APPLICATION OF THERMALLY ENHANCED HUISGEN CYCLOADDITION ON POLYSILOXANE FUNCTIONALIZATION

APPLICATION OF THERMALLY ENHANCED HUISGEN CYCLOADDITION ON POLYSILOXANE FUNCTIONALIZATION

By

MARK PASCOAL, B.Sc., M.Sc.

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirement

for the Degree

Master of Science

McMaster University

MASTER OF SCIENCE (2012)	McMaster University
(Chemistry)	Hamilton, Ontario

TITLE:	Application of Thermally Enhanced Huisgen Cycloaddition on Polysiloxane Functionalization
AUTHOR:	Mark Pascoal, B.Sc. M.Sc.
SUPERVISOR:	Professor Michael A. Brook
NUMBER OF PAGES:	xiii, 57

Abstract

The thermal azide-alkyne cycloaddition using electron deficient alkynes was used to functionalize polysiloxanes at low temperatures and without the need of a metal catalyst. We observed that the temperature at which cycloaddition began can be attributed to the identity of the alkyne's substituents (Chapter 2). We propose that the location of functionalization can be controlled by the specific introduction of electron deficient alkynes on terminal or pendant points on the polysiloxane. Polysiloxanes, each containing two electronically different alkynes, were prepared to show preferential functionalization of the more reactive alkyne without consuming the less reactive alkyne. The alkyne's reactivity can be modified by our choice of substituents. The extension of these results led to polysiloxane difunctionalization where the more reactive alkyne was consumed by a small azide followed by consumption of the less reactive alkyne with a bisazide siloxane. Thermal cycloaddition was used to introduce carbohydrates onto polysiloxanes without complicated protection/deprotection schemes and without catalysts (Chapter 3). The process was successful as propiolate-functionalized siloxane and azide-functionalized gluconamide reacted to produce a trisiloxane-functionalized gluconamide. Trisiloxane-functionalized gluconamide gelled diethyl ether at 3.0% gelator/solvent volume ratio becoming one of the few siloxane-based gelling agents.

Preface

The research work presented in this Master's thesis was carried out by the author between July 2010 and June 2012. The project was borne out of successes achieved in utilizing Cu(I)-catalyzed and non-catalyzed azide-alkyne cycloaddition on polysiloxane functionalization and crosslinking. Numerous publications using Cu(I)-catalyzed azide-alkyne cycloadditions for the functionalization and preparation of a wide range of materials depict its general usefulness. This led to our group using these reactions for polysiloxane functionalizations and crosslinking. Fortunately, our early studies were successful leading to the work on catalyst-free polysiloxane functionalization that is presented in this thesis.

The preparation of alkyne-functionalized siloxanes and polysiloxanes was carried out by the author under the guidance of Ferdinand Gonzaga. The preparation of the azide-functionalized carbohydrate and siloxane-functionalized carbohydrates were prepared by the author under the guidance of Ferdinand Gonzaga and Yang Chen.

Acknowledgement

I would like to thank Dr. Mike Brook for giving me the opportunity to work in his laboratory. He has provided me with guidance not only on research matters but also on personal matters. I have been fortunate to work with a supervisor who not only challenged me but also gave me encouragement when times were tough.

I would like to thank all of the professors who I had a chance to learn from over the years, Dr. Harald Stover, Dr. Alex Adronov, Dr. James McNulty, Dr. William Leigh and Dr. Todd Hoare. A special thanks goes out to Dr. Harald Stover and Dr. Alex Adronov for being part of my graduate committee and for giving good advice and assistance at those meetings.

I would also like to thank the Brook research group-Vinodh, Alan, Amanda, Helen, Marlena, Talena, Laura, Madiha, Jason, Nick, Yunping, Martin and Anna-for all their help and support. Special thanks to Dr. Ferdinand Gonzaga, John Grande and Dr. Yang Chen for all of the help with experimentation and the general direction of the thesis. I would have not gotten as far as I did without them.

A special thanks to Frank Gibbs, Dr. Steve Kornic and Dr. Bob Berno for their help with the instrumentation and DSC analysis. A special thanks to NSERC for funding.

A special thanks also goes out to my undergraduate classmates-Sam, Spencer, Dave, Fan, and Janice- for their support and the good times.

Finally, I would like to give my gratitude to my family for giving me the much needed support and encouragement in completing the thesis.

Table of Contents

List of Figures

List of Tables

List of Abbreviations and Acronyms

$CDCl_3$	Deuterated Chloroform
CuAAC	Copper(I)-Catalyzed Azide Alkyne Cycloaddition
D_4	Octamethylcyclotetrasiloxane
DCC	Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DSC	Differential Scanning Calorimetry
EDC	1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide
FMO	Frontier Molecular Orbitals
GPC	Gel Permeation Chromatography
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
NMR	Nuclear Magnetic Resonance
PEG	Polyethylene glycol
SEM	Scanning Electron Microscopy
THF	Tetrahydrofuran

Chapter 1

Introduction

Silicones-Preparation

Polysiloxanes, or silicones, are polymers comprising repeating siloxane (Si-O) linkages with organic substituents attached to the silicon center. Usually these substituents are alkyl, allyl, hydride, hydroxy or phenyl groups. Silanes, precursors to silicones, are attractive materials because they possess reactive functional groups that can be introduced onto polysiloxanes for subsequent reactions to prepare materials with different properties not found with pure silicones. Silicones, including functional silicones, are widely used in the contact lens[1], electronic coatings[2], adhesives and sealants[3] and the cosmetics[4] industry. Expanding their utility by increasing the breadth of available silicones is a focus of our work in silicone research. Polysiloxanes are prepared according to the Direct process, in which elemental silicon is reacted with methyl chloride under copper catalysis to prepare predominantly dimethyldichlorosilane (80%) along with other chlorosilanes (Figure 1A). These chlorosilanes undergo hydrolysis into silanediols, which condense into a mixture of linear oligomers and cyclic siloxanes (Figure 1B,C). The products of the hydrolysis step are strongly dependent on the reaction conditions. An important factor is the water concentration, which dictates what functional groups exist on the termini of the low molecular weight oligomers. With excess water present, the linear siloxanes will have terminal hydroxy groups while with minimal water present they will bear chloro groups[5]; cyclic silicones like D_3 $(Me_2SiO)_3$ and D_4 $(Me_2SiO)_4$ are also major products of the process. It is worth noting that linear siloxanes that possess a mixture of end groups are also possible. In either case, the terminal groups can be converted into organo-functional groups if

desired, but normally these 'hydrolyzates' are directly converted into higher molecular weight materials using condensation catalysts.[6]

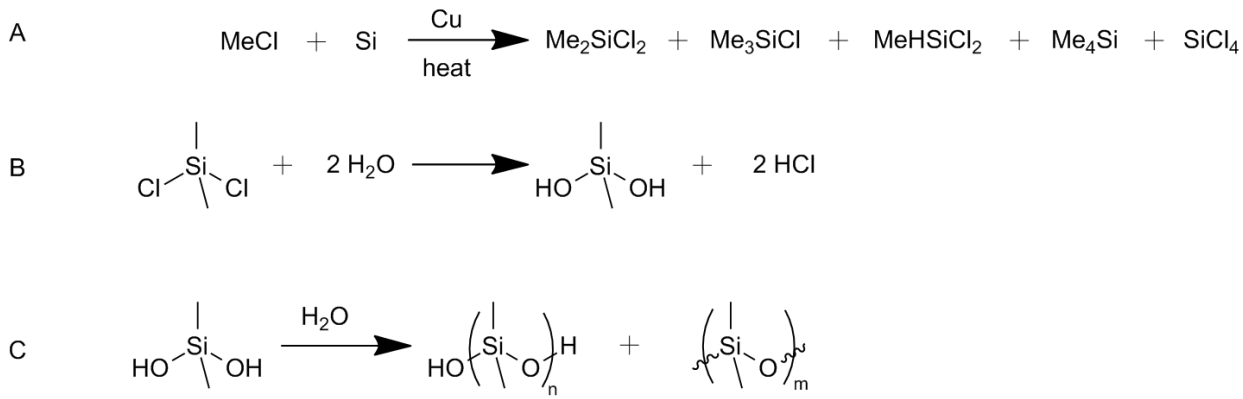


Figure 1: A: Oxidative Addition B: Hydrolysis C: Condensation

High molecular weight polysiloxanes are normally prepared from siloxane hydrolyzates typically by two methods: kinetic and equilibration control. The choice between the two methods depends on whether well-defined silicones are required. If well-defined materials are needed, kinetic control leads to polysiloxanes with narrow polydispersity ($M_w/M_n \approx 1$) and very high molecular weights (Figure 2).[7] Under kinetic control, the polymerization is driven by the release of ring strain upon ring opening of D_3 (hexamethylcyclotrisiloxane) by the initiator. The molecular weight is increased by continuous D_3 opening by terminal silanolates of the growing chain. Termination caps the growing chain with a chlorosilane; the chemical nature of the other terminus is determined by the catalyst that initiates the process.

The alternative method, and the one most relevant to our work, is equilibration polymerization, which is used when well-defined materials are not needed. Using this method, polysiloxanes with broad polydispersities ($M_w/M_n > 2$) are produced. Equilibration polymerization is carried out by mixing cyclic oligomers (i.e., D_4), a catalyst (strong acid or base), and monofunctional

end groups to prepare high molecular weight polysiloxanes (Figure 3). However, the polymerization produces not only the linear polymer but also cyclic siloxanes during the equilibration. The concentration of the cyclic siloxanes is nearly equal to long chain polymers, as indicated by the equilibrium constant of approximately 1. This has an effect on the polymer yield, as diluting the components by the addition of solvents or even by using siloxanes with bulky groups will lead to a reduction in the yield of polymer.[8] The polymerization is driven completely by the increase in entropy of the growing linear chain, as it possesses higher conformational mobility compared to the cyclic siloxanes. The molecular weight of the linear polymer is dependent on the ratio of the equilibrium concentration of R_2SiO to the concentration of terminal groups according to Eq. 1.[9]

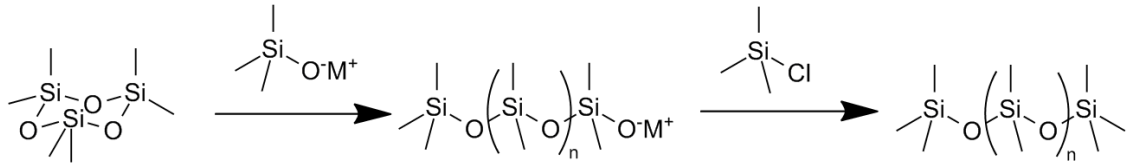


Figure 2: Kinetic Polymerization

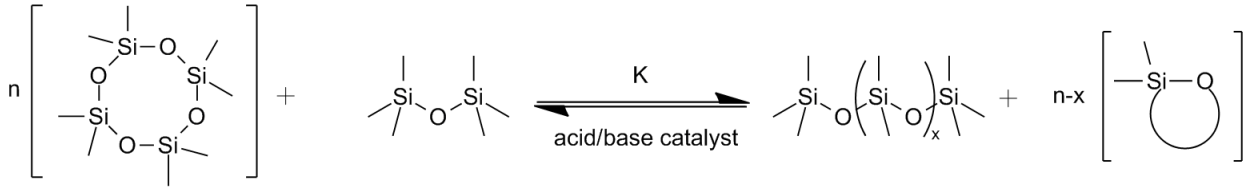


Figure 3: Equilibration Polymerization

$$M_n = \frac{2[R_2SiO]_{eq} M_o}{[Term]}$$

Eq. 1: Molecular weight dependence on $[R_2SiO]_{eq}$: [Term]

Silicone Functionalization

Reactive polysiloxanes are widely used in industry. For example, in the sealants and coatings industry they are coupled to other materials such as polyurethanes. Functional groups are usually introduced as either terminal or pendant groups. There are two general methods of

functionalizing polysiloxanes: i) direct functionalization of an existing polymer chain and ii) polymerization of functionalized starting materials. The first method involves introducing new functional groups onto already functionalized polysiloxanes. The most famous reaction for direct functionalization is hydrosilylation. Hydrosilylation involves the addition of the Si-H bond across a π bond, typically a C=C bond, such as an allyl group containing a functional group (Figure 4).[10] The reaction is catalyzed by a platinum catalyst and produces primarily the anti-Markovnikov product with very little of the Markovnikov product (Figure 4A). Another method of direct functionalization of groups already on side chains is to use substitution reactions. This can include the displacement of chloro and bromo groups by a reactive nucleophilic substrate (Figure 4B).

