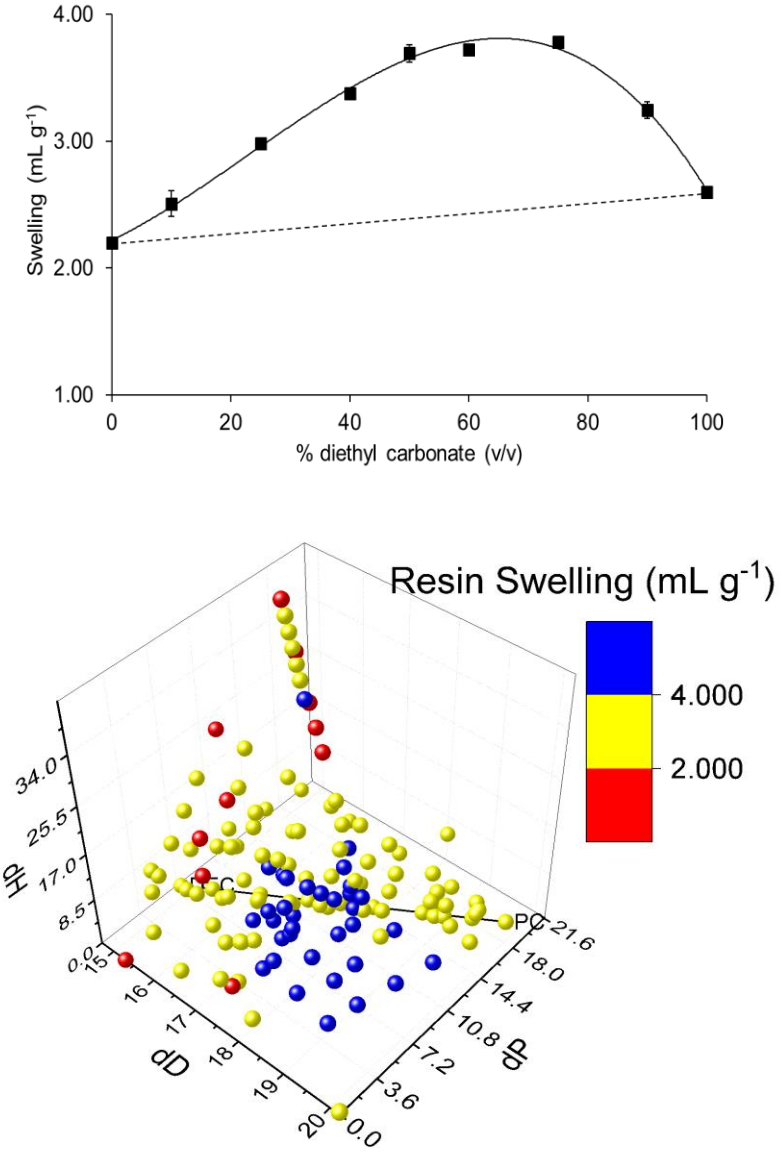


Figure 5-23: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and diethyl carbonate (DEC) (v/v) ratio

Table 5-29: Resin swelling data used to construct Figure 5-23

HypoGel™200 resin in propylene carbonate and diethyl carbonate							
%diethyl carbonate(v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature date			2.20	0.00
10	0.40	0.42	0.41	0.0997	0.16	2.51	0.10
25	0.42	0.42	0.42	0.1005	0.12	2.99	0.00
40	0.50	0.50	0.50	0.1037	0.15	3.38	0.00
50	0.49	0.48	0.48	0.1011	0.11	3.69	0.07
60	0.48	0.48	0.48	0.1021	0.10	3.72	0.00
75	0.49	0.49	0.49	0.1031	0.10	3.78	0.00
90	0.43	0.42	0.42	0.0996	0.10	3.25	0.07
100			Literature date			2.60	0.00

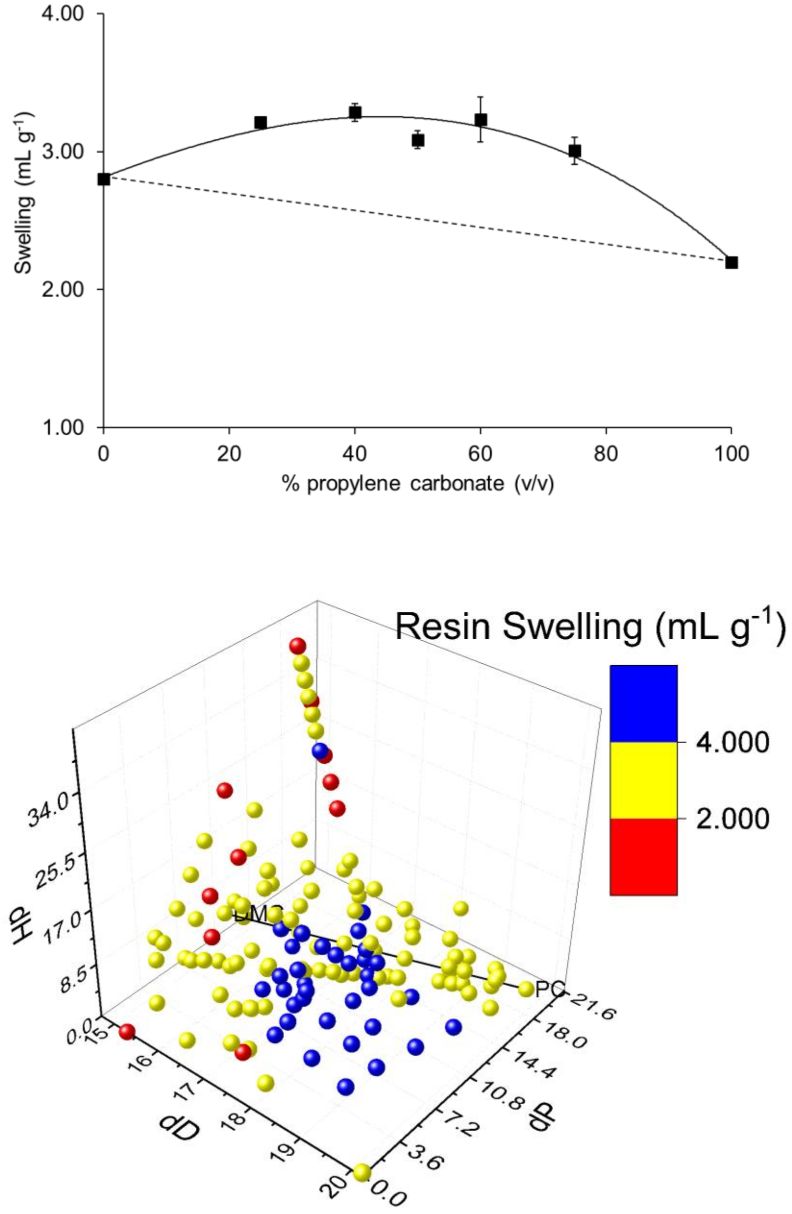


Figure 5-24: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and dimethyl carbonate (DMC) (v/v) ratio

Table 5-30: Resin swelling data used to construct Figure 5-24

HypoGel™200 resin in propylene carbonate and dimethyl carbonate							
%propylene carbonate (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			2.80	0.00
25	0.42	0.42	0.42	0.0996	0.10	3.21	0.00
40	0.46	0.45	0.45	0.1015	0.12	3.28	0.07
50	0.43	0.44	0.43	0.1015	0.12	3.09	0.07
60	0.45	0.42	0.43	0.1031	0.10	3.23	0.16
75	0.40	0.42	0.41	0.1031	0.10	3.01	0.10
100			Literature data			2.20	0.00

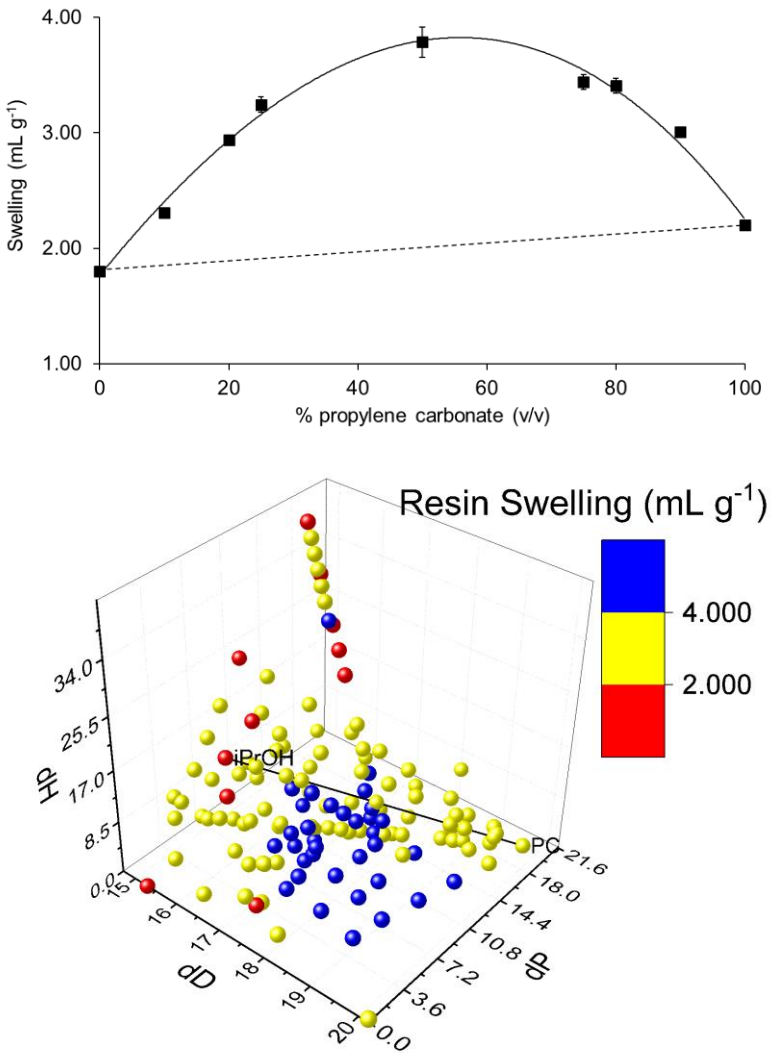


Figure 5-25: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and isopropanol (iPrOH) (v/v) ratio

Table 5-31: Resin swelling data used to construct Figure 5-25

HypoGel™200 resin in propylene carbonate and isopropanol							
%propylene carbonate (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	Literature data					1.80	0.00
10	0.33	0.33	0.33	0.0996	0.10	2.31	0.00
20	0.40	0.40	0.40	0.1021	0.10	2.94	0.00
25	0.49	0.48	0.48	0.0997	0.16	3.24	0.07
50	0.48	0.48	0.50	0.1021	0.10	3.79	0.13
75	0.51	0.50	0.51	0.1037	0.15	3.44	0.06
80	0.51	0.50	0.50	0.1037	0.15	3.41	0.06
90	0.46	0.46	0.46	0.0997	0.16	3.01	0.00
100	Literature data					2.20	0.00

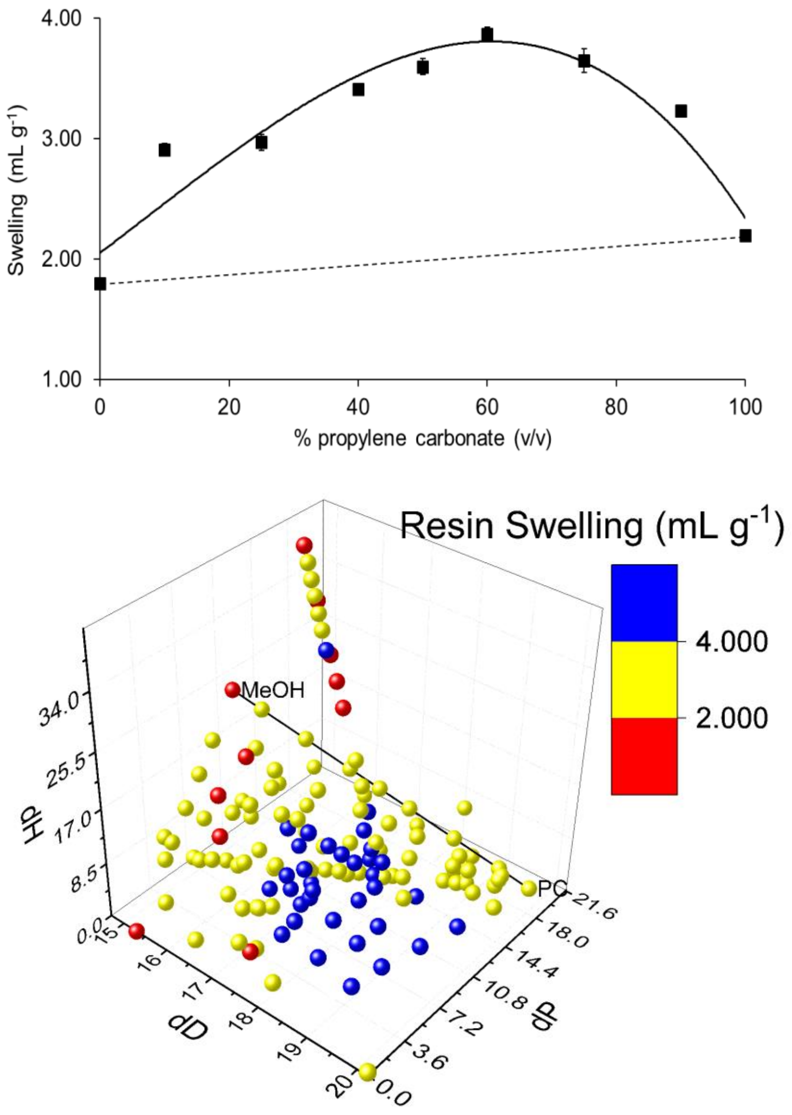


Figure 5-26: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and methanol (MeOH) (v/v) ratio

Table 5-32: Resing swelling data used to construct Figure 5-26

HypoGel™200 resin in propylene carbonate and methanol							
%propylene carbonate (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
10	0.40	0.39	0.39	0.1015	0.10	2.91	0.05
25	0.40	0.40	0.41	0.1021	0.10	2.97	0.07
40	0.50	0.50	0.50	0.0997	0.16	3.41	0.00
50	0.52	0.53	0.52	0.1037	0.15	3.60	0.06
60	0.49	0.48	0.48	0.0996	0.10	3.87	0.06
75	0.48	0.50	0.49	0.10	0.12	3.65	0.10
90	0.49	0.48	0.48	0.1037	0.15	3.23	0.05
100			Literature data			2.20	0.00

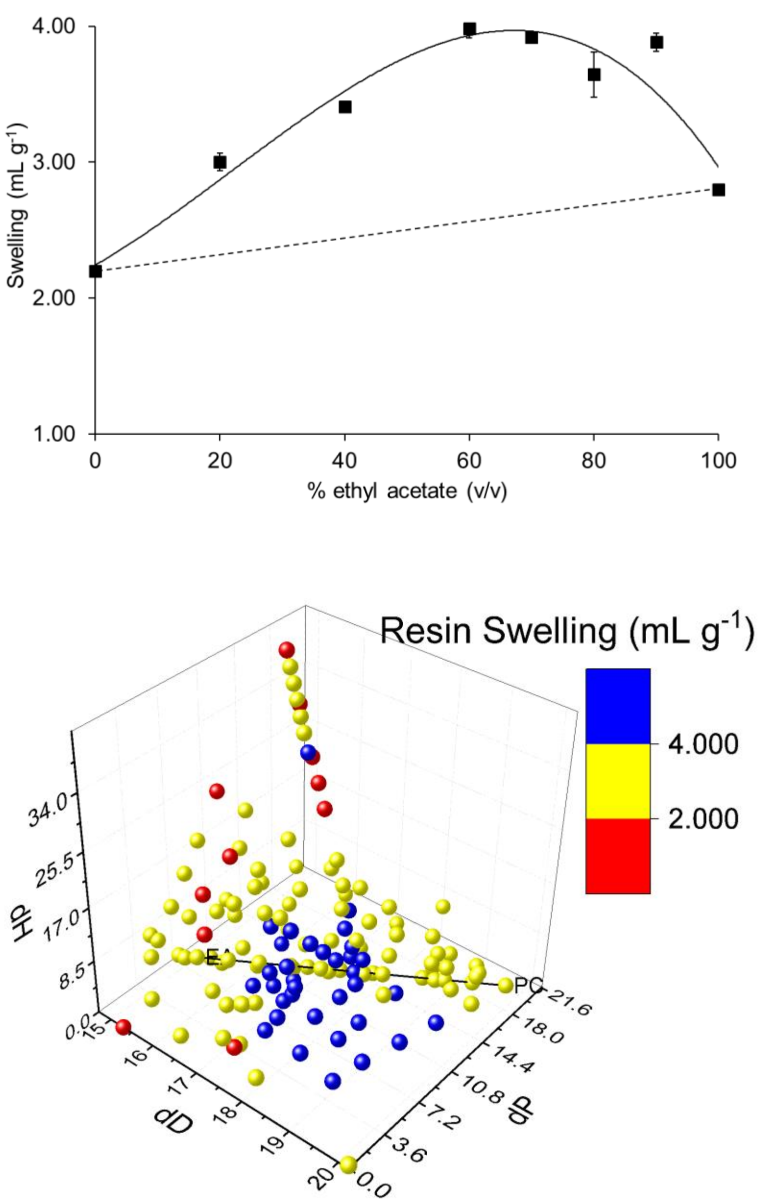


Figure 5-27: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and ethyl acetate (EA) (v/v) ratio

Table 5-33: Resin swelling data used to construct Figure 5-27

	HypoGel™200 resin in propylene carbonate and ethyl acetate						
%ethyl acetate (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			2.20	0.00
20	0.41	0.40	0.41	0.1021	0.10	3.00	0.07
40	0.50	0.50	0.50	0.0997	0.16	3.41	0.00
60	0.50	0.49	0.50	0.0996	0.10	3.98	0.07
70	0.50	0.50	0.50	0.1021	0.10	3.92	0.00
80	0.51	0.54	0.52	0.0997	0.16	3.64	0.17
90	0.49	0.49	0.48	0.10	0.10	3.88	0.07
100			Literature data			2.80	0.00

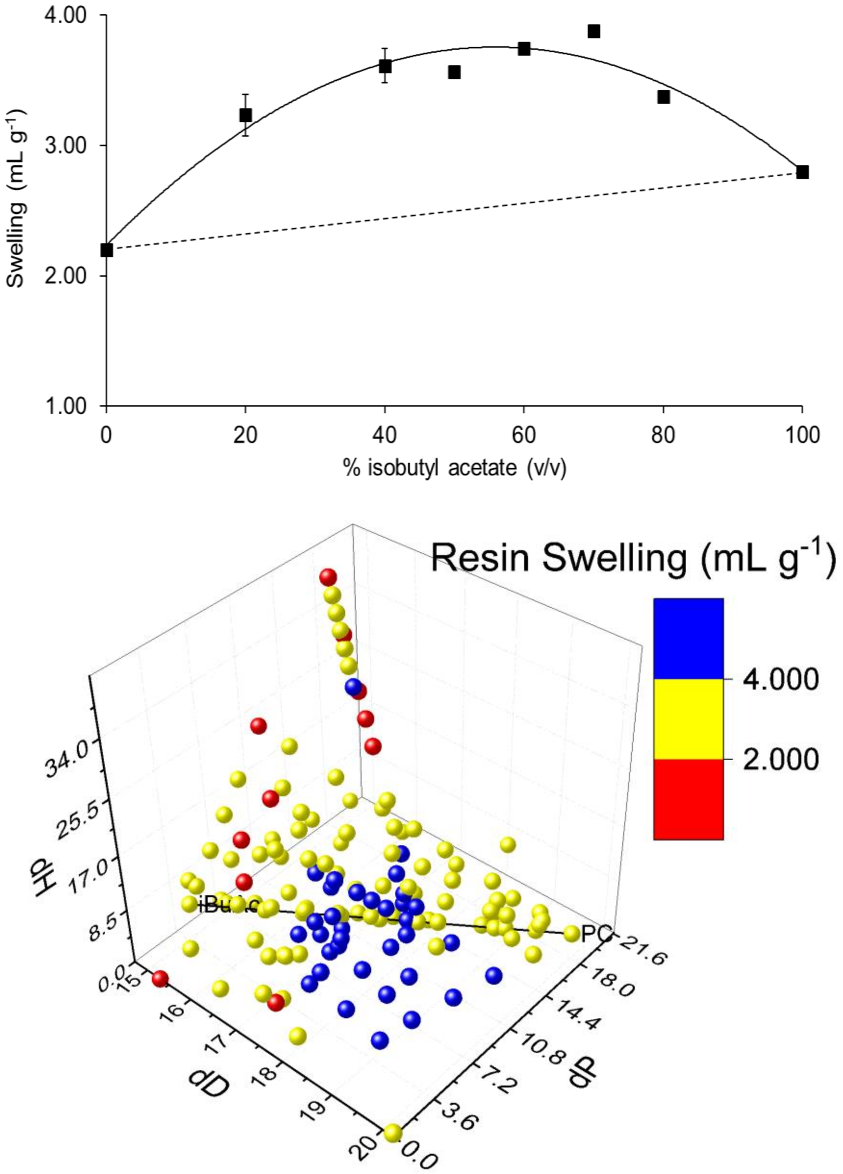


Figure 5-28: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and isobutyl acetate (iBuAc) (v/v) ratio

Table 5-34: Resin swelling data used to construct Figure 5-28

HypoGel™200 resin in propylene carbonate and isobutyl acetate							
%isobutyl acetate (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			2.20	0.00
20	0.42	0.45	0.43	0.1031	0.10	3.23	0.16
40	0.48	0.50	0.48	0.1015	0.12	3.61	0.13
50	0.52	0.52	0.52	0.1037	0.15	3.57	0.00
60	0.50	0.50	0.50	0.1015	0.12	3.74	0.00
70	0.50	0.50	0.50	0.1031	0.10	3.88	0.00
80	0.50	0.50	0.50	0.1037	0.15	3.38	0.00
100			Literature data			2.80	0.00

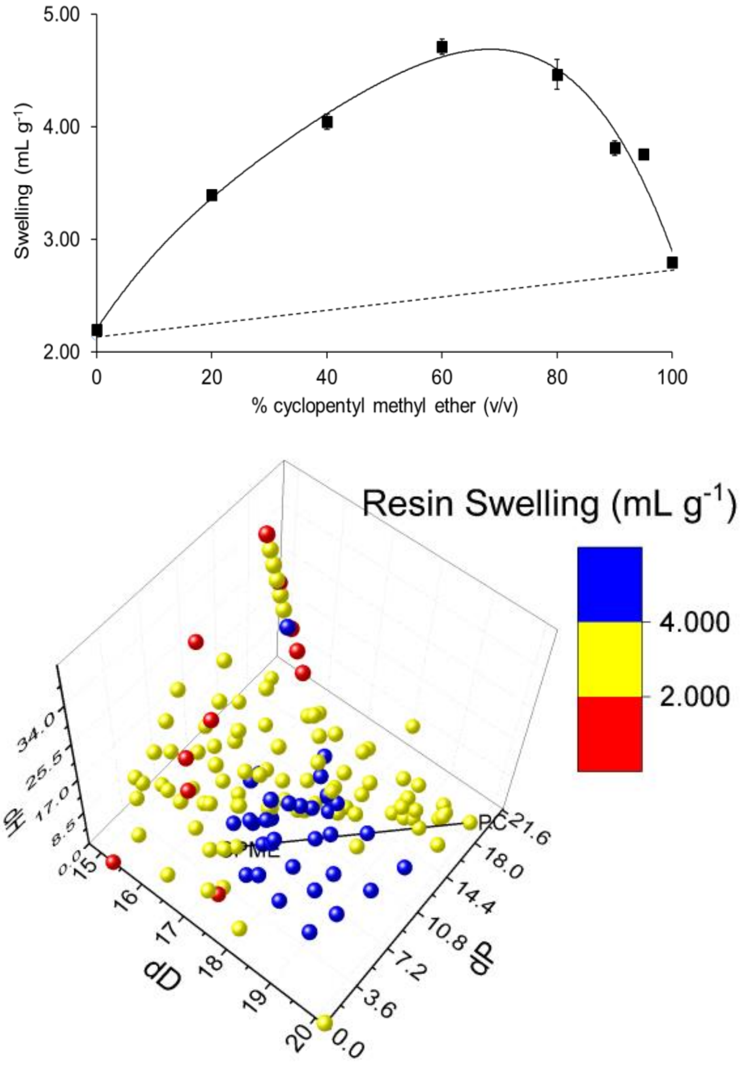


Figure 5-29: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and cyclopentyl methyl ether (CPME) (v/v) ratio

Table 5-35: Resin swelling dataata used to construct Figure 5-29

HypoGel™200 resin in propylene carbonate and cyclopentyl methyl ether							
%cyclopentyl methyl ether (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			2.20	0.00
20	0.45	0.45	0.45	0.1000	0.11	3.40	0.00
40	0.53	0.52	0.53	0.1005	0.12	4.05	0.07
60	0.59	0.58	0.59	0.1011	0.11	4.71	0.07
80	0.55	0.55	0.57	0.1000	0.11	4.47	0.13
90	0.50	0.50	0.51	0.1005	0.12	3.81	0.07
95	0.49	0.49	0.49	0.1011	0.11	3.76	0.00
100			Literature data			2.80	0.00

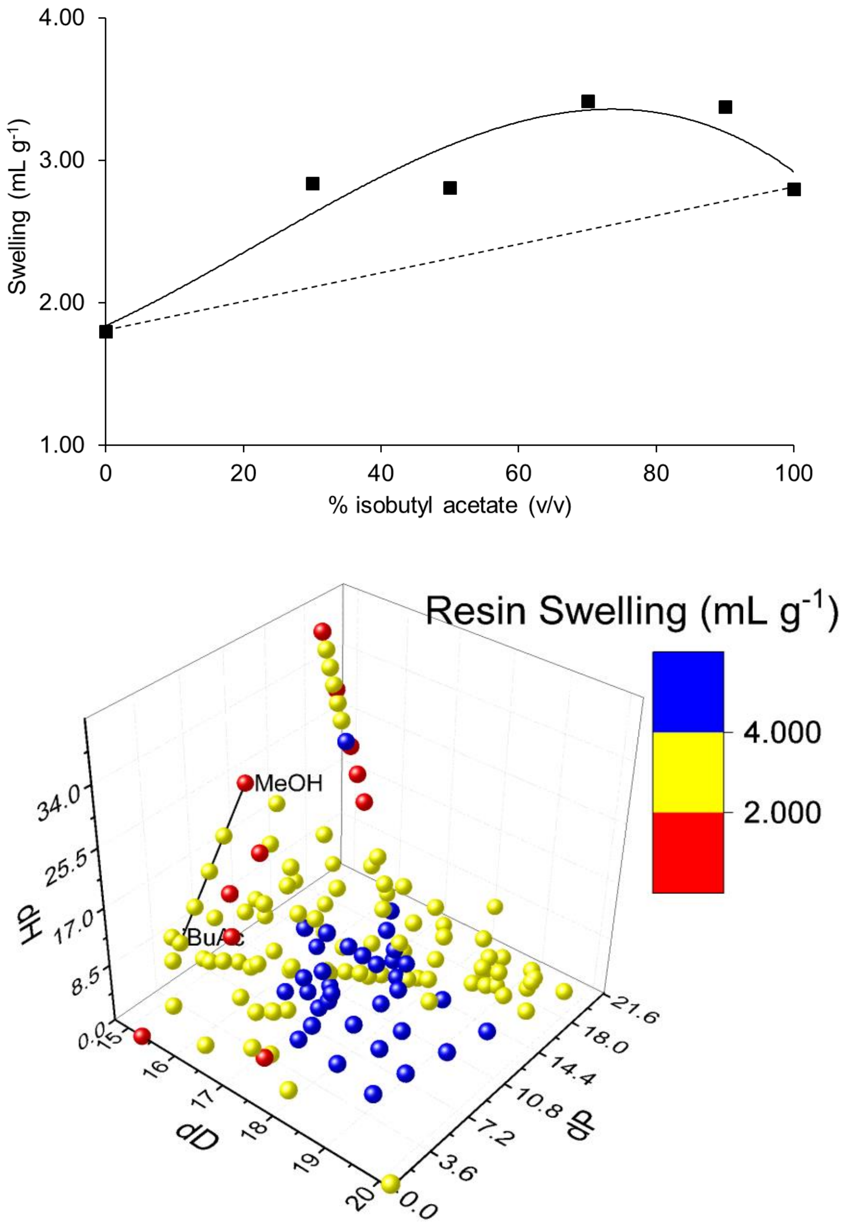


Figure 5-30: Line graph showing the resin swelling changes by changing the methanol (MeOH) and isobutyl acetate (iBuAc) (v/v) ratio