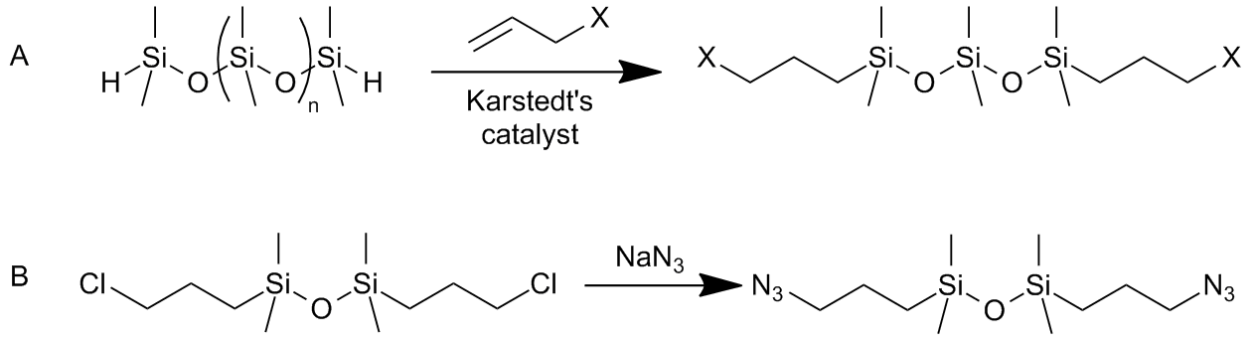


Figure 4: A: Hydrosilylation and B: S_N2 reaction to give functional silicones

The second method of functionalizing polysiloxanes involves using equilibration polymerization with functionalized, low molecular weight siloxanes or cyclic siloxanes (Figure 5). The choice of which functionalized siloxane to use is dependent upon where the functional group is to be located: either at terminal or pendant positions.[11] To introduce functional groups as terminal groups, the polymerization is done with a functionalized disiloxane M^xM^x, where X represents the functional group, along with cyclic siloxane D_4 (octamethylcyclotetrasiloxane) and the catalyst (Figure 5A). To introduce functional groups as pendant groups, functionalized cyclic

siloxane D_4^x where one of the silicon atoms has a functional group X, is used for polymerization (Figure 5B). The drawback with this method is that introducing functional groups onto cyclic siloxanes can potentially cause ring opening which will complicate purification prior to polymerization. This difficulty is circumvented by using a functionalized trisiloxane in the form of MD^xM where X represents the functional group, in addition to D_4 for polymerizations (Figure 5C).

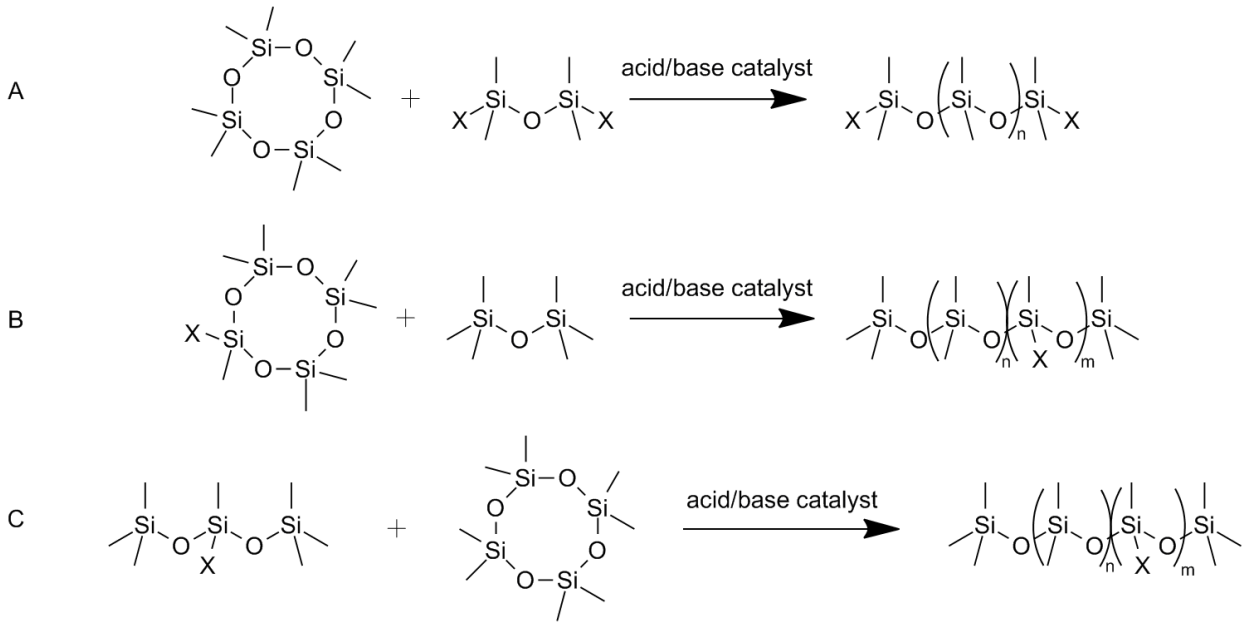


Figure 5: Terminal functionalization A: $D_4 + M^xM^x$. Pendant functionalization B: D_4^x + MM and C: $MD^xM + D_4$

As stated beforehand, reactive polysiloxanes are used to attach substrates onto polysiloxanes to prepare materials with properties not found with pure silicones. However, there are disadvantages with common functionalization processes such as hydrosilylation where expensive platinum catalysts are needed. Therefore, we studied the application of an alternative coupling reaction that is proven to provide efficient and easy coupling between materials: Cu(I) azide-alkyne cycloaddition (CuAAC) and the metal-free or click chemistry (Figure 6).

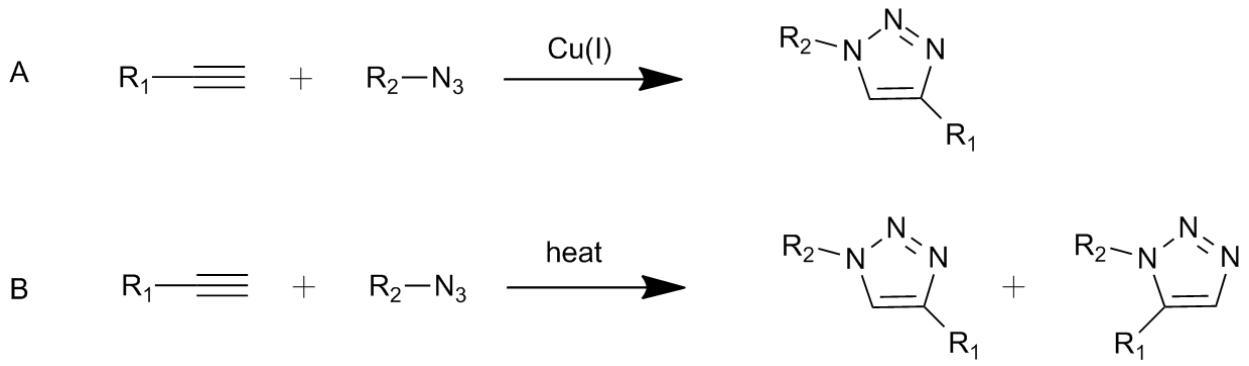


Figure 6: A: Cu(I)-catalyzed click reaction. B: Huisgen cycloaddition

Cu(I)-catalyzed cycloaddition (CuAAC)

Click chemistry is a concept that utilizes selective, high-yielding reactions under mild, water-tolerant conditions to bind two molecular building blocks together. The most famous click reaction used is the Cu(I) azide-alkyne cycloaddition (CuAAC) developed by Sharpless.[12] The reaction involves the cyclization of an azide and terminal alkyne into the 1,4-regioisomer of the 1,2,3-triazole (Figure 6A). The benefits of this reaction are that it is easy to carry out, a variety of Cu(I) sources can be used, and the reaction can be done in many solvents, including water. Although many copper sources can be used, normally a Cu(II) source is used, such as $CuSO_4$, in conjunction with a reducing agent like sodium ascorbate: this is currently the most popular method in the literature to generate reactive Cu(I) in situ.[13]

The Cu(I) click reaction has been utilized in materials and polymer functionalization using a wide range of substrates which gives it great versatility.[14] Although the success of Cu(I) click reactions are well documented, disadvantages still exist with its use. According to Sletten et al., the Cu(I) catalyst causes mammalian cell death when the Cu(I) click reaction was used for intercellular couplings.[15] Another important disadvantage with the Cu(I) click reaction is the

difficulty of removing the Cu(I) catalyst after reaction. As the triazoles are nucleophilic, they are capable of binding the Cu(I) catalyst (acting as ligands) making purification difficult.

Huisgen Cycloaddition

Due to the drawbacks with CuAAC, research into using the non-catalyzed alternative to CuAAC, the Huisgen cycloaddition (Figure 6B)[16], has been done. The theoretical foundation behind the Huisgen cycloaddition is explained by Fukui's Frontier Molecular Orbital (FMO) theory.[17] FMO theory simplifies the orbital interactions of the dipole and dipolarophile by only looking at the orbital interactions that produce a net energy change, that is, the HOMO and LUMO. For the two reaction partners, there will be two frontier orbital interactions with orbital symmetry appropriate for cycloaddition to occur: $HOMO_{dipole}$-$LUMO_{dipolarophile}$ and $HOMO_{dipolarophile}$-$LUMO_{dipole}$. However, the interaction with the lower HOMO-LUMO gap will have a lower activation barrier for cycloaddition to occur.[18]

Thermally allowed [3+2] dipolar cycloadditions involving terminal dipolarophiles typically produce regioisomers. Each regioisomer is a consequence of one of the frontier orbital interactions: $HOMO_{dipole}$-$LUMO_{dipolarophile}$ or $HOMO_{dipolarophile}$-$LUMO_{dipole}$. As stated above, the interaction with the smaller HOMO-LUMO gap is favoured and produces more of the regioisomer than the alternative interaction. Regioselectivity can be explained by looking at the HOMO-LUMO arrangements (Figure 7A). For azides and alkynes, if the thermal cycloaddition occurs via the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction, it is a type I cycloaddition that produces the 1,4 regioisomer. If the thermal cycloaddition occurs via the $HOMO_{dipolarophile}$-$LUMO_{dipole}$ interaction, it is a type III cycloaddition, which produces the 1,5 regioisomer. If the two frontier orbitals possess a similar HOMO-LUMO gap then both interactions must be taken into account when discussing reactivity conditions. These arrangements are type II cycloadditions. For type II

cycloadditions, both regioisomers are produced. However, one would have to pay special attention to the substituents as it could alter the regioisomeric distribution.