Table 5-36: Resin swelling data used to construct Figure 5-30

HypoGel™200 resin in methanol and isobutyl acetate							
%isobutyl acetate (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
30	0.39	0.39	0.39	0.1021	0.10	2.84	0.00
50	0.44	0.44	0.44	0.0997	0.16	2.81	0.00
70	0.44	0.44	0.44	0.0996	0.10	3.41	0.00
90	0.50	0.50	0.50	0.1037	0.15	3.38	0.00
100			Literature data			2.80	0.00

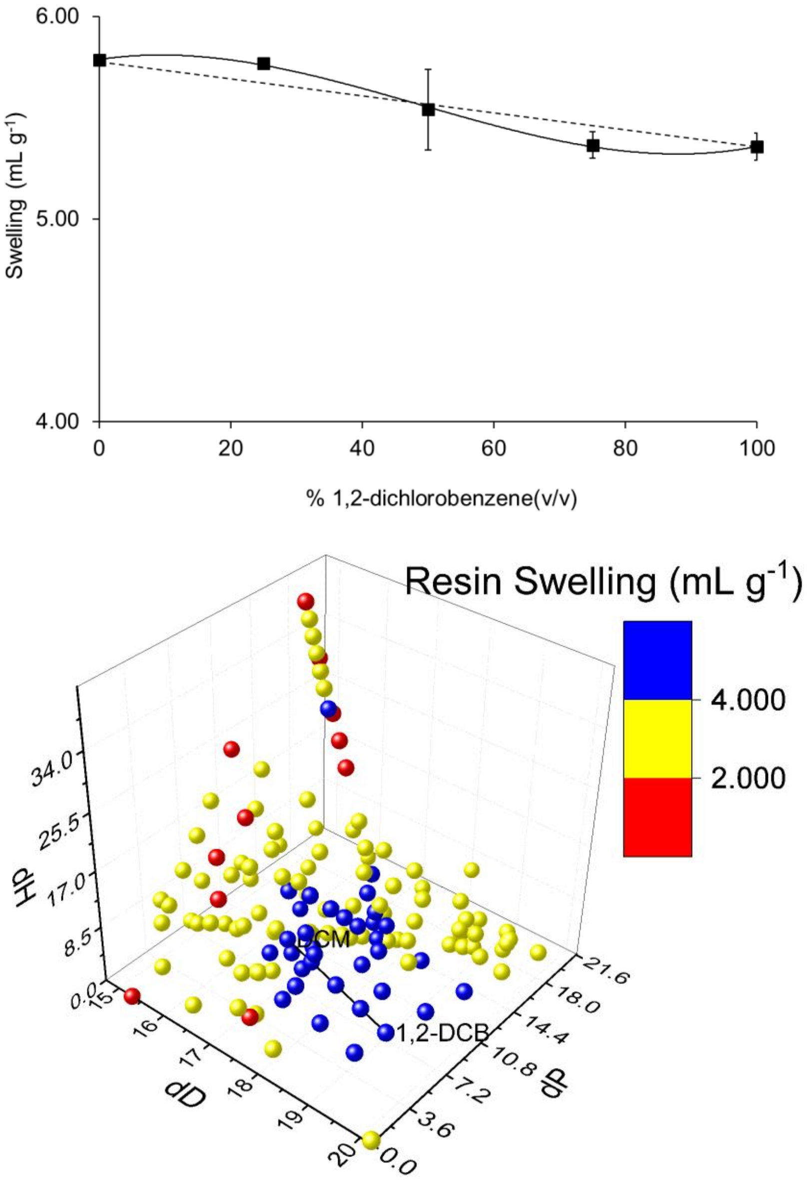


Figure 5-31: Line graph showing the resin swelling changes by changing the 1,2-dichlorobenzene (1,2-DCB) and dichloromethane (DCM) (v/v) ratio

Table 5-37: Resin swelling data used to construct Figure 5-31

HypoGel™200 resin in 1,2-dichlorobenzene and dichloromethane							
%1,2-dichlorobenzene (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.70	0.70	0.70	0.1020	0.11	5.78	0.00
25	0.70	0.70	0.70	0.1023	0.11	5.77	0.00
50	0.68	0.65	0.68	0.1011	0.11	5.54	0.20
75	0.66	0.65	0.66	0.1019	0.11	5.36	0.07
100	0.65	0.65	0.64	0.1002	0.11	5.36	0.07

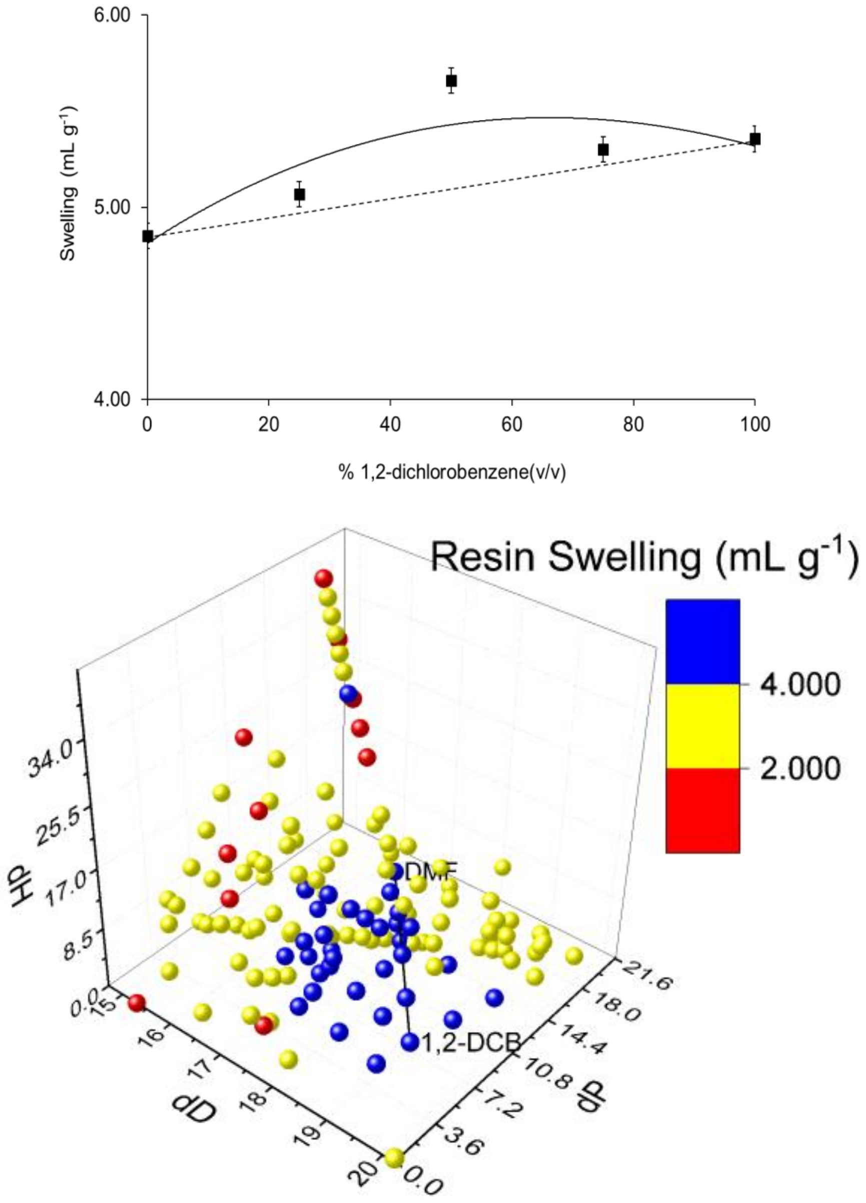


Figure 5-32: Line graph showing the resin swelling changes by changing the 1,2-dichlorobenzene (1,2-DCB) and dimethylformamide (DMF) (v/v) ratio

Table 5-38: Resin swelling data used to construct Figure 5-32

HypoGel™200 resin in 1,2-dichlorobenzene and dimethylformamide							
%1,2-dichlorobenzene (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.60	0.61	0.61	0.1024	0.11	4.85	0.07
25	0.64	0.64	0.65	0.1013	0.13	5.07	0.07
50	0.69	0.68	0.68	0.1013	0.11	5.66	0.07
75	0.65	0.65	0.66	0.1006	0.12	5.30	0.07
100	0.65	0.65	0.64	0.1002	0.11	5.36	0.07

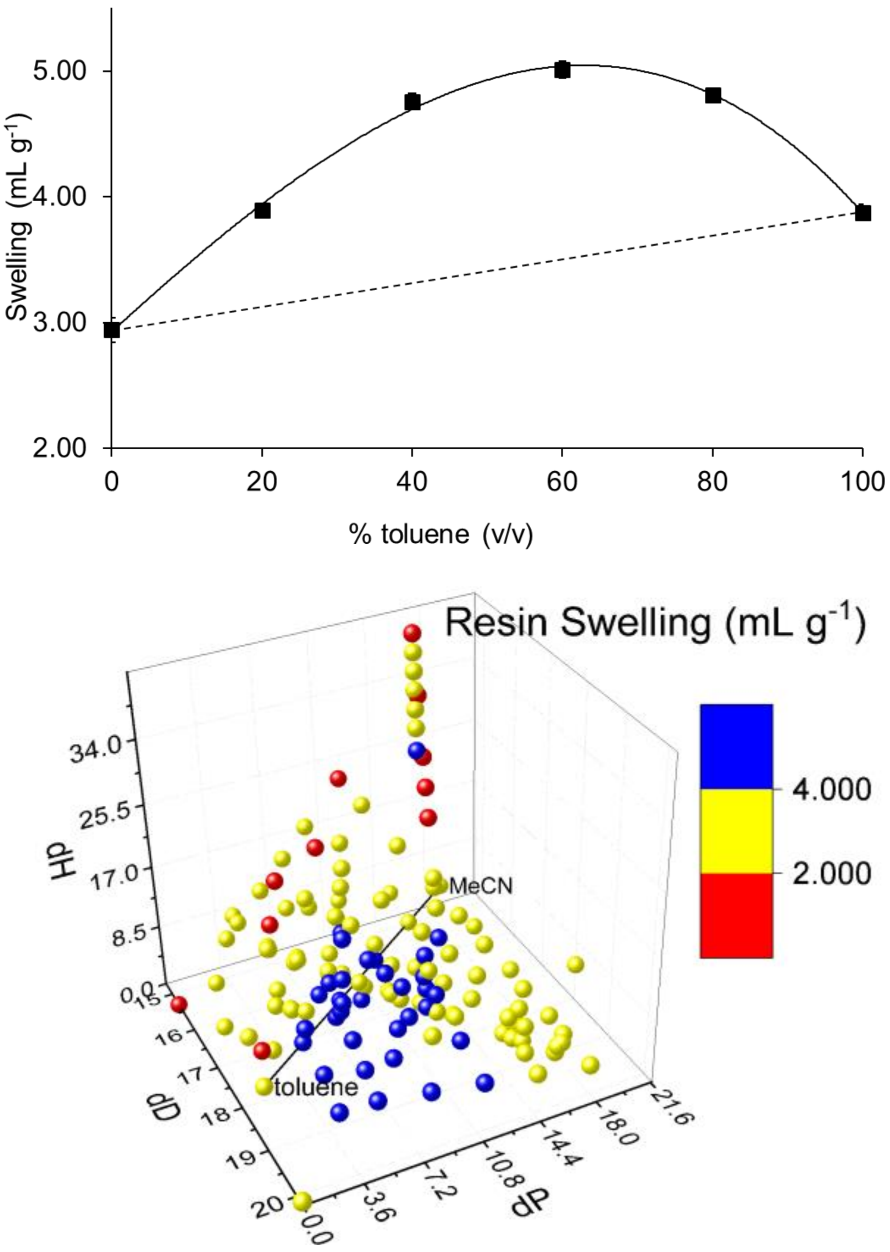


Figure 5-33: Line graph showing the resin swelling changes by changing the acetonitrile (MeCN) and toluene (v/v) ratio

Table 5-39: Resin swelling data used to construct Figure 5-33

		HypoGel™200 resin in acetonitrile and toluene					
%toluene (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.42	0.41	0.40	0.1020	0.11	2.94	0.10
20	0.50	0.50	0.50	0.1002	0.11	3.89	0.00
40	0.60	0.60	0.59	0.1023	0.11	4.76	0.07
60	0.62	0.62	0.61	0.1011	0.11	5.01	0.07
80	0.60	0.60	0.60	0.1019	0.11	4.81	0.00
100	0.50	0.51	0.51	0.1024	0.11	3.87	0.07

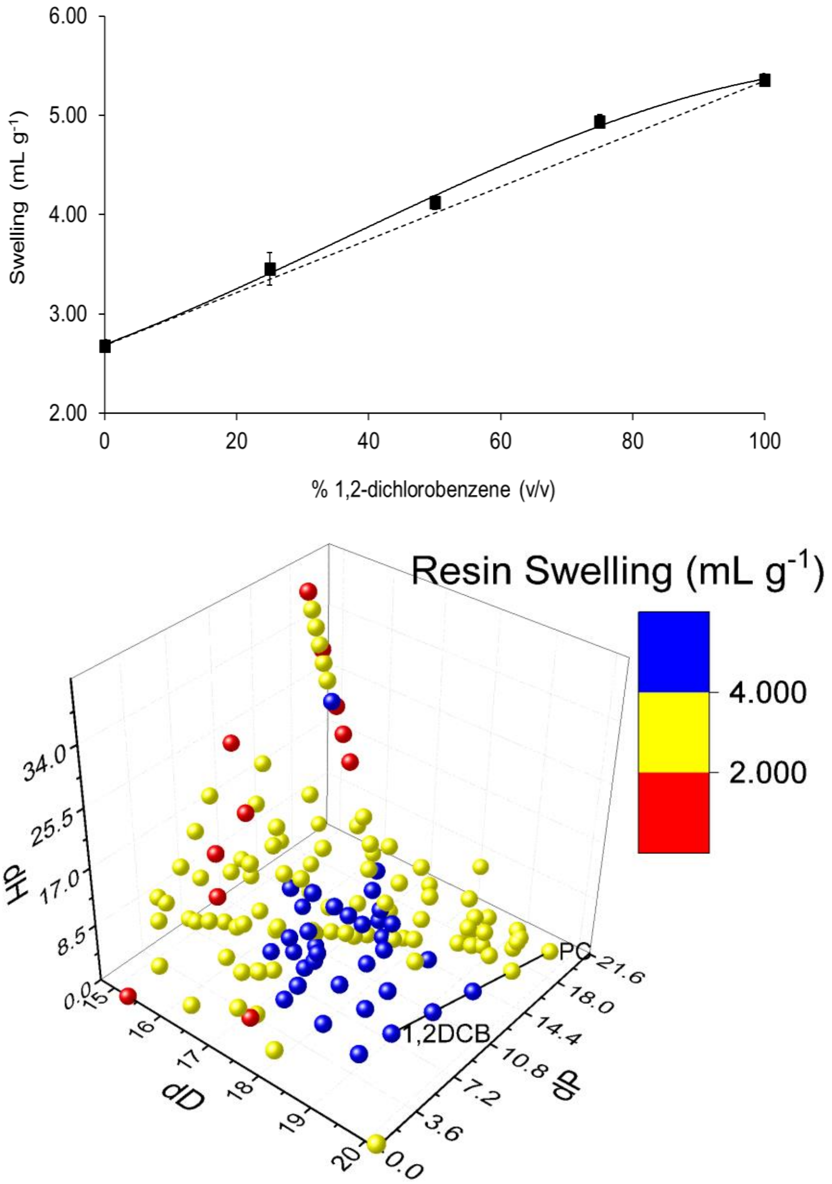


Figure 5-34: Line graph showing the resin swelling changes by changing the 1,2-dichlorobenzene (1,2-DCB) and propylene carbonate (PC) (v/v) ratio

Table 5-40: Resin swelling data used to construct Figure 5-34

HypoGel™200 resin in propylene carbonate and 1,2-dichlorobenzene							
%1,2-dichlorobenzene (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.38	0.39	0.38	0.1020	0.11	2.68	0.07
25	0.48	0.45	0.46	0.1023	0.11	3.45	0.16
50	0.53	0.53	0.52	0.1011	0.11	4.12	0.07
75	0.62	0.61	0.61	0.1019	0.11	4.94	0.07
100	0.65	0.65	0.64	0.1002	0.11	5.36	0.07

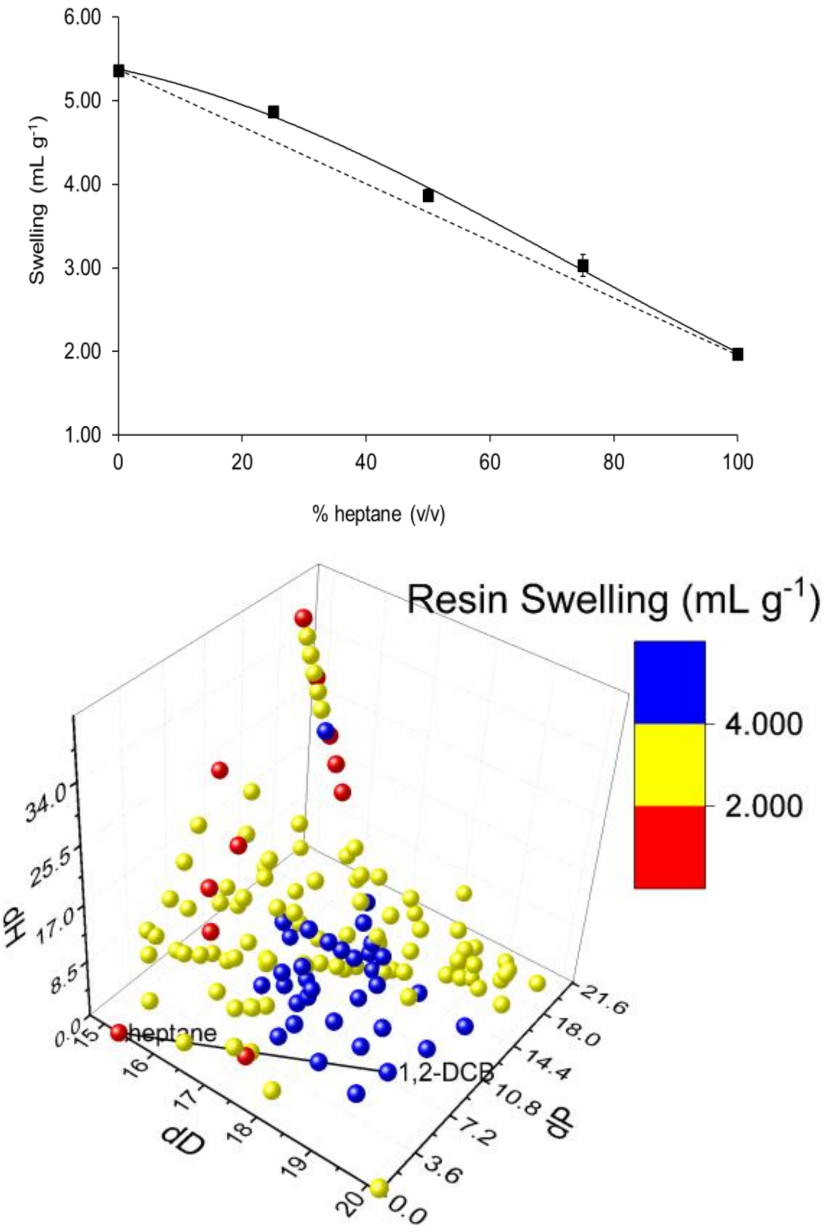


Figure 5-35: Line graph showing the resin swelling changes by changing the 1,2-dichlorobenzene (1,2-DCB) and heptane (v/v) ratio

Table 5-41: Resin swelling data used to construct Figure 5-35

HypoGel™200 resin in heptane and 1,2-dichlorobenzene							
%heptane (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.65	0.65	0.64	0.1002	0.11	5.36	0.07
25	0.61	0.61	0.61	0.1006	0.12	4.87	0.00
50	0.51	0.51	0.50	0.1024	0.11	3.87	0.07
75	0.42	0.42	0.40	0.1002	0.11	3.03	0.13
100	0.31	0.31	0.31	0.1013	0.11	1.97	0.00

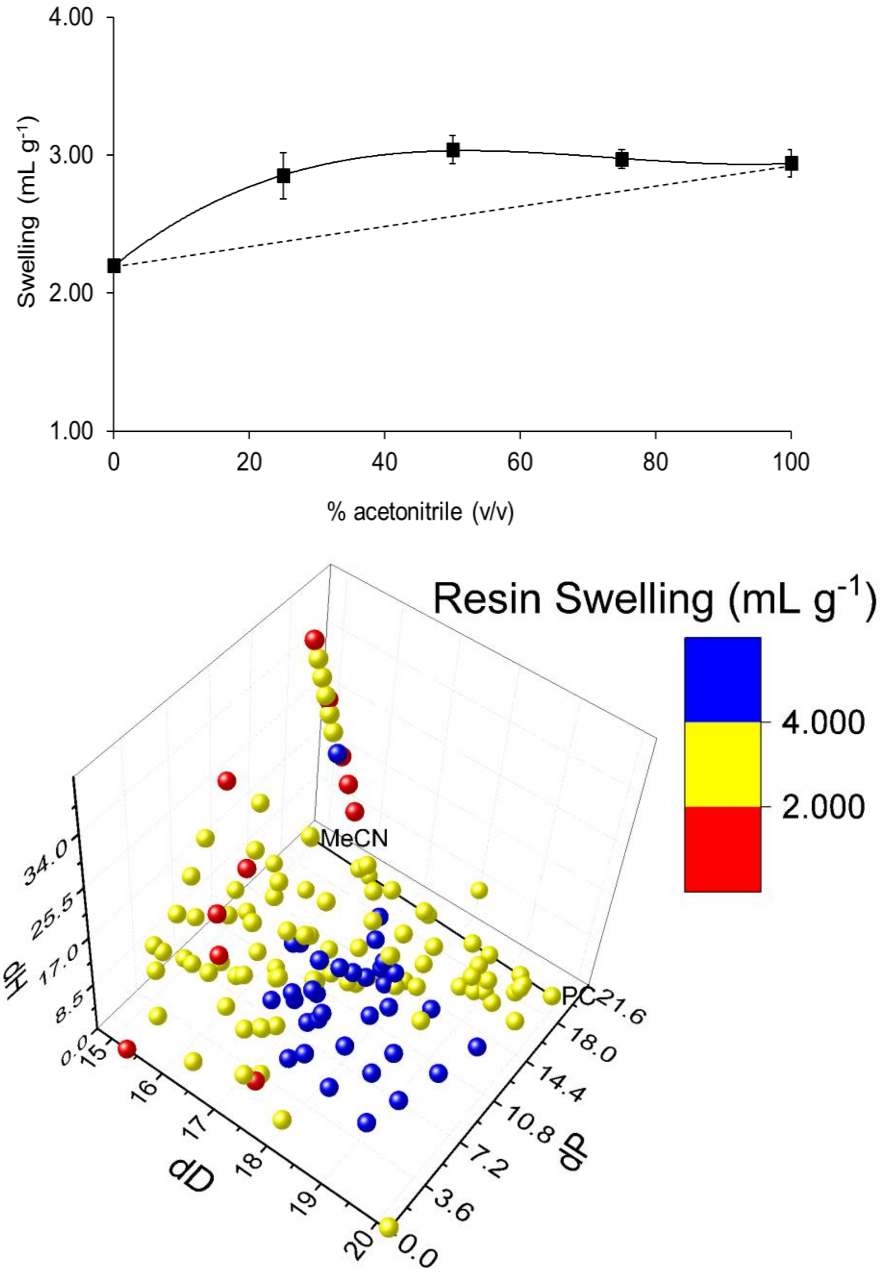


Figure 5-36: Line graph showing the resin swelling changes by changing the propylene carbonate (PC) and acetonitrile (MeCN) (v/v) ratio

Table 5-42: Resin swellingata used to construct Figure 5-36

HypoGel™200 resin in propylene carbonate and acetonitrile							
%acetonitrile (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			2.20	0.00
25	0.39	0.42	0.41	0.1003	0.12	2.85	0.17
50	0.43	0.41	0.42	0.1019	0.11	3.04	0.10
75	0.41	0.42	0.41	0.1020	0.11	2.97	0.07
100	0.42	0.41	0.40	0.1020	0.11	2.94	0.10

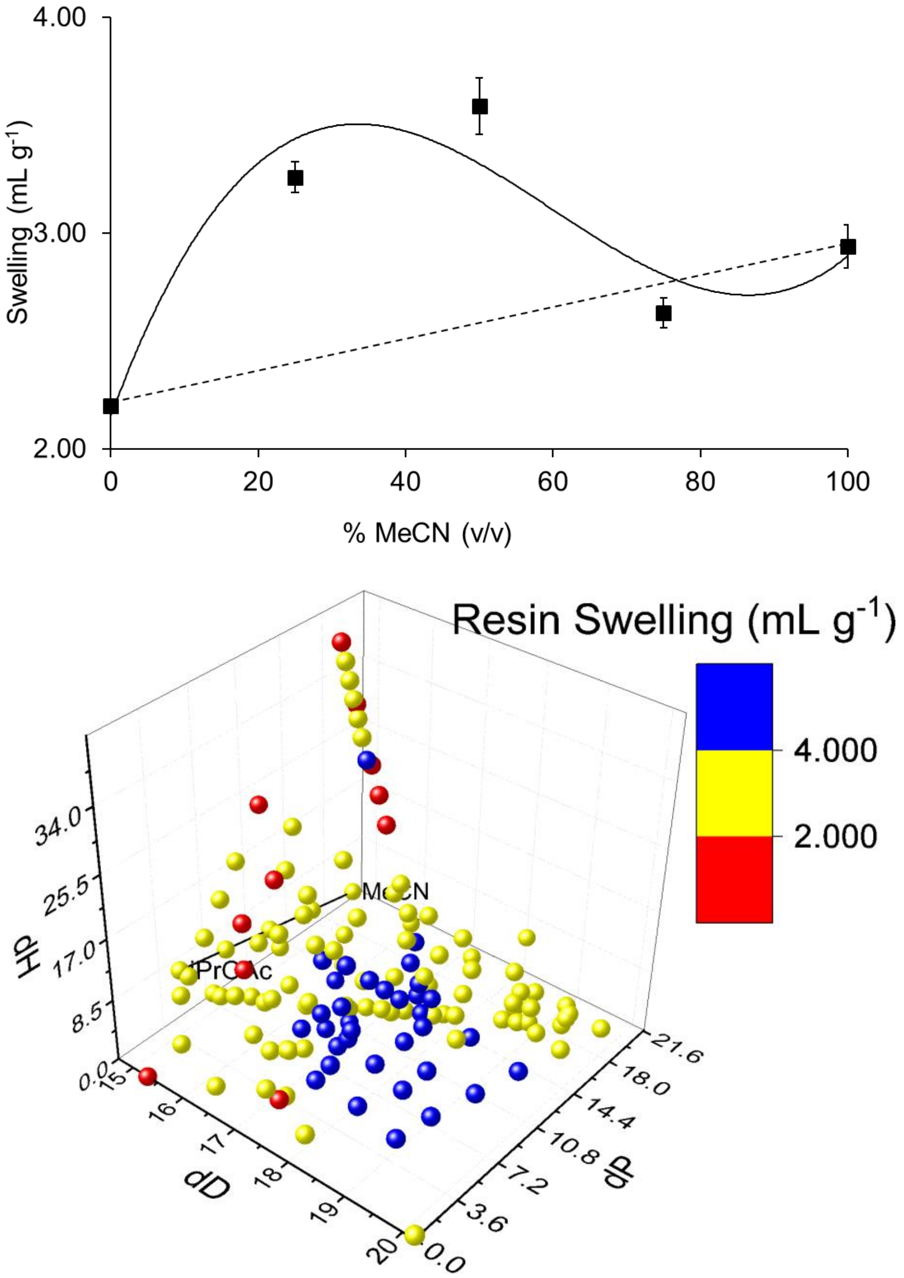


Figure 5-37: Line graph showing the resin swelling changes by changing the isopropyl acetate (iPrOAc) and acetonitrile (MeCN) (v/v) ratio