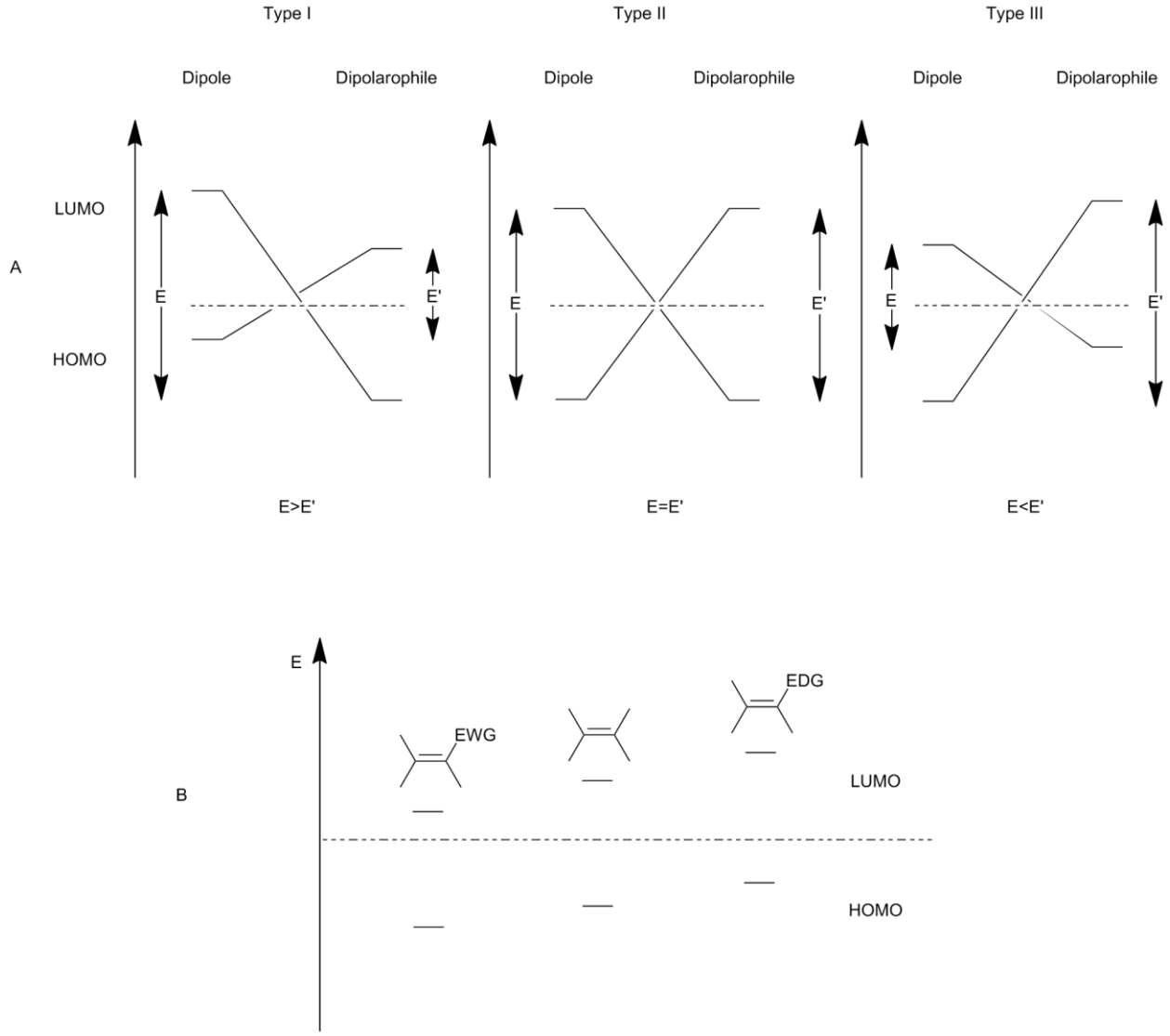


Figure 7: A: HOMO-LUMO types. B: Effect of substituents on orbital energies

The reactivity of thermal cycloadditions is influenced by the presence of substituents adjacent to the dipoles and dipolarophiles. This leads to alterations in the HOMO and LUMO energies which affects the HOMO-LUMO gap.[19] In other words, by choosing the correct combination of substituents one can alter the cycloaddition thermal reactivity (Figure 7B). Three types of substituents affect the outcome of [3+2] dipolar cycloadditions: electron withdrawing (EWG),

electron donating (EDG) and conjugated groups.[20] Electron withdrawing groups lower the energies of the LUMO and HOMO of the dipolarophile leading to the acceleration of type I cycloadditions, inhibition of type III cycloadditions and an increase in the formation of an excess of 1,4-regioisomers in type II cycloadditions. In contrast, electron donating groups increase the energies of the HOMO and LUMO of the dipolarophile, which inhibits type I cycloadditions, accelerates type III cycloadditions and increases the formation of an excess of the 1,5-regioisomer in type II cycloadditions. For conjugated substituents, the HOMO's energy is increased while the LUMO's energy is lowered. This causes the HOMO-LUMO gap to decrease, which is associated with an accelerated cycloaddition. So far, the energy changes we discussed were for only the dipolarophile, the HOMO-LUMO gap is also affected by the substituents on the dipole.[21] For dipoles, the trends are reversed compared to dipolarophiles. Electron donating groups accelerate type I cycloadditions and decelerate type III cycloadditions. Electron withdrawing groups accelerate type III cycloadditions and decelerate type I cycloadditions.

This thesis will discuss the formation of specific silicones and, in particular, demonstrate functionalization control using thermally activated alkynes incorporating azide-functionalized hydrophiles without either protection/deprotection steps or metal catalysts. Our group has had success in attaching small molecules and PEG onto polysiloxanes using Cu(I) and catalyst-free cycloaddition. Our objective is to expand the utility of the Huisgen cycloaddition by studying the possibility of thermal functionalization control by modifying the electronic properties of alkynes tethered to the silicone backbone. The extension of this work leads to the functionalization of polysiloxanes with carbohydrates; a difficult substrate to incorporate as the hydroxy groups complicate synthesis and analysis.

Thesis Objectives

The experimental work is divided into two chapters. Chapter 2 demonstrates functionalization control of pendant alkynes versus terminal alkynes using electronically different alkynes. We introduced thermally activated alkynes with different substituents onto polysiloxanes to show selective functionalization of one alkyne of higher reactivity over less reactive ones. Chapter 3 demonstrates the functionalization of propiolate-functionalized siloxanes with azide-functionalized carbohydrates without using protection or deprotection steps or catalysts. Furthermore, the carbohydrate-functionalized siloxane was able to gel diethyl ether with a 3.0% gelator/solvent volume ratio. Finally, Chapter 4 presents a brief conclusion.

References

[1] Domschke, A. M.; Holland, T. V.; Turek, R. C. W.O Patent 2011/034801 A1 (2011).
[2] Lien, Q. S.; Nakos, S. T. U.S. Patent 4,528,081 (1985).
[3] Blizzard, J. D. U.S. Patent 4,309,520 (1982).
[4] Horino, M. U.S. Patent 7,682,622 (2010).
[5] Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*, John Wiley & Sons, Inc.: Toronto, 2000, p. 258.
[6] Ref. 5, p. 262-263.
[7] Ref. 5, p. 268-9.
[8] Semlyen, J. A., *Cyclic Siloxane Polymers*, In *Siloxane Polymers*, Clarson, S. J.; Semlyen, J. A. Eds., Prentice Hall: Englewood Cliffs, NJ, 1993, Chap. 3, p. 135.
[9] Ref. 5, p. 263.
[10] Hayakawa, K.; Kawase, K.; Yamakita, H.; Yumoto, T. *J. Polym. Sci., Polym. Chem. Ed.* **1981**, *19*, 3145-3153.
[11] Ref. 5, p. 266-8.
[12] Liang, L.; Astruc, D. *Coord. Chem. Rev.* **2011**, *255*, 2933-2945.
[13] Meldal, M. *Macromol. Rapid Commun.* **2008**, *29*, 1016-1051.
[14] Li, H.; Sun, J.; Qin, A.; Tang, B. Z. *Chin. J. Polym. Sci.* **2012**, *30*, 1-15.
[15] Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974-6998.
[16] Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Nat. Acad. Sci.* **2007**, *104*, 16793-16797.
[17] Fleming, I. *Frontier Orbitals and Organic Chemicals Reactions*, Wiley and Sons, Inc. New York, 1976, p.88-95.
[18] Ess, D. H.; Jones, G. O.; Houk, K. N. *Adv. Synth. Catal.* **2006**, *348*, 2337-2361.
[19] Houk, K. N.; Sims, J.; Watts, C.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301-7315.
[20] Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569-594.

[21] Fleming, I. *Frontier Orbitals and Organic Chemicals Reactions*, Wiley and Sons, Inc. New York, 1976, p.110-121.

Chapter 2

Thermal control of Silicone Network Structure Using Metal-Free Click Crosslinking

Abstract

The thermal azide-alkyne cycloaddition using electron deficient alkynes has been previously applied to the room temperature crosslinking of polysiloxanes. However, to date, only propiolates have been used as an electron deficient alkynes to functionalize polysiloxanes. Herein, we extend the methodology of functionalizing polysiloxanes using alkynes with differing electronic demands and, therefore, with different reactivities. To obtain a more thorough knowledge of the effect of the alkyne's electron density on the cycloaddition, differential scanning calorimetry was used to determine the temperature at which triazole formation is initiated for a variety of alkynes. The study showed propiolates to have the lowest onset cycloaddition temperature of those studied: that is, it was a more reactive alkyne than propargyl esters or amides. Two distinct difunctional polysiloxane copolymers were prepared containing two electronically different alkynes in each case. Benzyl azide was used to demonstrate that the propiolate alkyne could be reacted in preference to the more electron rich amide-functionalized alkyne on polysiloxane **14**, although not specifically. By contrast, the reaction of propiolates was specific when compared to propargyl alkynes on polysiloxane **15** as shown by monitoring the alkyne proton signals via ^{1}H NMR. The residual propargyl alkynes were available for a second reaction as demonstrated in a chain extension reaction with azide-terminated disiloxanes using copper assisted click chemistry.

Introduction

The Cu(I)-catalyzed click reaction (CuAAC) involves the cyclization of an azide and alkyne pair into the 1,4-regioisomer of the 1,2,3-triazole. CuAAC has been widely applied in the literature in polymerizations, surface modifications and polymer functionalizations due to its efficiency, tolerance of a wide range of solvents and its chemoselectivity with many other functional groups.[1] The tolerance of the CuAAC process to a wide range of reaction conditions is particularly advantageous for polymer functionalizations by substrates of opposite polarity. For example, the coupling of carbohydrates onto polysiloxanes is difficult and usually requires OH and NH protection prior to coupling. However, Halila et al. functionalized azide-containing polysiloxanes with N-propargylglycosylamines using CuAAC without the need for protection/deprotection steps.[2] Similarly, Gonzaga et al. demonstrated the versatility of CuAAC by introducing a variety of small molecule substrates, ranging from alkyne-functionalized non-polar compounds to saccharides, onto azide-functionalized siloxanes and polysiloxanes without protection/deprotection.[3]

In addition to inorganic and polymeric materials, CuAAC has been extensively applied to the process of functionalizing biological materials.[4] Unfortunately, CuAAC is not applicable in intercellular couplings as the Cu(I) causes mammalian cell death.[5] Although less biologically active Cu(I) catalytic systems have been developed, CuAAC is not applicable for biological functionalizations within living cells[6,7] or, therefore, for polymers that will ultimately be used as biomaterials.

Due to the challenges associated with CuAAC for biologically relevant systems, research into the non-catalyzed Huisgen cycloaddition as an alternative coupling reaction has been explored.[8] The major drawback of the Huisgen cycloaddition is the slow reaction rate; when compared to the

rate of the CuAAC at room temperature, there exists a 10^7 difference in magnitude.[9] Fortunately, the reactivity of the Huisgen cycloaddition can be enhanced by altering the alkyne's electronic properties. According to the Woodward-Hoffmann rules for orbital-controlled cycloadditions, if the energy gap between the azide HOMO and alkyne LUMO orbitals is reduced with the use of electron deficient alkynes, electron rich azides, or both, then the cyclization rate will be enhanced.[10]

Gonzaga et al.[8] demonstrated that the application of the Huisgen cycloaddition to room temperature crosslinking is feasible by preparing propiolate-functionalized polysiloxanes that were reacted with bisazide-functionalized poly(ethylene glycol). In contrast, Bertozzi et al. performed low temperature non-catalyzed cycloadditions with cyclooctynes functionalized with propargylic fluorines. By subjecting the alkyne to ring strain, the release of strain energy is the driving force for the cycloaddition.[11] The presence of electron-withdrawing fluorine atoms further lowers the alkyne LUMO, which additionally enhances the cycloaddition rate.[5] Bertozzi and her group have developed catalyst-free, ring strained cycloadditions as one of the few viable methods for in vivo functionalization of biological entities without significant cell death and with reaction rates comparable to Cu(I)-catalyzed reactions.[7]

Since the Huisgen cycloaddition rate is dependent on alkyne electron density, it should be possible to control the introduction of more than one functional group by the use of both highly reactive, and less reactive alkynes on a single polymer chain. Therefore, we have examined the ability to selectively modify polysiloxane chains using the click reaction in a controlled manner by use of multiple, electronically different alkynes. First, a model series of siloxanes was prepared with different substituents at the alkyne's α-position in order to study the temperature where cyclization begins and establish relative reactivities. Using this data, we prepared two

polysiloxanes, each possessing two electronically different alkynes, by siloxane polymerization of alkyne-functionalized siloxanes. In one case, the difference in click reactivity was not sufficient for complete modification of pendant alkyne to occur preferentially to terminal, more electron rich alkynes. In the other case, specific modification was possible by first consuming very reactive pendant alkynes, and second less reactive propargyl groups.