Table 5-43: Resin swelling data used to construct Figure 5-37

HypoGel™200 resin in isopropyl acetate and acetonitrile							
%acetonitrile (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			2.20	0.00
25	0.44	0.44	0.45	0.1024	0.11	3.26	0.07
50	0.48	0.48	0.46	0.1013	0.11	3.59	0.13
75	0.39	0.40	0.40	0.1013	0.13	2.63	0.07
100	0.42	0.41	0.40	0.1020	0.11	2.94	0.10

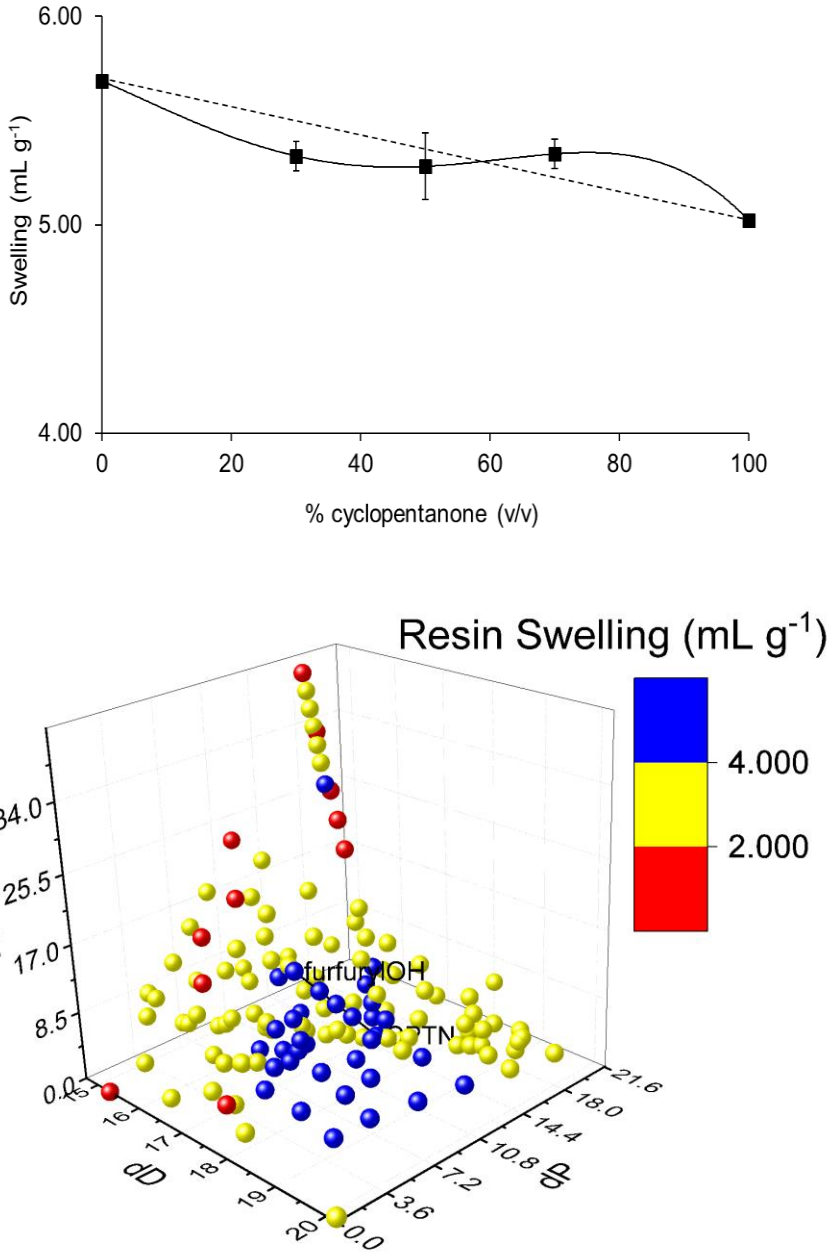


Figure 5-38: Line graph showing the resin swelling changes by changing the furfuryl alcohol (furfurylOH) and cyclopentanone (CPTN) (v/v) ratio

Table 5-44: Resin swelling data used to construct Figure 5-38

HypoGel™200 resin in furfuryl alcohol and cyclopentanone							
%cyclopentanone (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.69	0.69	0.69	0.1020	0.11	5.69	0.00
30	0.66	0.65	0.65	0.1019	0.11	5.33	0.07
50	0.64	0.66	0.63	0.1011	0.11	5.28	0.16
70	0.66	0.65	0.66	0.1023	0.11	5.34	0.07
100	0.60	0.60	0.60	0.0996	0.10	5.02	0.00

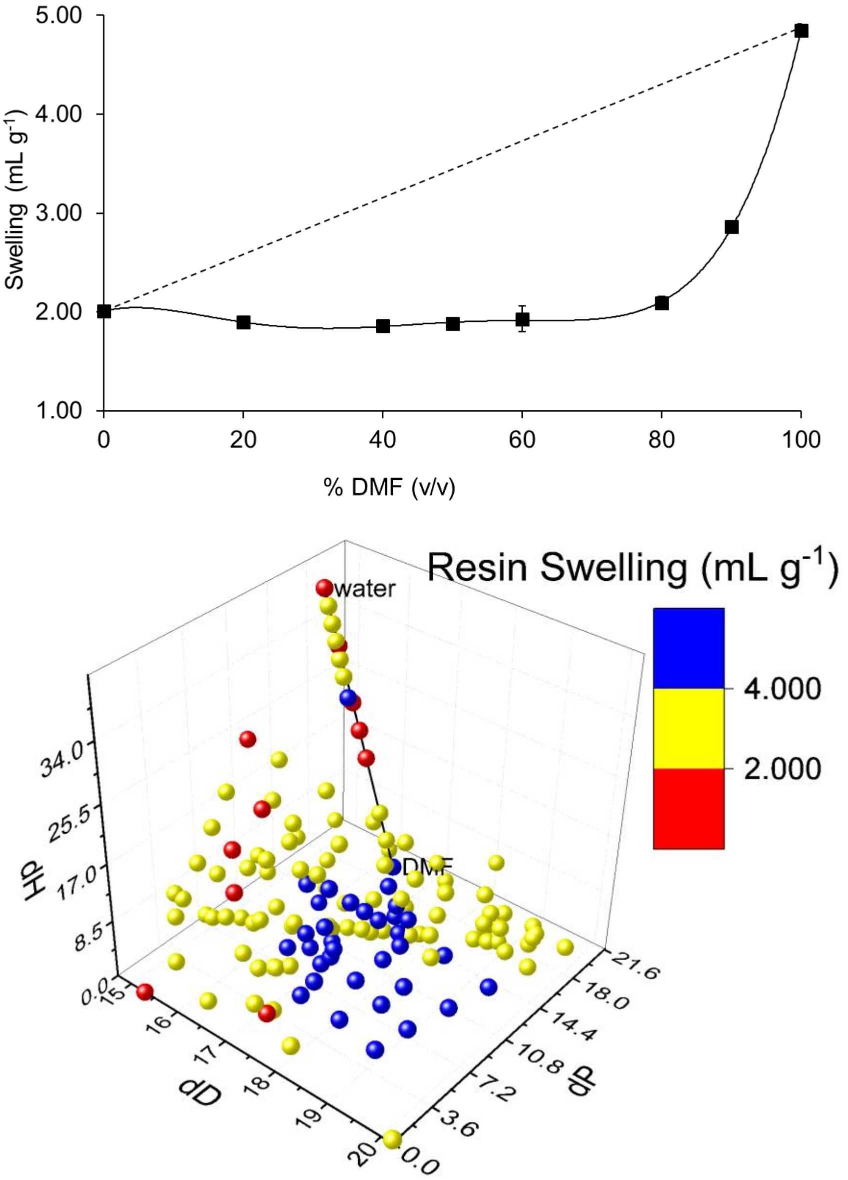


Figure 5-39: Line graph showing the resin swelling changes by changing the water and dimethylformamide (DMF) (v/v) ratio

Table 5-45: Resin swelling data used to construct Figure 5-39

HypoGel™200 resin in water and dimethylformamide							
%DMF (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.30	0.30	0.30	0.0996	0.10	2.01	0.00
20	0.30	0.30	0.30	0.1002	0.11	1.90	0.00
40	0.30	0.30	0.30	0.1023	0.11	1.86	0.00
50	0.30	0.30	0.30	0.1011	0.11	1.88	0.00
60	0.32	0.30	0.30	0.1019	0.11	1.93	0.13
80	0.33	0.32	0.32	0.1020	0.11	2.09	0.07
90	0.41	0.41	0.41	0.1014	0.12	2.86	0.00
100	0.60	0.61	0.61	0.1024	0.11	4.85	0.07

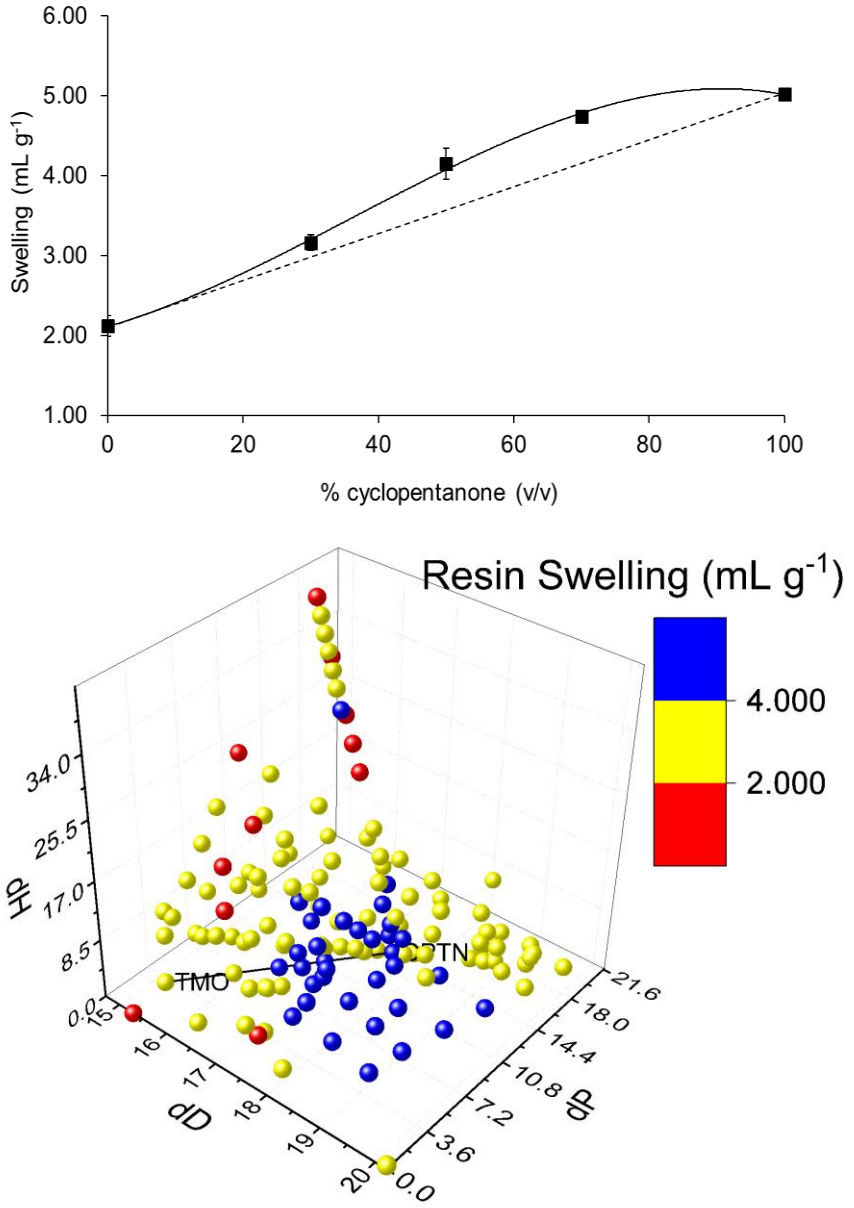


Figure 5-40: Line graph showing the resin swelling changes by changing the TMO and cyclopentanone (CPTN) (v/v) ratio

Table 5-46: Resin swelling data used to construct Figure 5-40

HypoGel™200 resin in TMO and cyclopentanone							
%cyclopentanone (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0	0.34	0.32	0.32	0.1024	0.11	2.12	0.13
30	0.44	0.46	0.45	0.1013	0.13	3.16	0.10
50	0.52	0.55	0.52	0.1013	0.11	4.15	0.20
70	0.60	0.59	0.60	0.1006	0.12	4.74	0.07
100	0.60	0.60	0.60	0.0996	0.10	5.02	0.00