Experimental Section

Materials and Methods

1,3-Bis(chloropropyl)tetramethyldisiloxane was obtained from ABCR. 1,3-Bis(trimethylsiloxy)methylsilane, 3-aminopropylmethylbis(trimethylsiloxy)silane, octamethylcyclotetrasiloxane (D_4), and 1,3-bis(aminopropyl)tetramethyldisiloxane were obtained from Gelest. Sodium azide (95%) was purchased from J.T. Baker. Propiolic acid (95%), triflic acid (98%), benzyl bromide (98%), sodium bicarbonate, 4-dimethylaminopyridine (99%), succinic anhydride (99%), 1-ethyl-3-(3-dimethylaminopropylcarbodiimide hydrochloride)(EDC)(98%), dicyclohexylcarbodiimide (DCC) (99%), allyl alcohol (98%), diethyl acetylenedicarboxylate (98%), 4-(trimethylsilyl)-3-butyn-2-one (98%), propargyl alcohol (99%) and (~2% Pt) platinum(0)-1,1,3,3-tetramethyldisiloxane complex (Karstedt's catalyst) in xylenes were obtained from Sigma-Aldrich. All materials were used as received. 1,3-Bis(azidopropyl)tetramethyldisiloxane was prepared using a literature procedure.[3] Benzyl propiolate[12] and benzyl propiolamide[13] were prepared using literature procedures. Benzylazide was prepared using a literature procedure.[14]

^{1}H NMR and ^{13}C NMR were recorded at room temperature on a Bruker AC-200 and AC-600 spectrometer using deuterated solvents ($CDCl_3$). High-resolution mass spectrometry was

performed using a Hi-Res Waters/Micromass Quattro Global Ultima (Q-TOF mass spectrometer).

Differential Scanning Calorimetry (DSC) analysis

The alkyne under study was added into a vial containing 1,3-bis(azidopropyl)tetramethyl-disiloxane (~5 mg). The sample was prepared according to [C≡C]:[N_3] ratios of 1:1; the sample size ranges between 5-10 mg. The sample was examined using a TA Instruments DSC 2910 in a standard aluminum pan purged with nitrogen gas. The pan was placed into the standard cell and heated at 5 °C/minute over a temperature range from room temperature to 150 °C.

3-Hydroxylpropylmethylbis(trimethylsiloxy)silane

1,3-Bis(trimethylsiloxy)methylsilane (15 g, 70 mmol) was added into a 150 mL flask containing allyl alcohol (4.76 g, 85 mmol) and toluene (8 mL). Karstedt's catalyst (4 drops) was added and the reaction was flushed with nitrogen and left overnight. Decolorizing charcoal was added into the reaction and, after 30 min, filtered off. The solvent and excess allyl alcohol were evaporated in vacuo to afford a clear oil (17.18 g, yield 90%).

^{1}H NMR 200 MHz ($CDCl_3$): 0.07 (s, 21H), 0.40 (m, 2H), 1.52 (m, 2H), 3.55 (t, 2H, J = 6.72 Hz).

^{13}C NMR 200 MHz ($CDCl_3$): -0.23, 1.97, 13.35, 26.55, 65.60.

HRMS (ESI): m/z $[M+H]^+$: calcd for $C_{10}H_{29}O_3Si_3$: 281.62; found 283.0.

General Procedure for Propiolate Ester Synthesis, Shown for Trisiloxane 9

Dicyclohexylcarbodiimide (7.22 g, 35 mmol), dissolved in dichloromethane (5 mL), was added into a 150 mL flask cooled to -35 °C containing dichloromethane (10 mL) and propiolic acid (2.94 g, 42 mmol). 3-Hydroxylpropylmethylbis(trimethylsiloxy)silane (4.45 g, 20 mmol) and 4-dimethylamino-pyridine (50 mg, 0.41 mmol), dissolved in dichloromethane (10 mL), were added portionwise and the reaction was kept at around -35 °C for 3-4 h. The reaction was then cooled

to -75 °C and left overnight to warm to room temperature. Dicyclohexylurea was filtered through Celite using dichloromethane as a solvent. The solvent was removed in vacuo and the crude product was refiltered in diethyl ether. The product was purified using silica gel gravity chromatography (19:1 v/v hexane:ethyl acetate) to produce a clear colorless oil (1.67 g, yield 88%).

^{1}H NMR 200 MHz ($CDCl_3$): -0.06 (s, 3H), 0.00 (s, 18H), 0.38 (m, 2H), 1.60 (m, 2H), 2.76 (s, 1H), 4.05 (t, 2H, J = 7.02 Hz).

^{13}C NMR 200 MHz ($CDCl_3$): -0.26, 1.95, 13.42, 22.34, 68.74, 74.49, 74.97, 152.93.

HRMS (EI): m/z $[M+H]^+$ calcd for $C_{16}H_{29}O_4Si_3$: 332.1295; found: 332.1279.

Trisiloxane 10

Dicyclohexylcarbodiimide (8.86 g, 42.9 mmol); propiolic acid (3 g, 42.8 mmol); 3-amino-propylmethylbis(trimethylsiloxy)silane (10 g, 35.7 mmol); 4-dimethylaminopyridine (50 mg, 0.41 mmol). The product was purified with silica gel gravity chromatography (4:1 v/v hexane: ethyl acetate) to produce a viscous orange oil (6.88 g, yield 58%).

^{1}H NMR 200 MHz ($CDCl_3$): 0.04 (s, 21H), 0.46 (m, 2H), 1.55 (m, 2H), 2.76 (s, 1H), 3.22 (m, 2H), 6.02 (bs, 1H).

^{13}C NMR 200 MHz ($CDCl_3$): 0.35, 1.81, 14.41, 22.91, 42.53, 72.98, 79.25, 152.30.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{29}O_2NSi_3$: 332.1501; found: 332.1501.

Trisiloxane 11

Dicyclohexylcarbodiimide (1.76 g, 8.82 mmol); monopropargyl ester of butanedioic acid (1.71 g, 10.95 mmol); 3-hydroxypropylmethylbis(trimethylsiloxy)silane (1.92 g, 6.85 mmol); 4-dimethylaminopyridine (50 mg, 0.41 mmol). The product was purified with silica gel gravity chromatography (4:1 v/v hexane: ethyl acetate) to produce a clear oil (0.98 g, yield 35%).

^{1}H NMR 600 MHz ($CDCl_3$): -0.05 (s, 3H), 0.07 (s, 18H), 0.43 (m, 2H), 1.62 (m, 2H), 2.45 (t, 1H, *J* = 4.92 Hz), 2.65 (m, 4H), 4.02 (t, 2H, *J* = 6.90 Hz), 4.68 (d, 2H, *J* = 2.52 Hz).

^{13}C NMR 600 MHz ($CDCl_3$): -0.10, 1.92, 2.31, 13.73, 22.70, 29.24, 52.46, 53.72, 67.51, 75.23, 77.81, 171.84, 172.34.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{34}O_6Si_3Na$: 441.1561; found: 441.1548.

Disiloxane 12

Dicyclohexylcarbodiimide (6.03 g, 30 mmol); propiolic acid (2.60 g, 37.5 mmol); 1,3-bis(aminopropyl)tetramethyl-disiloxane (3.73 g, 15 mmol); 4-dimethylaminopyridine (40 mg, 0.32 mmol). The product was purified using silica gel gravity chromatography (2:1 v/v hexane:ethyl acetate) to produce a yellow solid (2.81 g, yield 64%).

^{1}H NMR 200 MHz ($CDCl_3$): 0.03 (s, 12H), 0.49 (m, 4H), 1.53 (m, 4H), 2.75 (s, 1H), 3.26 (m, 4H, J= 6.36 Hz), 6.34 (bs, 2H).

^{13}C NMR 200 MHz ($CDCl_3$): 0.29, 15.07, 23.02, 42.81, 73.58, 77.52, 152.67.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{29}O_3N_2Si_2$: 353.1717; found 353.1701.

Polysiloxane Copolymer 14

Octamethylcyclotetrasiloxane (1.66 g, 5.6 mmol) and trisiloxane **9** (0.5 g, 1.50 mmol) were added to a 20 mL vial containing a solution of disiloxane **12** (0.60 g, 1.70 mmol) and dichloromethane (2 mL). Trifluoromethanesulfonic acid (50 µL, 0.56 mmol) was added and the reaction was left stirring for 2 d at room temperature. After the second day, dichloromethane was evaporated by nitrogen and the reaction was left stirring for two more days. Magnesium oxide (0.5 g) was added to the vial and the reaction was allowed to stir for 30 min. Hexane (15 mL) was added and the magnesium oxide was filtered off. The crude product was transferred to the Kugelrohr apparatus and the mixture was distilled at 130 °C and 0.1 Torr for 2h to give a slightly

orange, viscous oil (0.76 g, yield 24%, GPC (M_n= 2910 g/mol; M_w= 3485 g/mol, M_w/M_n= 1.197).

^{1}H NMR 200 MHz ($CDCl_3$): 0.00 (s, 302H), 0.50 (m, 15H), 1.54 (m, 6H), 1.70 (m, 6H), 2.75 (s, 2H), 2.83 (s, 2H), 3.26 (m, 5H), 4.15 (t, 4H, *J* = 6.72 Hz), 5.97 (bs, 2H).

^{13}C NMR 600 MHz ($CDCl_3$): -0.32, 0.38, 1.06, 1.31, 1.43, 1.55, 2.05, 13.47, 15.60, 22.38, 23.49, 42.95, 68.80, 73.11, 74.59, 74.82, 75.10, 77.81, 152.34, 153.05.

^{29}Si NMR 600 MHz ($CDCl_3$): -23.52, -22.09, -21.96, -21.67, -21.43, -21.02, 7.22, 7.37

Polysiloxane Copolymer 15

Octamethylcyclotetrasiloxane (0.9 g, 3.04 mmol) was added to a 50 mL flask containing trisiloxane **9** (0.26 g, 0.81 mmol), disiloxane **13** (0.55 g, 1 mmol) and dichloromethane (2 mL). Trifluoromethanesulfonic acid (50 µL, 0.56 mmol) was added and the flask was placed under reduced pressure for 2 d. After the second day, dichloromethane was evaporated by nitrogen and the reaction was left stirring for two more days. Magnesium oxide (0.5 g) was added and allowed to stir for 30 min. Hexane was added and magnesium oxide was filtered off. The crude product was transferred to the Kugelrohr apparatus, distilled at 130 °C and 0.1 Torr for 2 h under high vacuum. After distillation, a light orange viscous oil was produced (1.03 g, yield 61%, GPC (M_n= 5170 g/mol, M_w= 6720 g/mol, M_w/M_n= 1.299)).

^{1}H NMR 500 MHz ($CDCl_3$): 0.07 (m, 852H), 0.52 (m, 35H), 1.38 (m, 12H), 1.63 (m, 10H), 1.70 (m, 10H), 2.45 (s, 2H), 2.66 (m, 13H), 2.82 (s, 4H), 4.07 (m, 6H), 4.11 (m, 6H), 4.68 (s, 4H).

^{13}C NMR 600 MHz ($CDCl_3$): -0.31, 0.42, 1.32, 1.41, 2.05, 13.60, 18.10, 19.93, 22.59, 29.03, 32.37, 52.57, 53.67, 64.94, 66.37, 67.49, 68.81, 74.61, 75.22, 153.05, 171.81, 172.38, 172.59, 172.66.

^{29}Si NMR 600 MHz ($CDCl_3$): -23.52, -22.26, -22.08, -21.96, -21.67, -21.42, 7.26.

Following Click Selectivity for the Different Alkynes of Polysiloxane 14 using ^{1}H NMR Spectroscopy

Benzyl azide (2 eq, 0.014 g, 0.0107 mmol) was added into each vial containing polysiloxane **14** (1 eq, 0.2 g, 0.053 mmol) and 500 µL of $CDCl_3$. Each vial was stirred and heated at i) 35 °C and ii) 60 °C, respectively, for one week. The ^{1}H NMR spectrum was obtained once every 2 d and alkyne integrations were measured (Table 1, Table 2).

Table 1: Alkyne selectivity measurements of Polysiloxane **14** done at 35°C

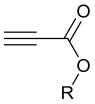
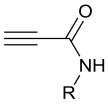
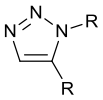
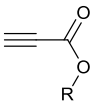
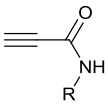
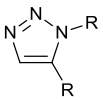
Time (d)			
0	2.26	1.81	0
2	1.84	1.70	0.52
4	2.06	1.92	1.28
6	1.61	1.45	1.00
8	1.54	1.46	1.06

Table 2: Alkyne selectivity measurements of Polysiloxane **14** done at 60°C

Time (d)			
0	2.25	1.82	0
2	1.25	1.17	1.64
4	1.20	1.11	1.75
6	1.16	1.07	1.83

Following Click Selectivity for the Different Alkynes of Polysiloxane 15 using ^{1}H NMR Spectroscopy

Benzyl azide (8eq, 0.004 g, 0.030 mmol) was added into each vial containing polysiloxane **15** (1 eq, 0.05 g, 0.0043 mmol) and 500 µL of $CDCl_3$. Each vial was stirred and heated at i) 35 °C and ii) 60 °C for two weeks. The ^{1}H NMR spectrum was obtained once every 2 d and alkyne integrations were measured (Table 3, Table 4).