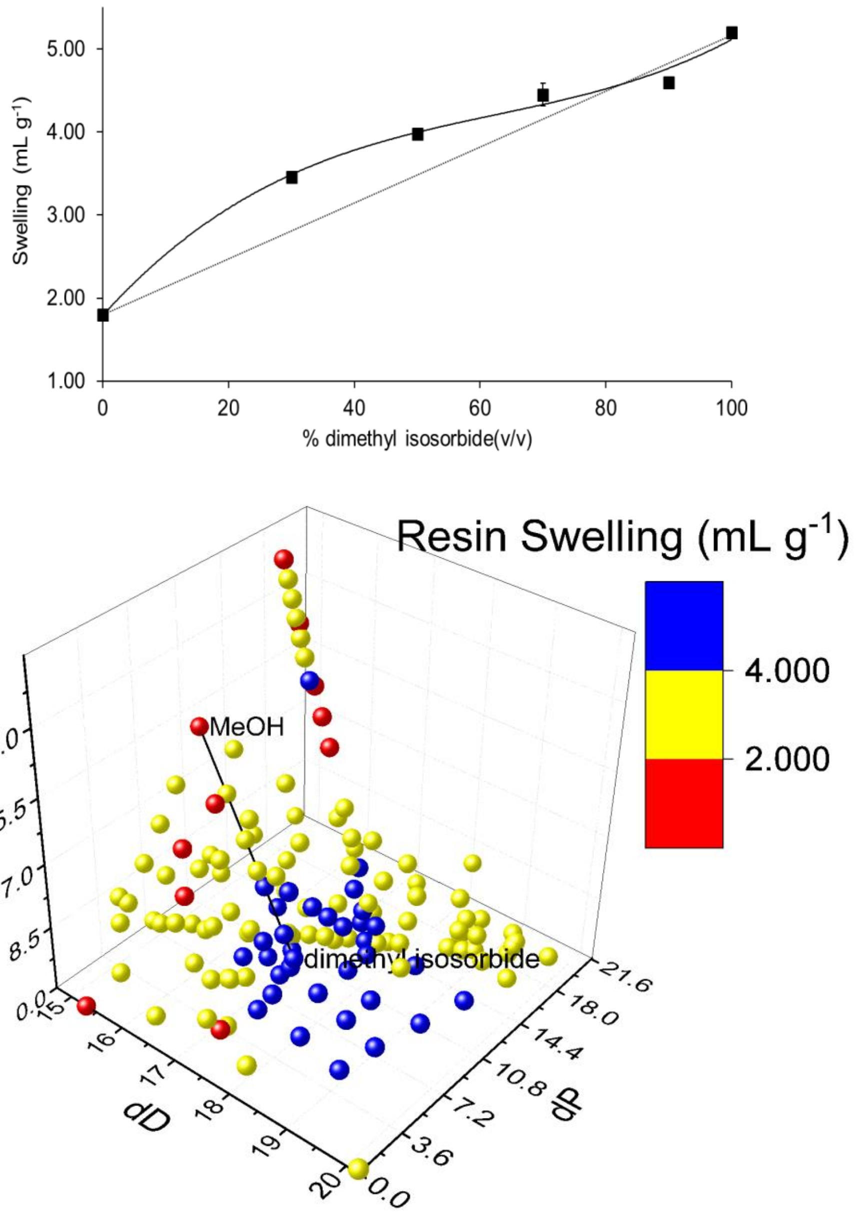


Figure 5-41: Line graph showing the resin swelling changes by changing the methanol (MeOH) and dimethyl isosorbide (v/v) ratio

Table 5-47: Resin swelling data used to construct Figure 5-41

HypoGel™200 resin in methanol and dimethyl isosorbide							
%dimethyl isosorbide (v/v)	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
0			Literature data			1.80	0.00
30	0.45	0.45	0.46	0.1021	0.10	3.46	0.07
50	0.55	0.56	0.56	0.0997	0.16	3.98	0.07
70	0.53	0.55	0.55	0.0996	0.10	4.45	0.13
90	0.62	0.63	0.63	0.1037	0.15	4.60	0.06
100			Literature data			5.20	0.00

5.3. Appendix C

5.3.1. ^{1}H NMR spectra supporting Table 2-4 in Chapter 2.1.4.1

^{1}H NMR spectra of cyclopentanone & water solvent system for HypoGel™200 resin

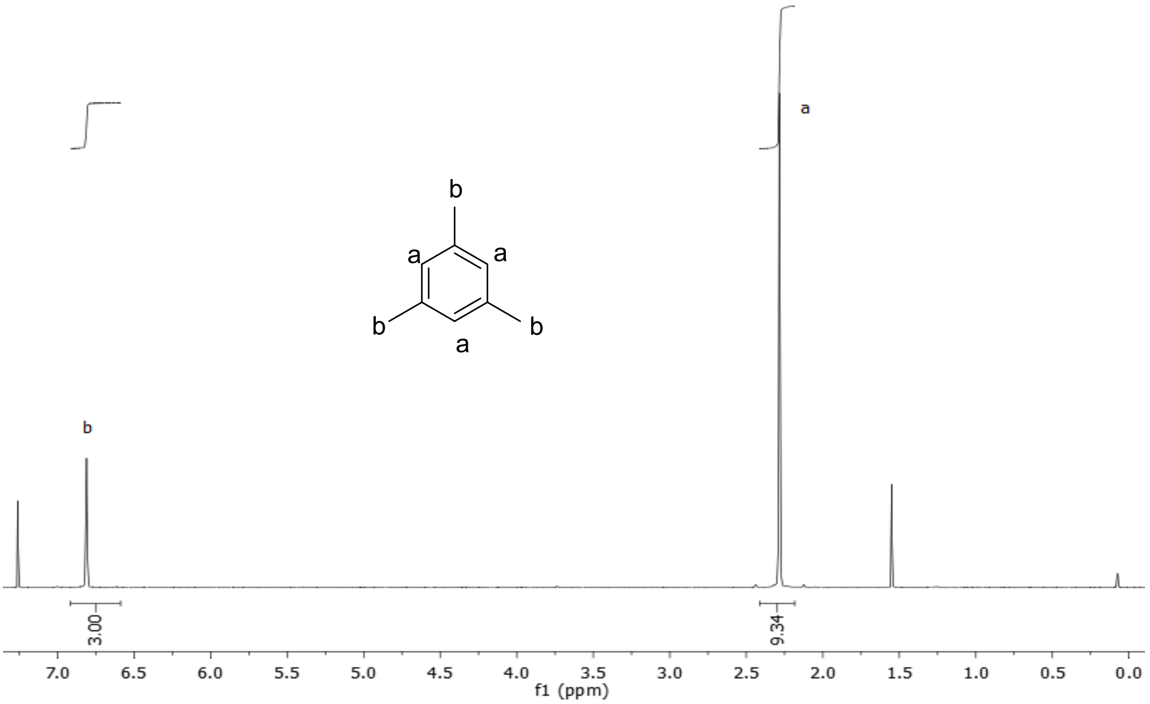


Figure 5-42: ^{1}HNMR spectrum of pure mesitylene (1,3,5-trimethylbenzene). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81-6.71 (m, 3H, ArH), 2.75-2.25 (dd, 9H, $ArCH_3$).

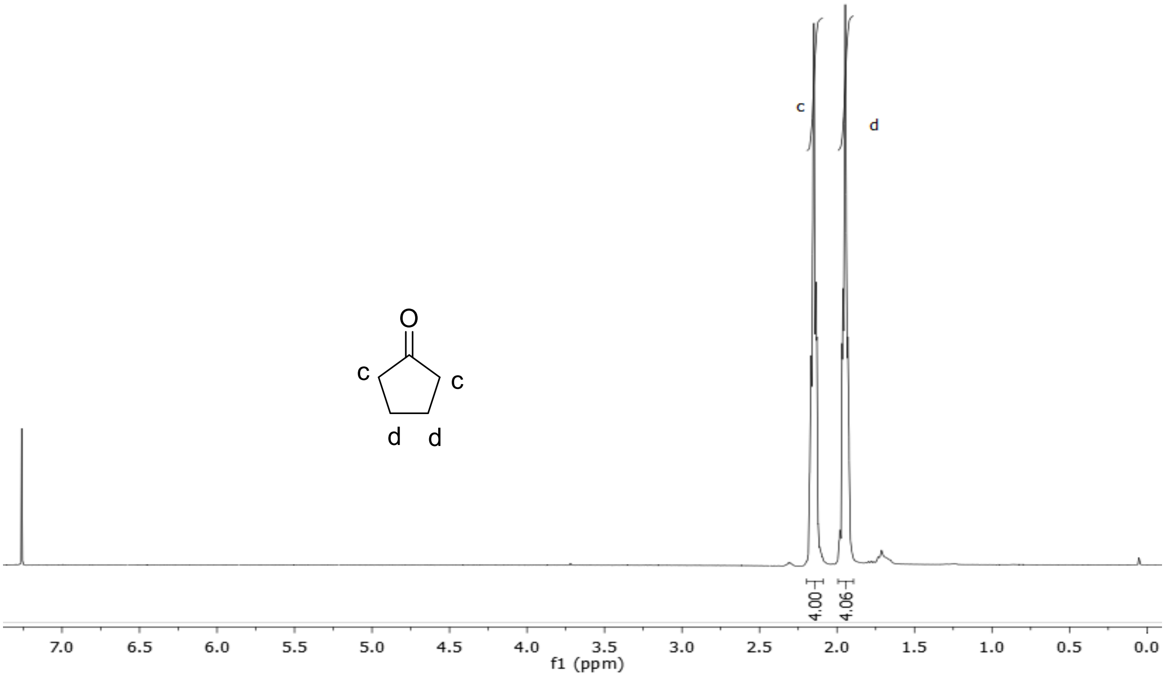


Figure 5-43: ^{1}HNMR spectrum of pure cyclopentanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ =2.20-2.09 (m, 4H, $COCH_2$), 2.00-1.88 (m, 4H, $COCH_2CH_2$).

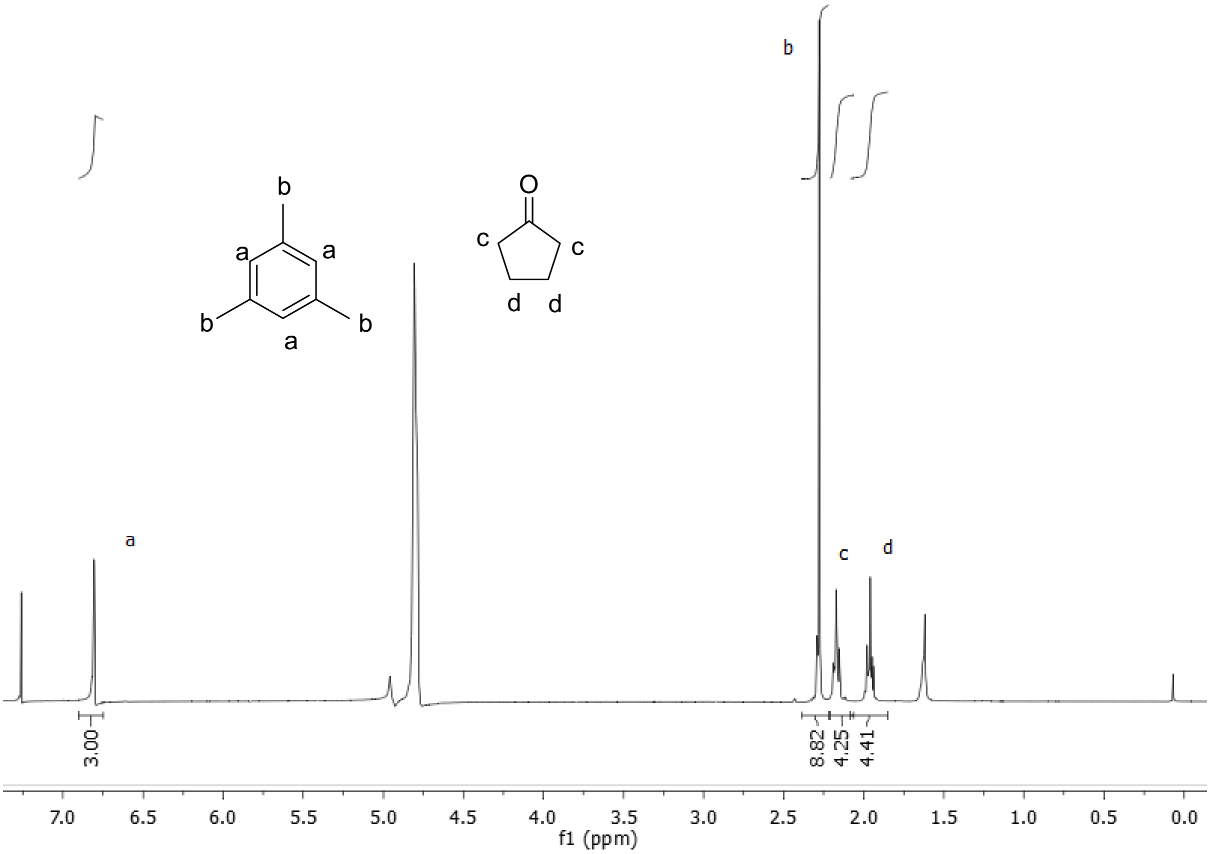


Figure 5-44: ^{1}HNMR spectrum of example 1: solvent blend of cyclopentanone:water=30:70 before swelling

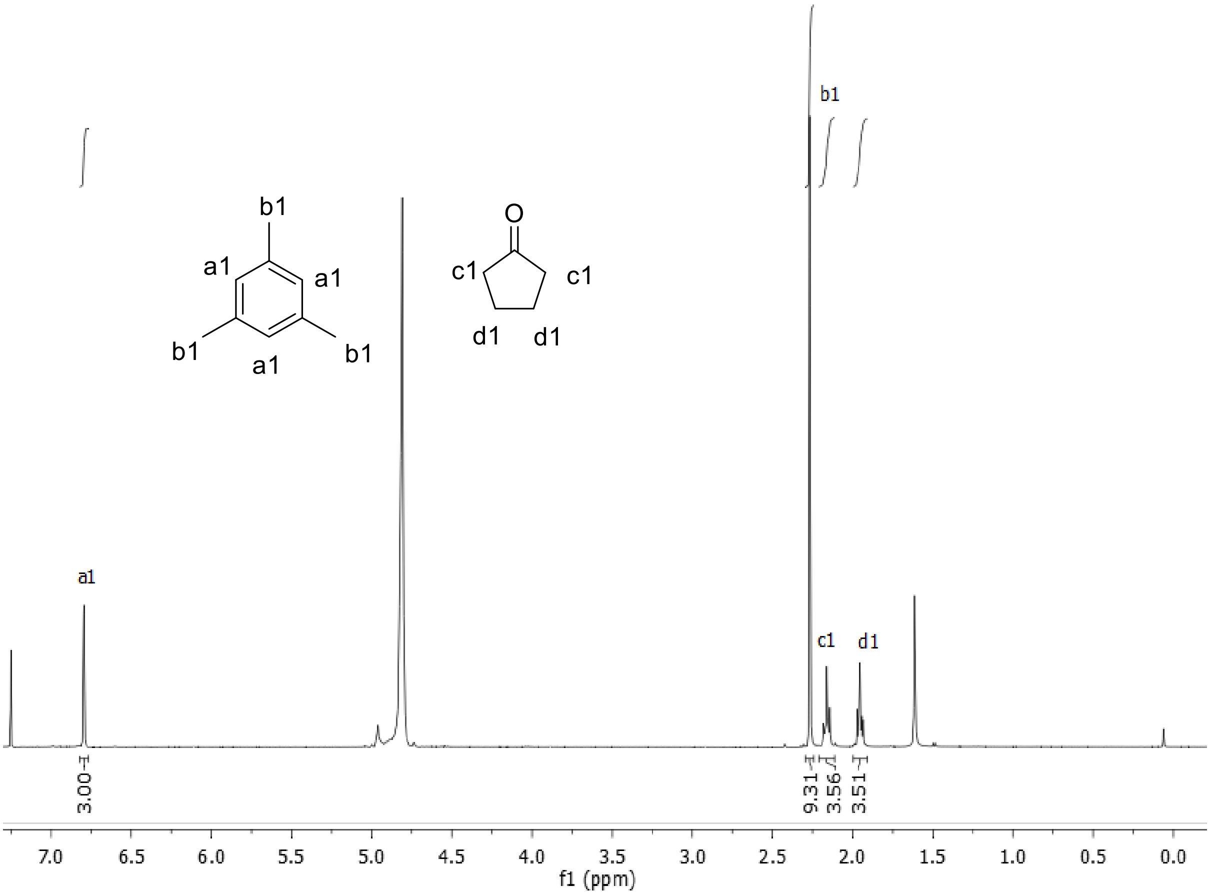


Figure 5-45: ^{1}HNMR spectrum of example 1: solvent blend of cyclopentanone:water=30:70 after swelling