Table 3: Alkyne selectivity measurements of Polysiloxane **15** done at 35°C

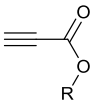
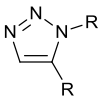
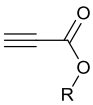
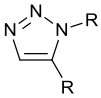
Time (d)			
0	6.11	2.42	0
1	6.07	2.45	0
2	5.83	2.70	0
3	5.88	2.65	0
9	4.26	2.5	1.77
15	4.34	3.01	1.18

Table 4: Alkyne selectivity measurements of Polysiloxane **15** done at 60°C

Time (d)			
0	6.97	3.29	0
1	5.15	3.28	1.83
4	5.69	3.41	1.16
6	5.26	3.71	1.28

Alkyne Selectivity Measurement Using of 1:1 Mixture of Trisiloxanes 9 and 10 using ^{1}H NMR Spectroscopy

Benzylazide (1 eq, 0.012 g, 0.09 mmol) was added into each vial containing trisiloxane **9** (1 eq, 0.03 g, 0.09 mmol) and **10** (1 eq, 0.03 g, 0.09 mmol) with 500 µL of $CDCl_3$. The reaction was carried out over one week at 35 °C and 60 °C, respectively, and the ^{1}H NMR spectra were obtained each day (Table 5, Table 6).

Table 5: Alkyne selectivity measurements of trisiloxanes **9** and **10** done at 35°C

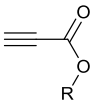
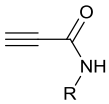
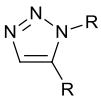
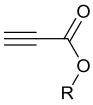
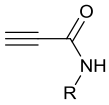
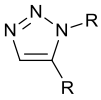
Time (d)			
0	0.90	0.80	0
1	0.79	0.75	0.17
3	0.68	0.67	0.35
4	0.68	0.57	0.45
15	0.48	0.23	0.98

Table 6: Alkyne selectivity measurements of trisiloxanes **9** and **10** done at 60°C

Time (d)			
0	0.64	0.77	0
1	0.36	0.7	0.34
2	0.29	0.67	0.45
4	0.28	0.66	0.46

Polysiloxane 17

Benzylazide (0.031 g, 0.156 mmoles) was added into a 50 mL round-bottomed flask containing polysiloxane **15** (0.3 g, 0.026 mmoles) and toluene (5 mL). The reaction was heated at 70 °C with stirring. After 3 d, more benzylazide (0.034 g, 0.25 mmoles) was added and allowed to stir

for another two days. Excess benzylazide was removed in vacuo using the Kugelrohr apparatus, heated at 120°C for 2h under high vacuum. The product was a viscous yellow oil (0.5 g, yield 99%).

^{1}H NMR 600 MHz ($CDCl_3$): 0.05 (bs, 924H), 0.53 (m, 20H), 1.37 (m, 8H), 1.63 (m, 12H), 1.77 (m, 8H), 2.44 (s, 1H), 2.63 (m, 10H), 4.06 (m, 8H), 4.25 (m, 8H), 4.67 (s, 1H), 5.90 (s, 2H), 7.31 (m, 21H), 7,91-8.08 (s, 1H).

^{13}C NMR 600 MHz ($CDCl_3$): -0.28-2.10, 13.63, 18.14, 19.96, 22.59, 29.31, 32.19, 52.50, 52.63, 53.63, 54.56, 64.87, 67.92, 127.46-129.65

Chain Extension of Benzyl-functionalized Polysiloxane 7 with 1,3-Bis(azidopropyl)-tetramethyldisiloxane, 18

1,3-Bis(azidopropyl)tetramethyldisiloxane (0.011 g, 0.036 mmol) was added into a 50 mL round-bottomed flask containing polysiloxane **17** (0.18 g, 0.015 mmol) in toluene (15 mL). The reaction was heated with stirring at 100 °C. After 2d, ^{1}H NMR showed no reaction had occurred. Toluene was removed by nitrogen and tetrahydrofuran (8 mL) was added. Copper (II) sulfate pentahydrate (0.010 g, 0.04 mmol) in water (1.5 mL) and (+)-sodium L-ascorbate (0.021 g, 0.10 mmol) in water (1.5 mL) were added to the reaction. The reaction was left stirring overnight at room temperature in an inert atmosphere, at which point the solvents were evaporated in vacuo. The reaction was extracted with dichloromethane (3 x 15 mL). The organic layers were combined and dried over sodium sulfate. Dichloromethane was removed in vacuo and the crude product was obtained as a orange viscous oil.

Results and Discussion

Effects of Alkyne Substituent on Thermal Cycloaddition Temperature

Model Compounds

A series of model alkynes was reacted with a silicone azide to better understand the thermal requirements of the Huisgen reaction with silicones. 1,3-Bis(azidopropyl)tetramethyldisiloxane **1** (Figure 8) was a convenient model azide to use to characterize alkyne reactivity in the click reaction; its transformation to chromatographically separable compounds has been previously documented.[3] Commercially available functional silicones are limited to a few organic functional groups, including monomers bearing vinyl or allyl groups, alkyl halides, alkylalcohol, alkylamine, alkylcarboxylic acids. Therefore, model (non-silicone) alkynes were prepared from compounds bearing similar functional groups, such as benzyl propiolamide and benzyl propiolate (Figure 8, Table 7).

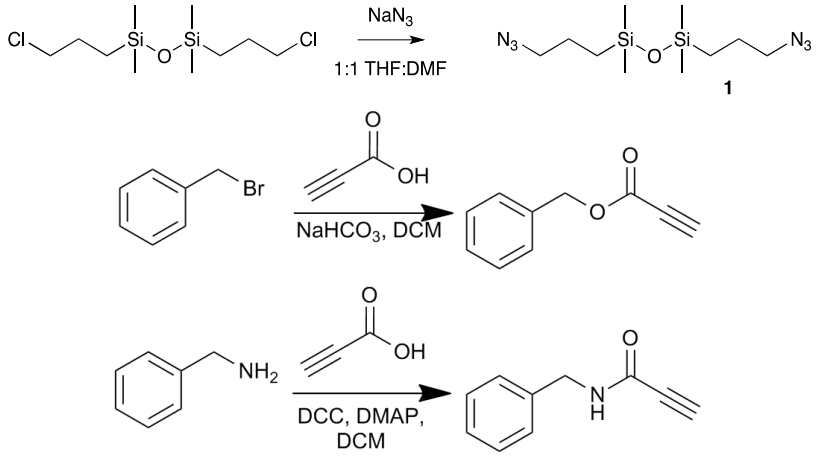
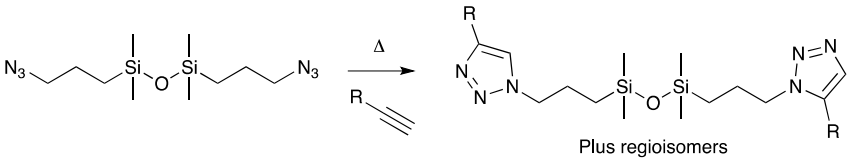


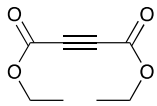
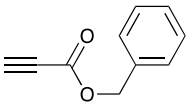
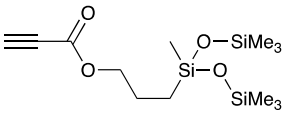
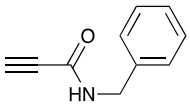
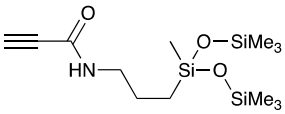
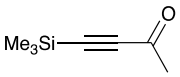
Figure 8: Preparation of 1,3-bis(azidopropyl)tetramethyldisiloxane and functional alkynes

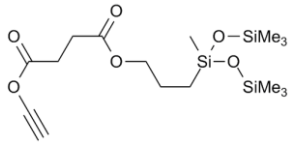
Alkynes **2**-**8** were typically mixed with the model azide compound, 1,3-bis(azidopropyl)-tetramethyldisiloxane, in a stoichiometric ratio of functional groups ([C≡C]:[N_3]) = 1:1; benzyl propiolate and benzyl propiolamide were mixed with the model azide compound on an equal

mass basis. The efficiency of cycloadditions was examined using a differential scanning calorimeter; samples were heated from room temperature to 150 at 5 °C / minute. The onset of cyclization for different alkynes is reported in Table 7.

Table 7: Onset cycloaddition temperatures for tested alkynes determined by DSC



Compound Number	Alkyne		Onset Cycloaddition Temperature (°C)
2	Diethyl acetylenedicarboxylate		37
3	Benzyl propiolate		51
4	Trisiloxane propiolate		64
5	Benzyl propiolamide		72
6	Trisiloxane amide		74
7	Trimethylsilyl-3-butyn-4-one		90

8	Propargyl Trisiloxane		101

As can be seen from Table 7, large differences were observed in the temperature at which the reaction starts. There was a clear, inverse correlation between the electronic density of the alkyne and the temperature at which uncatalyzed cyclization began. Electron-rich alkynes required much higher temperatures than electron-deficient alkynes. The efficiency of the reaction thus depends on the substituent on the alkyne, the reactivity of which followed the order: aryl group < amide < ester. The reactivity of the silyl-substituted alkyne **7** was low; in this case, any activation provided by the ketone is compensated by the electronic donation provided by the silyl substituent.[15,16]

Polysiloxanes: Functionalization followed by polymerization

The significant differences in thermal responsiveness between different alkynes presents an opportunity to develop generic pre-elastomers that can be both crosslinked and functionalized in a variety of ways. For example, if both reactive (e.g., propiolate esters) and unreactive (e.g., propiolamides) are found in the same siloxane in different, explicit locations, it should be possible to crosslink at a lower temperatures (with propiolates) and functionalize at a higher temperature (with propiolamides) to give one functional elastomer, or the inverse to produce a different functional elastomer. This hypothesis was tested by synthesizing multifunctional silicones.

Polyalkyne Synthesis

Two different strategies were explored for the synthesis of polysiloxanes containing more than one type of alkyne: i) direct functionalization of free alkylamines or aliphatic alcohols pendant on a silicone backbone, or, ii) functionalization of a small siloxane, followed by polymerization

into a higher molecular weight material. In either case, traditional DCC coupling reactions of propiolic acid with hydroxyl- and/or amino-functionalized polysiloxanes were performed to link the alkyne moiety to the silicone.

It was determined that direct functionalization of polysiloxanes by alkynes was problematic. For example, although attempts to modify amino- and hydroxy-pendant polysiloxanes with propiolic acid using DCC coupling were efficient, it was very challenging, based on ^{1}H NMR data, to completely remove the co-product dicyclohexylurea from the polymer using silica gel chromatographic purification. This difficulty was circumvented by first functionalizing small silicones, and then incorporating them into larger silicone polymers using acid-catalyzed equilibration polymerization with octamethylcyclotetrasiloxane (D_4).

Activated alkynes were introduced as pendant groups by first forming trisiloxane **9** by the hydrosilylation of 1,3-bis(trimethylsiloxy)methylsilane with allyl alcohol (Figure 9); the reaction was monitored by following the disappearance of the SiH signal at 4.7 ppm in the ^{1}H NMR spectrum. The hydroxyl group was converted into the ester-functionalized alkyne **9** by DCC coupling with propiolic acid. The analogous amide **10** was prepared by the DCC amidation of commercial 3-aminopropylmethylbis(trimethylsiloxy)silane with propiolic acid. Trisiloxane **11** was prepared by DCC esterification of 3-hydroxypropylmethylbis(trimethylsiloxy)silane with the monopropargyl ester of butanedioic acid. Terminal alkynes were prepared using analogous chemistry with difunctional disiloxanes (Figure 9). Less reactive amides **12** and esters **13**[17] were similarly prepared by carbodiimide coupling.

Siloxane equilibration chemistry can be used to create polysiloxanes with more than one type of functional alkyne. Polymers were created from starting materials of D_4, **9** and **12** giving **14**, and **9** and **13** leading to **15**, respectively (Figure 10). Two different end groups are present in this

process, the functional alkyne and $OSiMe_3$. However, the reaction was performed at reduced pressure to remove the most volatile byproduct that will continuous form during equilibration, $Me_3SiOSiMe_3$, which favors formation of polymers with alkyne end groups. Alternatively, an excess of end groups was used to favor the introduction of alkynes on the termini and avoid the presence of $OSiMe_3$ groups.

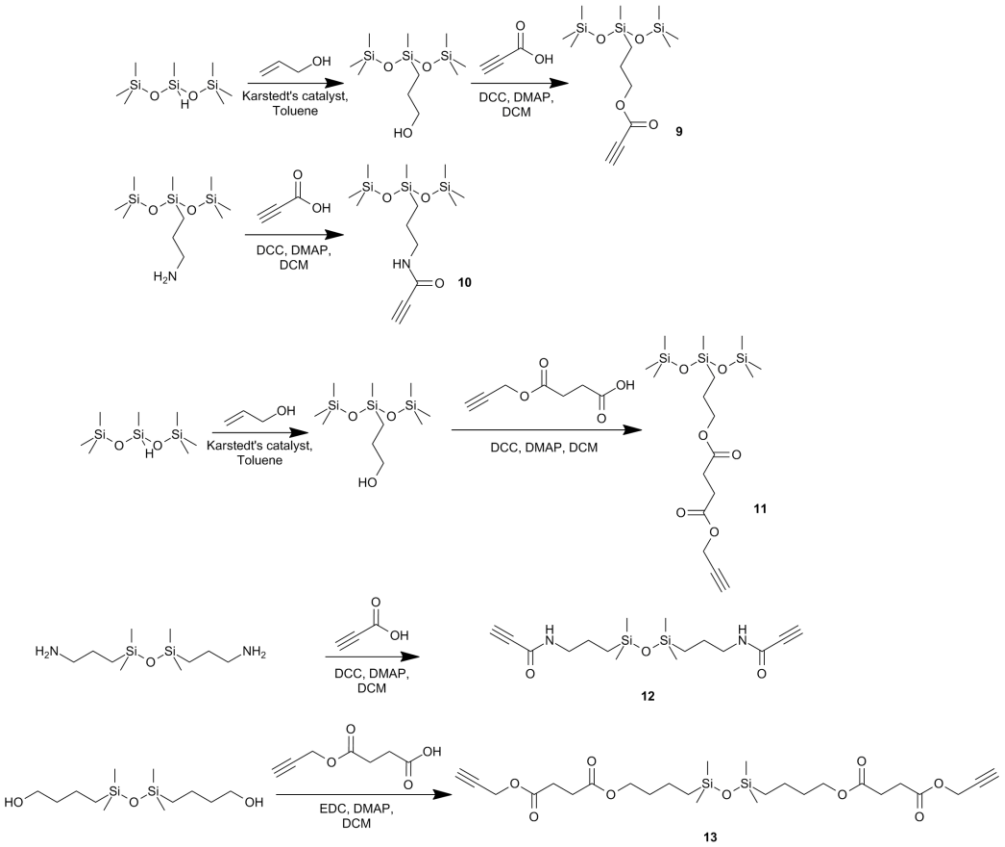


Figure 9: Preparation of functional siloxane precursors

According to ^{1}H NMR, polysiloxane **14** possessed both types of alkynes with an average MW of about 3485 g mol^{-1} based on ^{1}H NMR end group analysis and verified by GPC. In spite of the reaction conditions used, ^{29}Si NMR showed that $SiMe_3$ end groups were still present on the silicone. Polysiloxane **14** had a pendant to terminal alkyne ratio of approximately 1:1. Polysiloxane **15** had a MW of about 6,720 g mol^{-1} based on GPC and a pendant to terminal

alkyne ratio of approximately 4:2. Based on ^{29}Si NMR, only one type of end group – the alkyne – could be detected on the polysiloxane, demonstrating that using reduced pressure to remove the byproduct $Me_3SiOSiMe_3$ was successful.

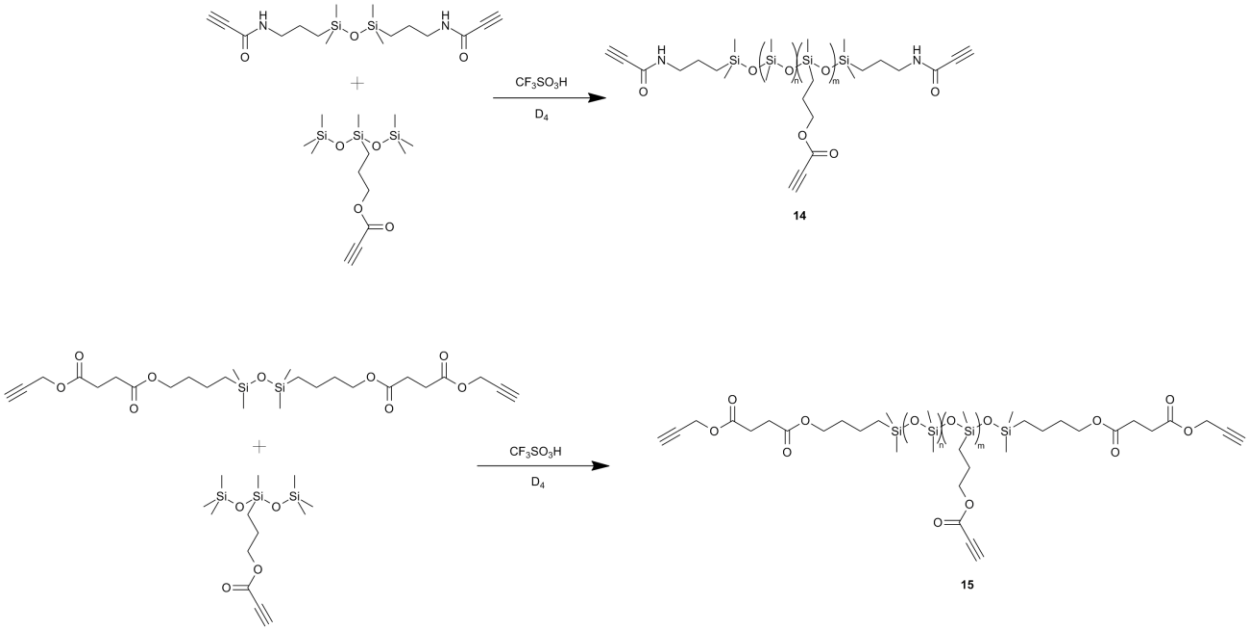


Figure 10: Preparation of different pendant and terminal alkyne-functionalized polysiloxanes using acid-catalyzed equilibration polymerization

Thermal control of Network Structure Using Click Crosslinking Selectivity measurements of multialkyne-functionalized polysiloxanes

It was expected that the different alkynes would distinguish themselves in thermal reactions with azides. Based on the results in Table 7, the pendant propiolate should react at much lower temperatures than either the termini propiolamide or propargyl ester. This proposal was initially tested using a small azide, $PhCH_2N_3$, with polysiloxane **14**. The cycloadditions with 2 equivalents of benzylazide (equimolar to the propiolate-based alkyne on the copolymer) were carried out at several temperatures in a NMR tube and monitored by ^{1}H NMR spectroscopy (Appendix Schemes 1 and 2). At 35 °C, the [propiolate:propiolamide] alkyne ratio decreased

from 2.26:1.81 to 1.54:1.46 in a span of one week to give **16** (Figure 11A, Table 1). At 60 °C, the [propiolate:propiolamide] ratio decreased from 2.25:1.82 to 1.16:1.07 in a span of one week (Table 2). Complete selectivity was not achieved, however. We initially hypothesized that, in addition to electronic conditions of the two alkynes which favor propiolates, the pendant propiolate is less reactive because it is more hindered, while the greater steric accessibility of the terminal alkyne renders it more reactive.

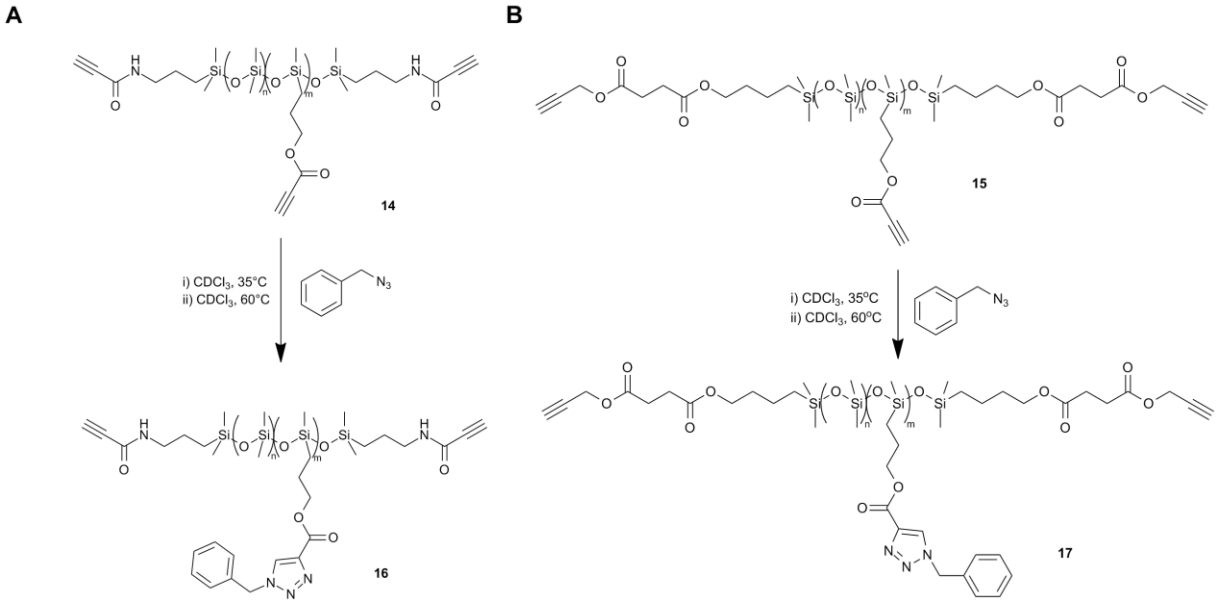


Figure 11: Alkyne selectivity of: A: Polysiloxane **14**, B: Polysiloxane **15**

Show additional byproduct with modified terminal group in both cases

To examine this proposal, the reactivity of two structurally related functional alkynes was tested by examining the reactivity of an equimolar mixture of trisiloxanes **9** and **10**, which tests reactivity based on electronic effects alone, not by its location on a polymer. The cycloadditions with 1 equivalent of benzylazide were carried out at two temperatures, respectively, in a NMR tube and monitored by ^{1}H NMR spectroscopy (Figure 12). At 35 °C, the [propiolate:propiolamide] alkyne ratio decreased from 0.90:0.80 to 0.23:0.48 over two weeks

(Table 5). At 60 °C, the [propiolate:propiolamide] ratio decreased from 0.64:0.77 to 0.28:0.66 during 4 d (Table 6). As expected, for both temperatures, the ester-functionalized alkyne reacted faster than the amide-functionalized alkyne, however, the process exhibited lower selectivity than was predicted from Table 7.

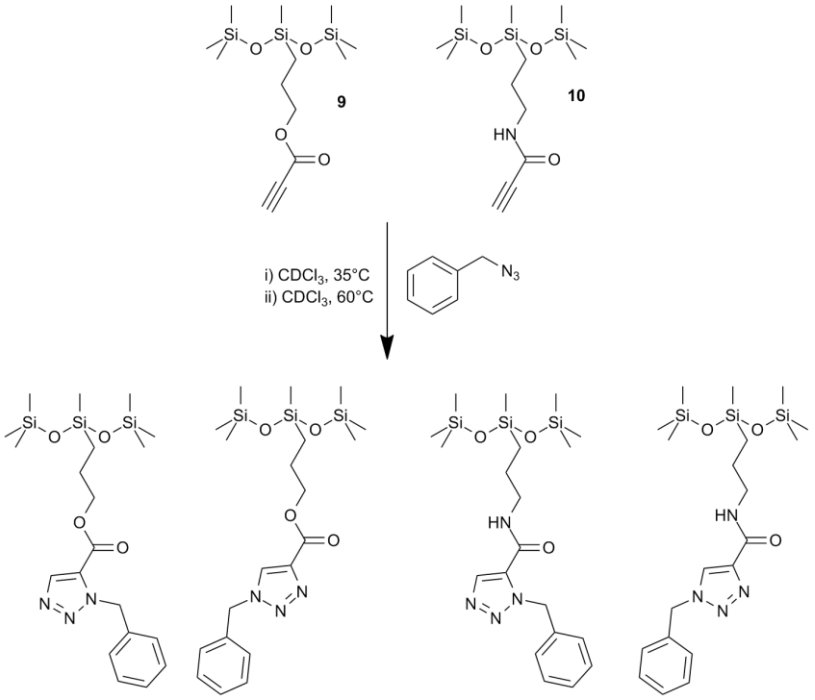


Figure 12: Alkyne Selectivity Measurement of Trisiloxane Mixture

The reaction of benzylazide with the two different alkynes in **14** demonstrated that the two were insufficiently different for specific, sequential reactions to occur. According to Table 7, propiolates and propargyls have a much larger difference in alkyne click reactivity than the propiolate/propiolamide groups in polysiloxane **14**. Therefore, cycloadditions of polysiloxane **15** with benzylazide were completed at two temperatures, respectively, in a NMR tube (Figure 11B, Appendix Schemes 3 and 4). At 35 °C, the [propiolate:propargyl] alkyne proton ratio decreased from 6.11:2.42 to 4.26:2.50 in two weeks giving **17** (Table 3): at 60 °C, the

[propiolate:propargyl] ratio decreased from 6.97:3.29 to 5.26:3.71 over one week (Table 4). At either temperature, propiolate alkynes were consumed while the propargyl alkynes were untouched, which is expected as propargyl alkynes are electron rich.