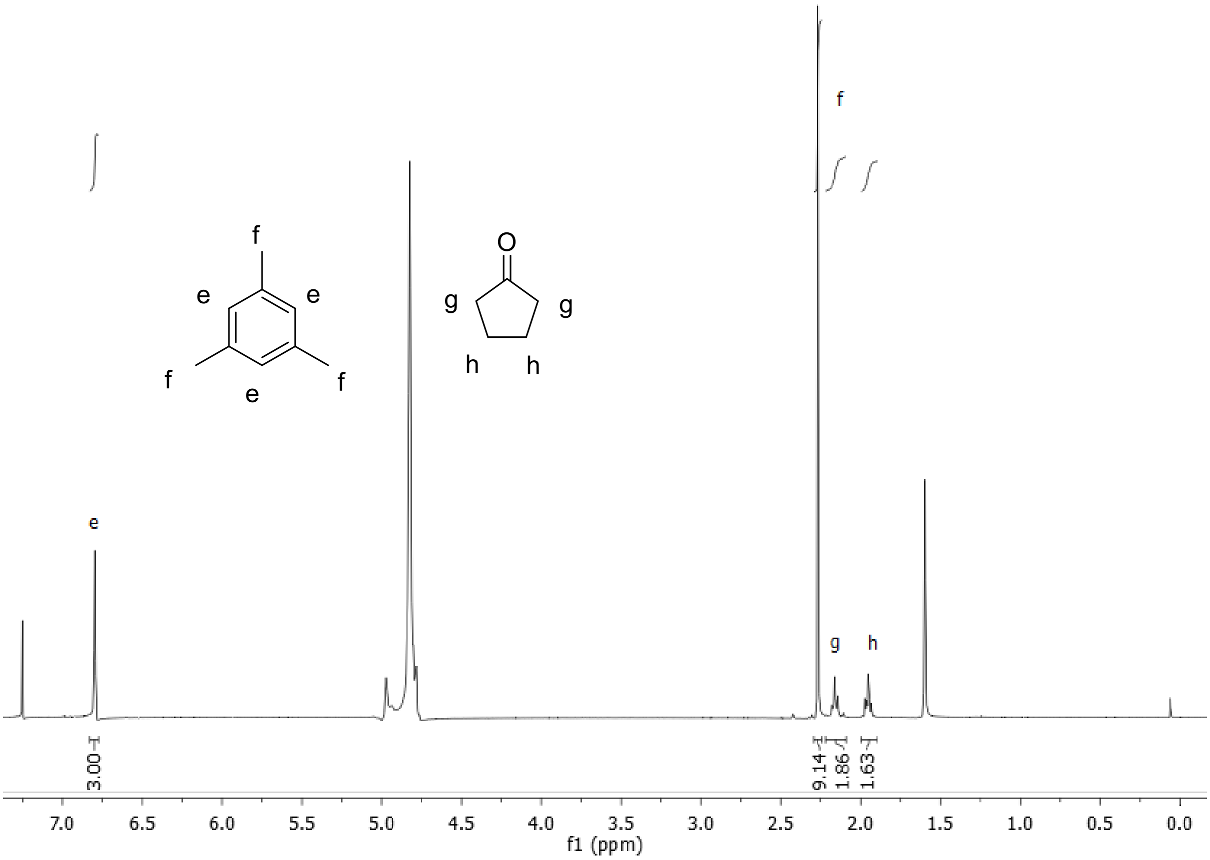


Figure 5-46: ^{1}HNMR spectrum of example 2: solvent blend of cyclopentanone:water=90:10 before swelling

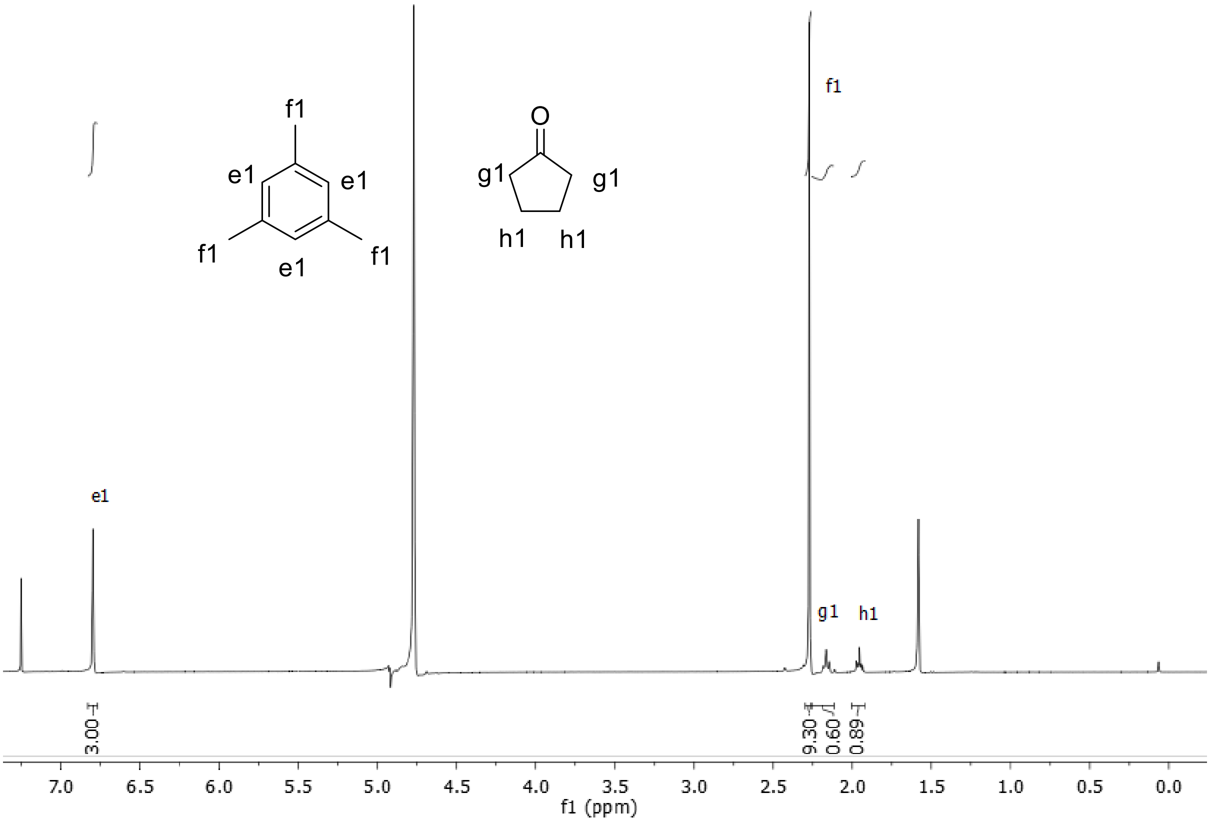
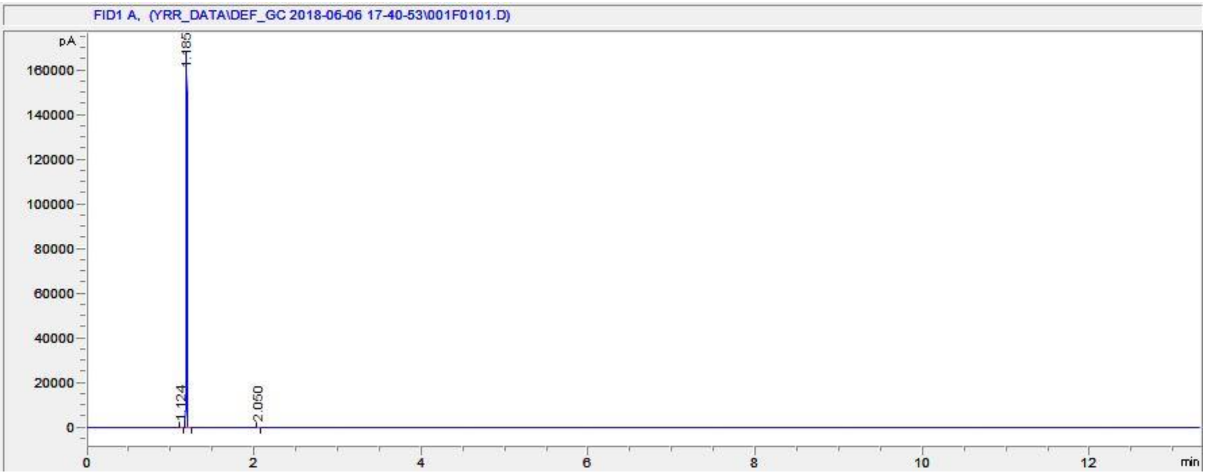


Figure 5-47: ^{1}HNMR spectrum of example 2: solvent blend of cyclopentanone:water=90:10 after swelling

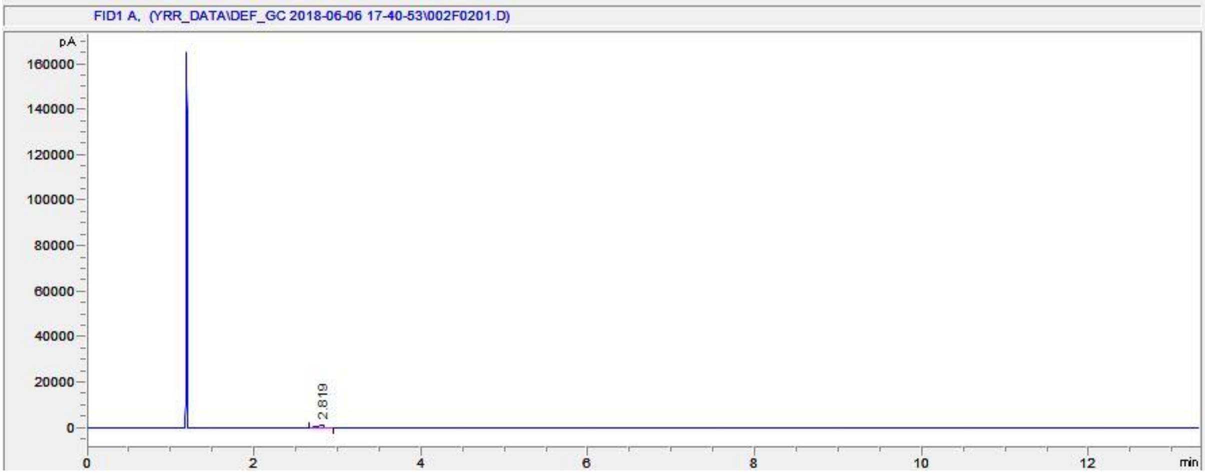
5.4. Appendix D

5.4.1. GC data supporting Chapter 2.1.4.4



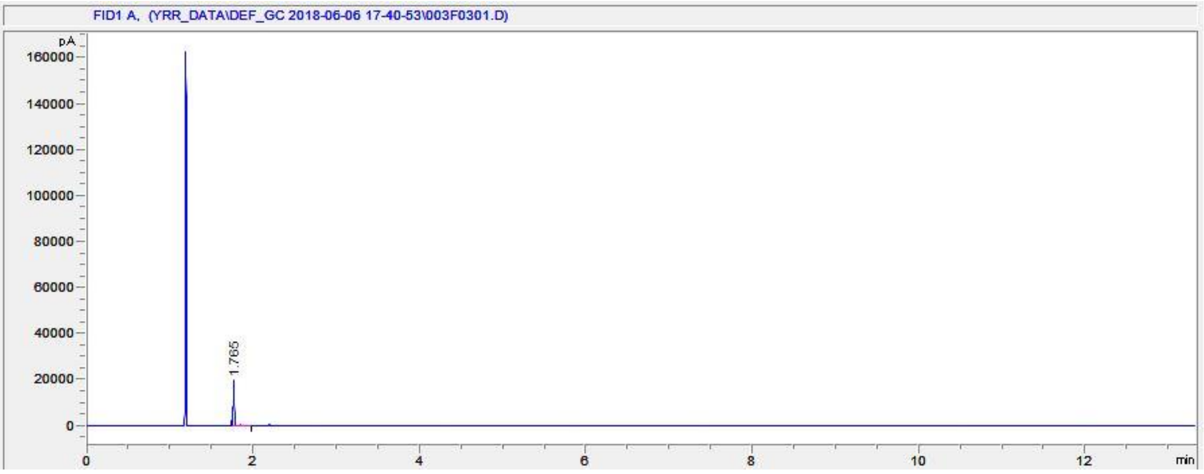
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	1.124	1	BB	11.68075	14.57287	0.00762
2	1.185	1	BB S	1.53E+05	1.64E+05	99.9884
3	2.05	1	BB	6.10799	9.55428	0.00399

Figure 5-48: Acetone was chosen as the background, and its retention time in GC chromatogram was 1.185 min on the Agilent (5HT column).



Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	2.819	1	BB	5459.248	1167.178	1.00E+02

Figure 5-49: The first strong peak was acetone, and propylene carbonate came out at 2.819 min on the Agilent (5HT column).



Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	1.765	1	BB S	1.67E+04	1.83E+04	1.83E+04

Figure 5-50: The first peak was acetone, TMO came out at 1.765 min on the Agilent (5HT column).