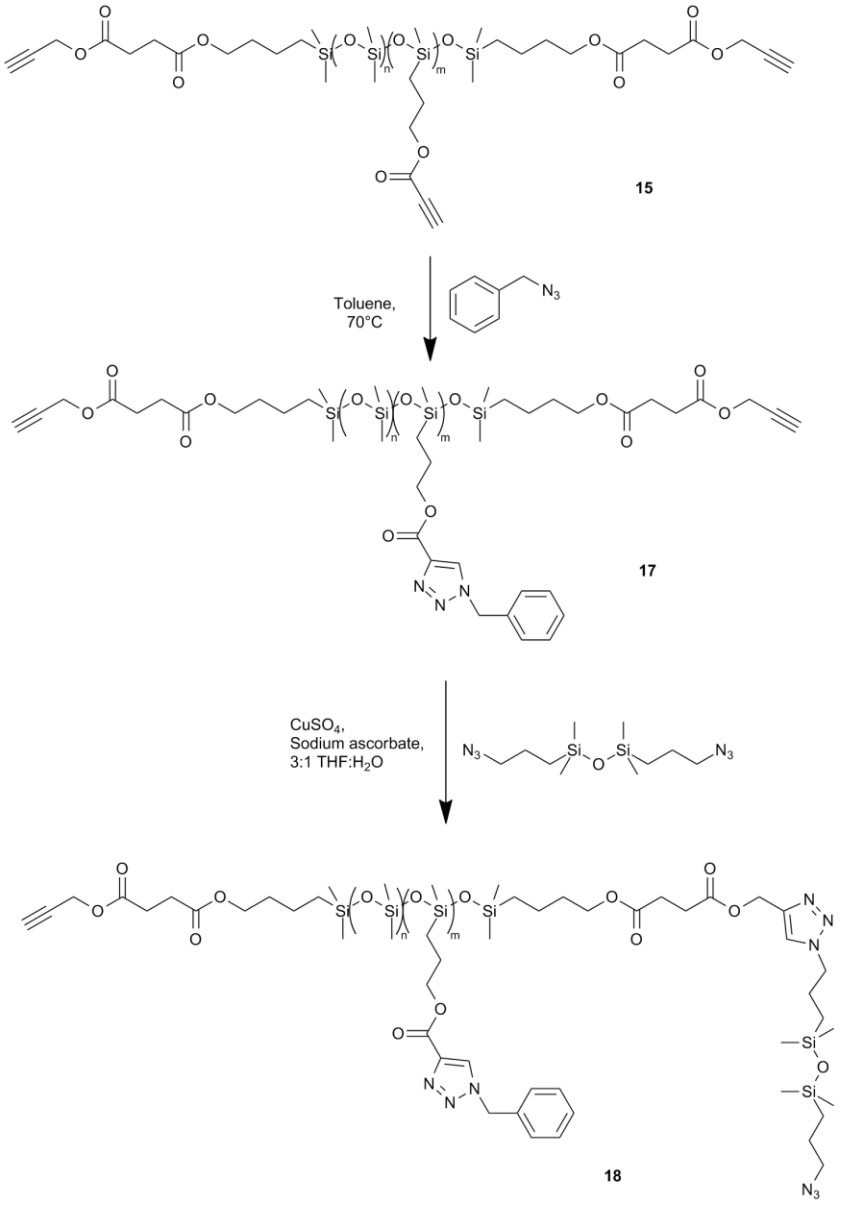


Figure 13: Difunctionalization of Polysiloxane **15**

The utility of these observations was exploited by performing a double modification of silicone **15**. Pendant propiolates were selectively and completely functionalized with benzylazide using

the Huisgen cycloaddition at 70 °C in toluene to give **17**, as shown by 1H NMR (Figure 13). It was expected that the residual propargyl groups could be made to react at elevated temperatures. However, after 2 days of reaction at 100 °C with 1,3-bis(azidopropyl)tetramethyldisiloxane, very little reaction had occurred. Therefore, **17** was modified using Cu(I) click chemistry overnight to give the chain extended, functional silicone **18**.

The reactions described here demonstrate that the difference in reactivity of alkynes in the Huisgen cyclization can be exploited to modify silicone polymers. It is relatively straightforward to place alkynes at either pendant, terminal or both locations along a silicone chain. Judicious choice of alkynes permits either selective or specific modification at the pendant vs terminal sites with functional substrates, or other silicones. This provides an opportunity to create several types of functional network structures from the same polymer backbone by using sequential click processes.

Conclusion

Diester- and ester-functionalized alkynes are more reactive in uncatalyzed click reactions than analogous amide-functionalized alkynes and propargyl alkynes based on the DSC studies on relative cycloaddition reactivity. These observations were used to selectively, and specifically modify siloxane polymers. Two distinct alkynes were located at terminal and pendant positions, respectively. Pendant propiolates reacted preferentially over terminal propiolamides. However, it was possible to selectively modify a silicone by first trapping pendant propiolates with benzylazide and then using CuAAC chemistry to chain extend the polymer using 1,3-bis(azidopropyl)tetramethyldisiloxane. This simple strategy shows promise for the preparation of a range of functional and crosslinked, organofunctional silicone polymers.

Acknowledgements

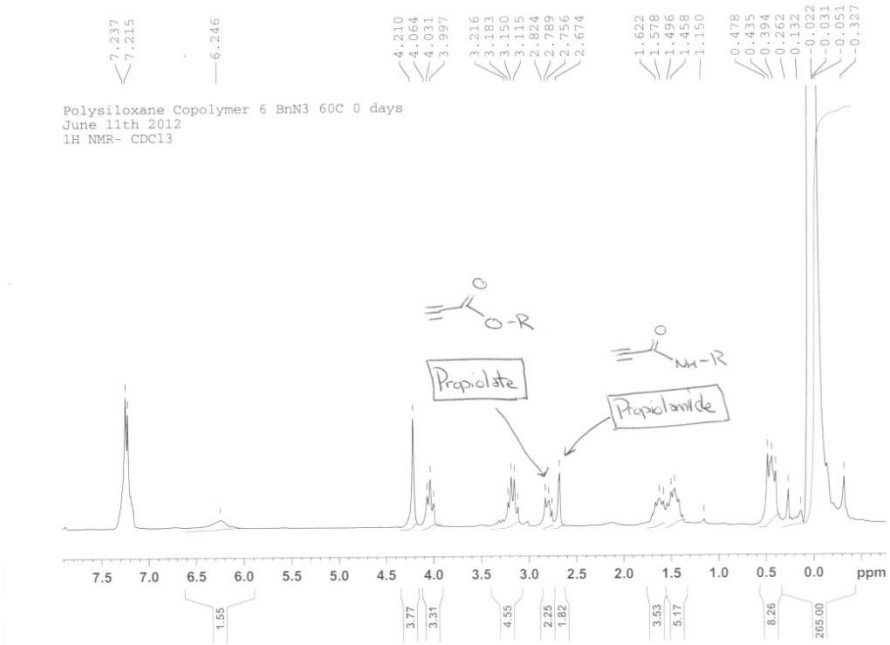
We gratefully acknowledge the financial support of the Natural Sciences and Engineering Council of Canada and Dr. Ferdinand Gonzaga for helpful advice.

References

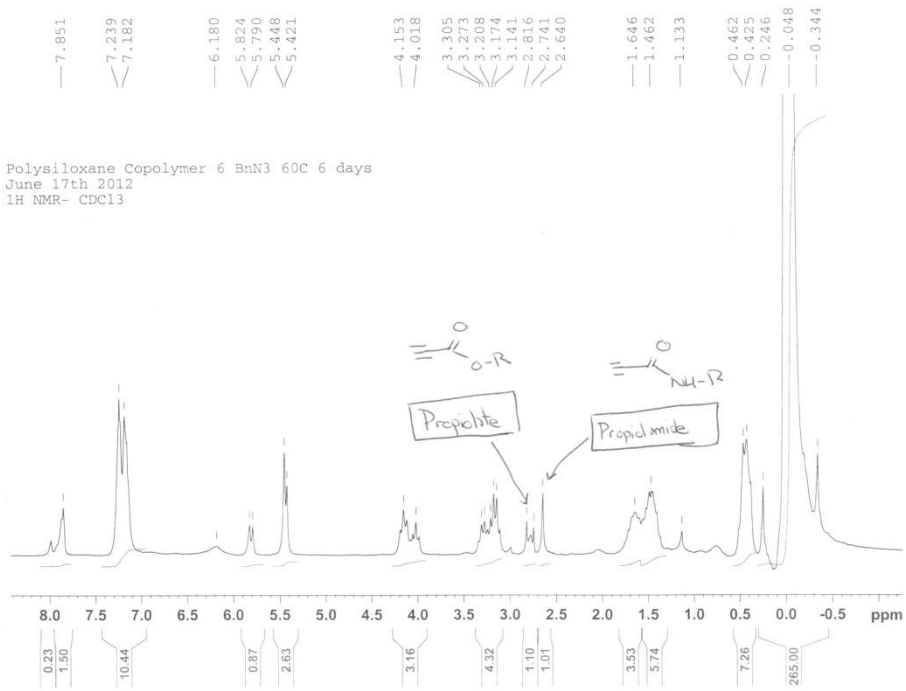
[1] Meldal, M. *Macromol. Rapid Commun.* **2008**, *29*, 1016-1051.
[2] Halila, S.; Manguian, M.; Fort, S.; Cottaz, S.; Hamaide, T.; Fleury, E.; Driguez, H. *Macromol. Chem. and Phys.* **2008**, *209*, 1282-1290.
[3] Gonzaga, F.; Yu, G.; Brook, M.A. *Chem. Commun.* **2009**, 1730–1732.
[4] Hong, V.; Steinmetz, N. F.; Manchester, M.; Finn, M. G. *Bioconjugate Chem.* **2010**, *21*, 1912-1916.
[5] Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974 - 6998.
[6] Jewett, J. C. Sletten, E. M.; Bertozzi, C. R. *Chem. Comm.* **2010**, 3688-3690.
[7] Jewett, J. C.; Bertozzi, C. R. *Chem. Soc. Rev.* **2010,** *39*, 1272-1279.
[8] Gonzaga, F.; Yu, G.; Brook, M. A. *Macromol.* **2009**, *42*, 9220-9224.
[9] Sletten, E. M.; Bertozzi, C. R. *Accounts of Chemical Research* **2011**, *44*, 666-676.
[10] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley: New York, 1977.
[11] Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Nat. Acad. Sci.* **2007**, *104*, 16793-16797.
[12] Meunier, S.; Siaugue, J.-M.; Sawicki, M.; Calbour, F.; Dézard, S.; Taran, F.; Mioskowski, C. *J. Comb. Chem.* **2003**, *5*, 201-204.
[13] Payne, R. J.; Peyrot, F.; Kerbarh, O.; Abell, A. D.; Abell, C. *ChemMedChem* **2007**, *2*, 1015-1029.
[14] Sun, S.; Wu, P. *J. Phys. Chem. A* **2010**, *114*, 8331-8336.
[15] Dallaire, C.; Brook, M.A. *Organometallics* **1993**, *12*, 2332-2338.
[16] Brook, M. A., Silicon in the Organic World: Electronic Effects of Silyl Groups. In *Silicon in Organic, Organometallic and Polymer Chemistry*, Wiley: New York, **2000**; pp 480-510.
[17] Rambarran, T.; Gonzaga, F.; Brook, M. A. *Macromolecules* **2012**, *45*, 2276-2285.