5.5. Appendix E

5.5.1. Data supporting Figure 2-43 in Chapter 2.2.2.4

Table 5-48: Data used to construct Figure 2-43

Resin swelling in each peptide sequence for Wang resin in PC: EtOAc=10: 90 (v/v)

Resin	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
Wang resin	0.58	0.58	0.58	0.0998	0.12	4.61	0.00
Fmoc-Phe-Wang resin	0.90	0.90	0.90	0.2005	0.12	3.89	0.00
H-Phe-Wang resin	0.80	0.80	0.80	0.1788	0.12	3.80	0.00
Fmoc-Ala-Phe-Wang resin	0.78	0.80	0.79	0.2091	0.12	3.20	0.05
H-Ala-Phe-Wang resin	0.76	0.74	0.74	0.1875	0.12	3.34	0.07
Fmoc-Leu-Ala-Phe-Wang resin	0.89	0.88	0.88	0.2227	0.12	3.43	0.03
H-Leu-Ala-Phe-Wang resin	0.81	0.80	0.80	0.2011	0.12	3.40	0.03
Wang resin (after cleave)	0.73	0.71	0.72	0.1411	0.12	4.25	0.07

5.6. Appendix F

5.6.1. ^{1}H NMR spectra supporting Chapter 2.3.2

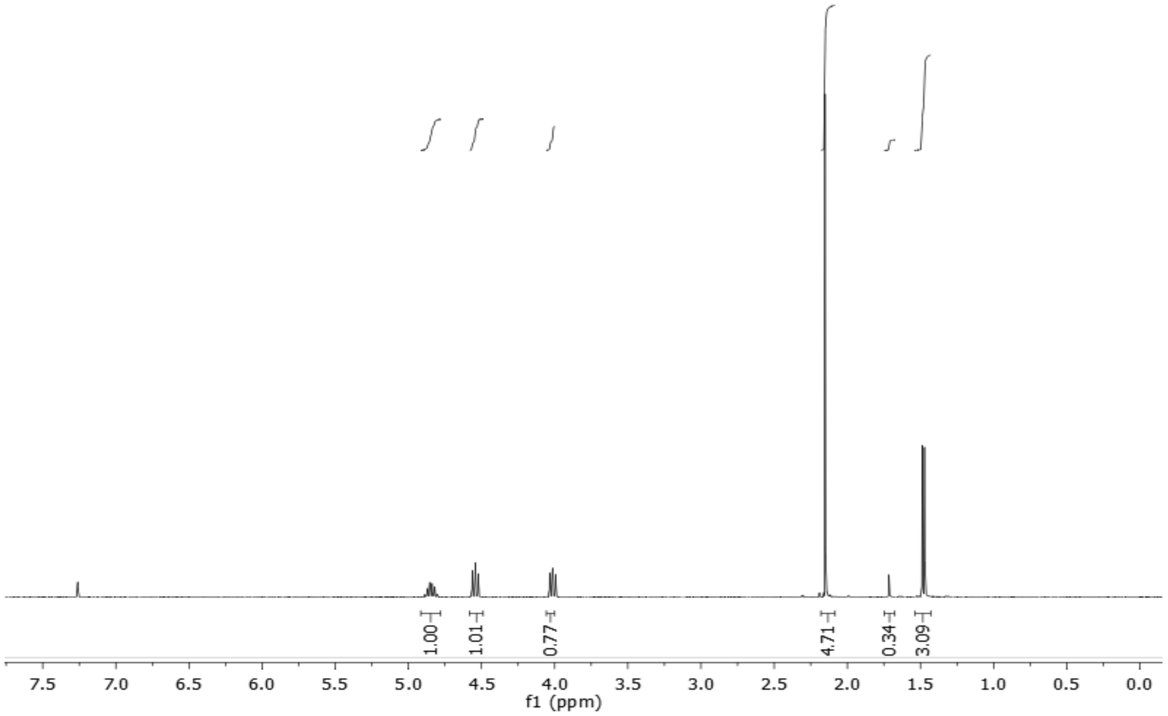


Figure 5-51: ^{1}H NMR (chloroform-d, δ =7.26) of polystyrene dissolving in propylene carbonate, then adding 10 µL acetone; propylene carbonate: δ=4.85 (1H, OCHCH$_3$), δ=4.56 (1H, OCH$_2$), δ=4.04 (1H, OCH$_2$), δ=1.50 (d, 3H, CH$_3$); acetone: δ=2.16. It shows no polystyrene dissolved in propylene carbonate as there is no signal around 7 ppm

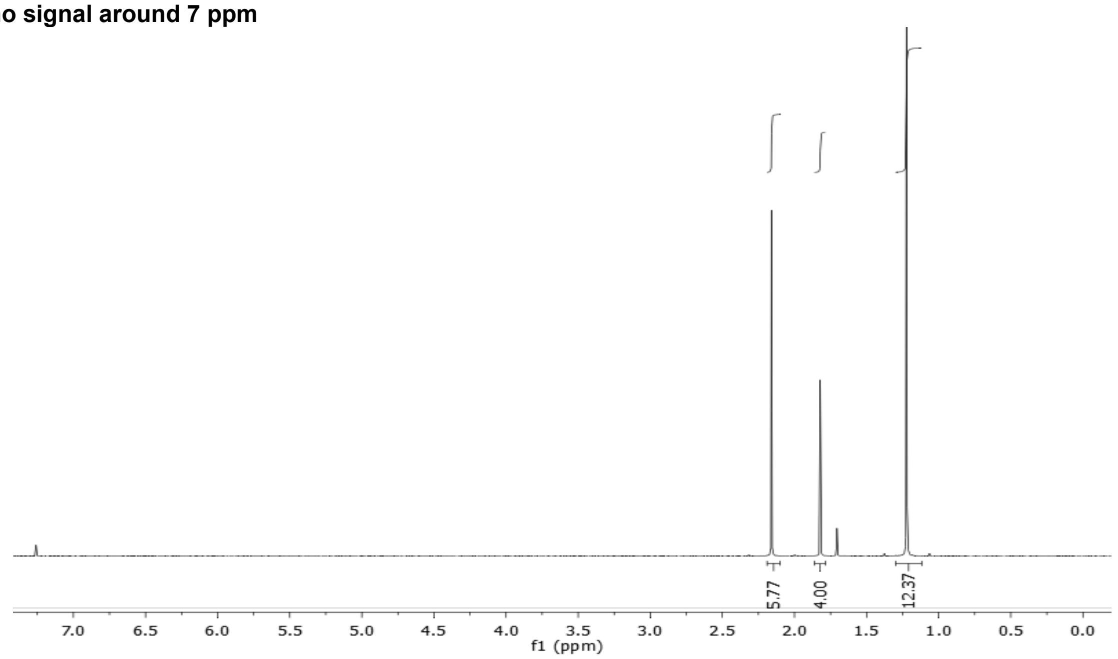


Figure 5-52: ^{1}H NMR (chloroform-d, δ =7.26) of polystyrene dissolving in TMO, then adding 10 µL acetone; TMO: δ=1.82 (4H, CH$_2$), δ=1.22 (12H, CH$_3$); acetone: δ=2.16. It shows no polystyrene dissolved in TMO as there is no signal around 7 ppm

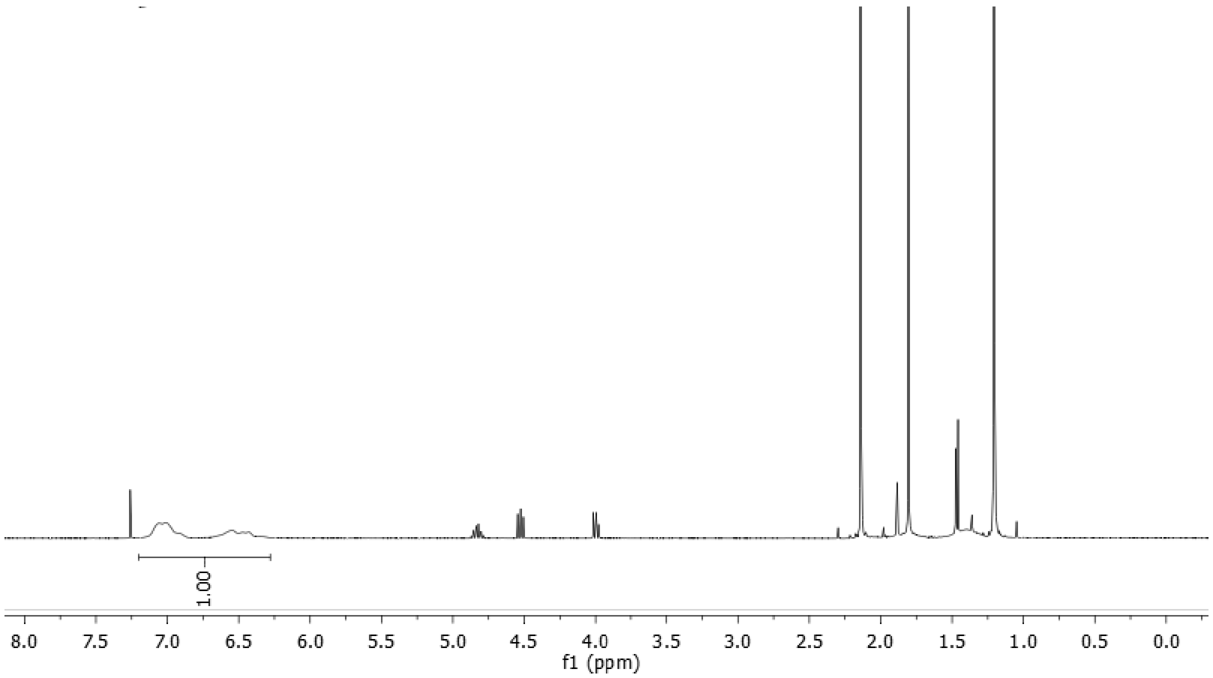


Figure 5-53: 1H NMR (chloroform-d, δ =7.26) of polystyrene dissolving in a mixture of PC and TMO (PC: TMO=10: 90), then adding 10 μL acetone. It shows polystyrene dissolves in this mixture as δ=7.25-6.25 corresponds to polystyrene units

Table 5-49: Swelling for crosslinked polystyrene resin, data used to construct Figure 2-68, Figure 2-69, Figure 2-70, Figure 2-71 and Figure 2-72

	Swelling for crosslinked polystyrene resin						
Solvent	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
propylene carbonate	0.30	0.32	0.31	0.1004	0.12	1.89	0.10
ethyl acetate	0.50	0.50	0.50	0.1004	0.12	3.78	0.00
PC:EA=10:90	0.53	0.55	0.53	0.1003	0.12	4.15	0.13
TMO	0.32	0.35	0.32	0.1006	0.12	2.09	0.20
PC:TMO=60:40	0.48	0.48	0.49	0.1004	0.12	3.62	0.07
ethanol	0.32	0.32	0.32	0.1004	0.12	1.99	0.00
cyclopentanone	0.78	0.78	0.78	0.1004	0.12	6.57	0.00
ethanol:cyclopentanone=15:85	0.80	0.78	0.78	0.1003	0.12	6.65	0.13
MeOH	0.35	0.35	0.36	0.1006	0.12	2.32	0.07
MeOH:cyclopentanone=10:90	0.80	0.80	0.80	0.1004	0.12	6.77	0.00
isopropanol	0.30	0.33	0.33	0.1008	0.12	1.98	0.20
isopropanol:cyclopentanone=20:80	0.78	0.78	0.78	0.0999	0.12	6.61	0.00

Table 5-50: Swelling for Wang resin, data used to construct Figure 2-68, Figure 2-69, Figure 2-70 , Figure 2-71 and Figure 2-72; more swelling supporting information for Wang resin can be seen in Appendix B (All line graphs of solvent systems for Merrifield resin)

			Swelling for Wang resin				
Solvent	Run1 (mL)	Run2 (mL)	Run3 (mL)	Weight (g)	Frit disc volume (mL)	Swelling (ml g^{-1})	Error (mL g^{-1})
propylene carbonate			Literatura data			1.80	0.00
ethyl acetate			Literatura data			3.80	0.00
PC:EA=10:90	0.58	0.58	0.58	0.0998	0.12	4.61	0.00
TMO	0.32	0.30	0.31	0.1009	0.13	1.78	0.10
PC:TMO=60:40	0.49	0.49	0.50	0.1008	0.12	3.70	0.07
ethanol			Literatura data			1.80	0.00
cyclopentanone			Literatura data			5.80	0.00
ethanol:cyclopentanone=15:85	0.80	0.80	0.80	0.1014	0.16	6.31	0.00
MeOH			Literatura data			1.80	0.00
MeOH:cyclopentanone=10:90	0.80	0.80	0.80	0.10	0.12	6.80	0.00
isopropanol			Literatura data			1.80	0.00
isopropanol:cyclopentane-one=20:80	0.79	0.79	0.78	0.1018	0.1	6.75	0.07

6. Abbreviations

BOP: (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

CPME: cyclopentyl methyl ether

CPME ether: cyclopentyl methyl ether

CPTN: cyclopentanone

CS_2: carbon disulphide

$CDCl_3$: chloroform-d

DCC: N, N'-dicyclohexylcarbodiimide

DIC: N, N′-Diisopropylcarbodiimide

1,2-DCB: 1,2-dichlorobenzene

DCM: dichloromethane

DMF: dimethylformamide

DIPEA: diisopropylethylamine

EA/EtOAc: ethyl acetate

EtOH: ethanol

FurfurylOH: furfuryl alcohol

HODhbt/HOOBT: 3-hydroxy-1,2,3-benzotriazin-4(3H)-one

HBTU:3-[bis(dimethylamino)methyliumyl]-3H-benzotriazol-1-oxide hexafluorophosphate

HOBt: hydroxybenzotriazole

IPrOAc: isopropyl acetate

IPrOH: isopropanol

MeCN: acetonitrile

MeOH: methanol

2-MeTHF: 2-methyl-THF, or 2-methyltetrohydrafuran

OxymaPure: ethyl 2-cyano-2-(hydroxyimino)acetate

PC: propylene carbonate

SPPS: solid-phase peptide synthesis

SPOS: solid-phase organic synthesis

TDBTU: N,N,N',N'-Tetramethyl-O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)uronium tetrafluoroborate

TBTU: O-(Benzotriazol-1-yl)-N, N, N′, N′-tetramethyluronium tetrafluoroborate

TMO: 2,2,5,5-tetramethyltetrahydrofuran or 2,2,5,5-tetramethyloxolane

TIPS: triisopropylsilane

TFA: trifluoroacetic acid

TFA-d: trifluoroacetic acid-d

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