Appendix

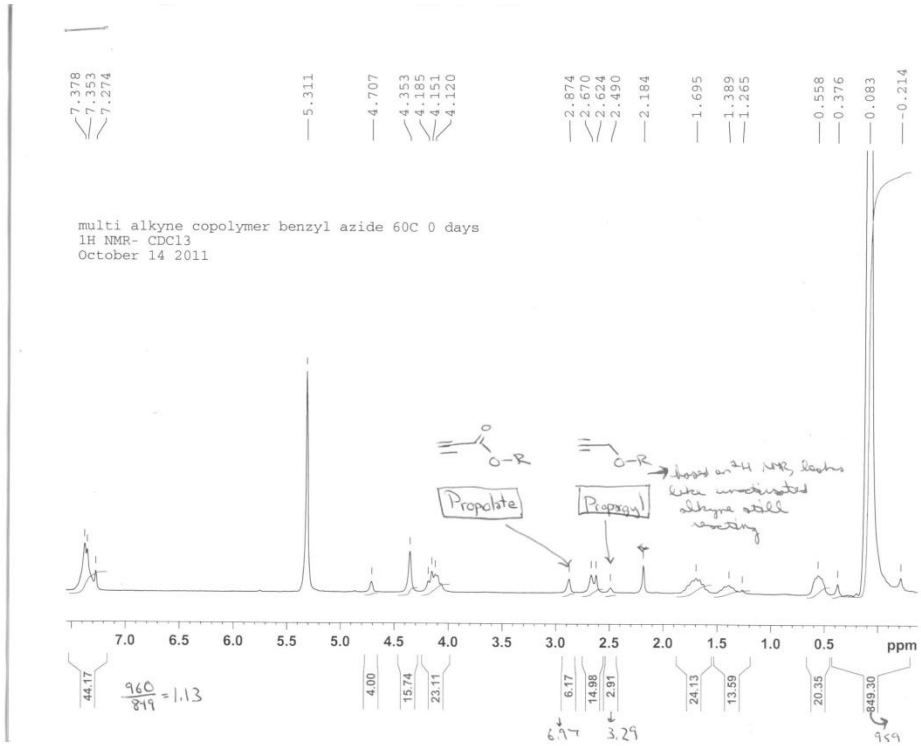
Scheme 1: ^{1}H NMR spectrum of alkyne selectivity measurement of Polysiloxane **14** with benzylazide (0 days of reaction) at 60°C



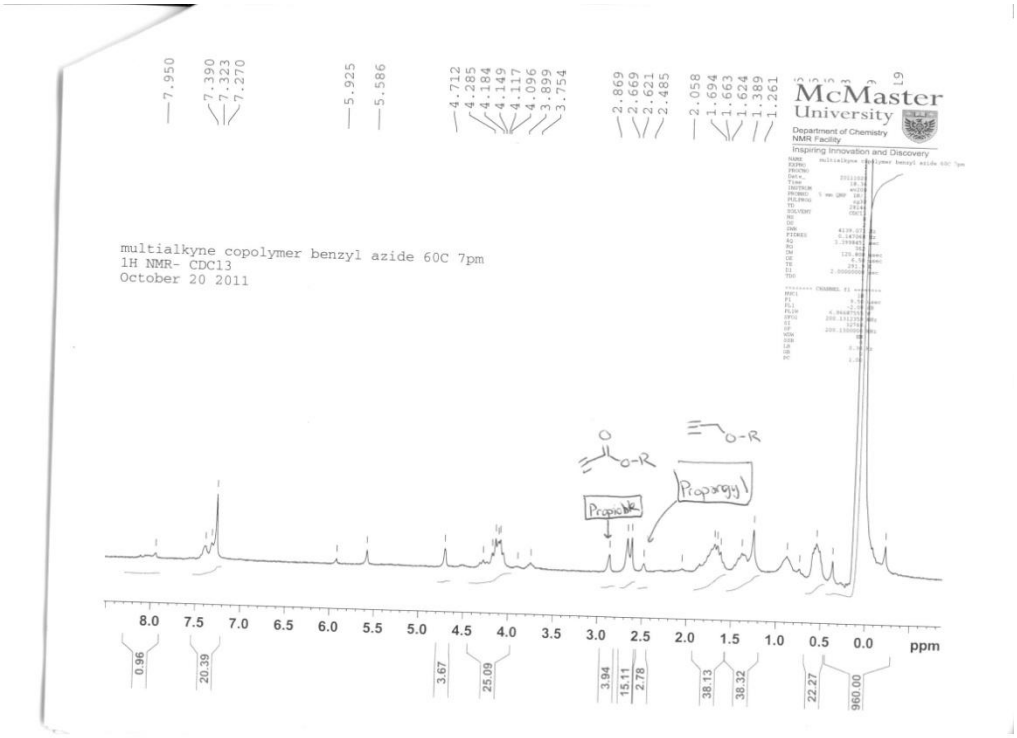
Scheme 2: ^{1}H NMR spectrum of alkyne selectivity measurement of Polysiloxane **14** with benzylazide (6 days of reaction) at 60°C



Scheme 3: ^{1}H NMR spectrum of alkyne selectivity measurement of Polysiloxane **15** with benzylazide (0 days of reaction) at 60°C



Scheme 4: ^{1}H NMR spectrum of alkyne selectivity measurement of Polysiloxane **15** with benzylazide (7 days of reaction) at 60°C



Chapter 3

Protecting Group-Free Preparation of Silicone-Saccharides: A Gelator for Diethyl Ether

Abstract

Carbohydrate-functionalized siloxanes and polysiloxanes, also known as glycosilicones, have been used as surfactants, wetting agents, emulsifiers and defoamers. Most methods of preparing glycosilicones have major drawbacks that include the use of protection/deprotection steps and possible side reactions. This makes industrial production of these materials impractical. Herein, we describe the functionalization of siloxanes and polysiloxanes with carbohydrates without using protection/deprotection steps or a metal catalyst by exploiting the Huisgen cycloaddition. The strategy required the attachment of azide-functionalized carbohydrates onto propiolate-functionalized siloxanes and polysiloxanes. The azide was introduced onto carbohydrates by performing a lactone opening reaction with a bifunctional linker, 3-azidopropylamine **1**. The Huisgen cycloaddition was successfully used to prepare trisiloxane triazolyl gluconamide **5**. Interestingly, this amphiphilic substrate was capable of gelling diethyl ether. In the optimized case, it was shown that **5** could gel 30 times its own weight in diethyl ether, although only with ether. This result must thus be seen to be an interesting oddity rather a practical result, as **5** only gelled one solvent. Preliminary examination with scanning electron microscopy did not provide precise structural information about the assembly of the gelator.

Introduction

Silicones are known for their high surface activity, with surface energies of about 20 mN m^{-1}.[1] The utility of these materials, which are widely used as surfactants, is dramatically increased by

grafting hydrophilic moieties to the silicone backbone.[2] Although hydrophiles including alkylamines, carboxylic acids and saccharides have been grafted onto silicones, PEG-functionalized polysiloxanes are easier to synthesize and analyze, and are thus the most common class of silicone surfactants in commerce.

Carbohydrate-functionalized siloxanes and polysiloxanes, also known as glycosilicones, have also been used as surfactants, wetting agents, emulsifiers and defoamers.[3] They are attractive compounds because of the natural materials from which they are constituted. A variety of strategies have been adopted to bind saccharides to polysiloxanes. Although it is possible to link the two using a Si-O-Sugar linkage,[4] this is complicated by the presence of multiple hydroxy groups on the saccharide, and the likelihood of hydrolytic siloxane cleavage. Alternative approaches take advantage of amides[5], esters[6] including those formed enzymatically[7] (Figure 14A), and acetals[8] (Figure 14B). It is also common to bind epoxy groups to the sugar, and then graft the silicone to the sugar by a nucleophilic ring opening of the epoxide.

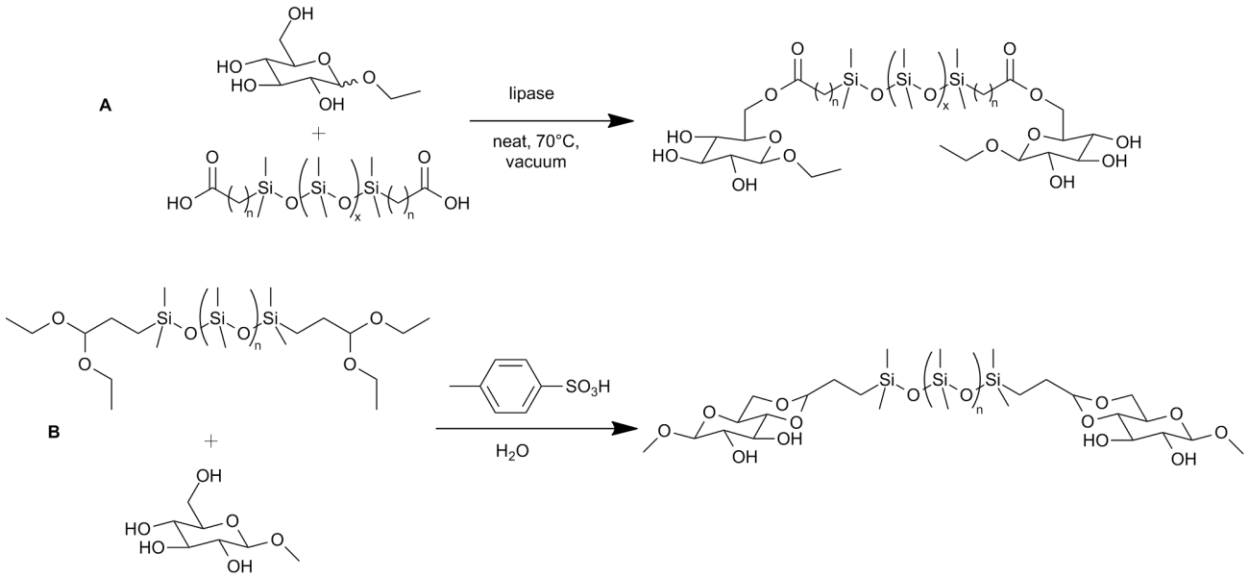


Figure 14: Glycosilicones formed by A: enzymatic coupling;[7] and B: acetalization[8]

Most strategies for glycosilicone synthesis involve the use of Si-C-O-Sugar linkages because of their greater hydrolytic stability. For the synthesis, the carbohydrate normally needs to be protected,[9] and then modified with a carbon-carbon π-bond (e.g., allyl, propargyl) that can be hydrosilylated onto a silicone,[10] and then deprotected (Figure 15). There are tremendous difficulties associated with the use of protection/deprotection steps in the presence of polysiloxanes. In particular, the acids/bases needed for the transformations can cause siloxane degradation.[3] Due to these drawbacks, alternative processes are needed to introduce carbohydrates onto polysiloxanes.

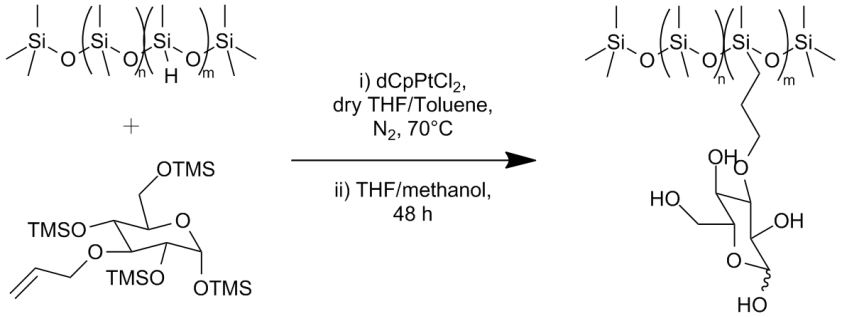


Figure 15: A typical hydrosilylation approach to glycosilicones.[10]

Our group has previously shown that small organic hydrophiles can be introduced onto polysiloxanes using copper catalyzed alkyne/azide click chemistry (CuAAC).[11] A variety of alkyne-containing substrates, ranging from phenylacetylene to *N*-propargylgluconamines, can be introduced onto azide-functionalized siloxanes in near quantitative yields after only a few hours of reaction time. The reactions are fast and efficient, exhibit high chemoselectivity, and lead to products that are easy to purify. In particular, the reaction is orthogonal to most organic chemistry reactions, and it is normally possible to avoid protecting functional groups on either reaction partner (although the absence of protecting groups makes the issue of finding a compatible solvent more challenging). However, a major drawback is the necessity of the Cu(I) catalyst which is cytotoxic[12] and is increasingly difficult to remove from materials as the

concentration of triazoles increase, as the triazole is a good ligand for copper. For these reasons, CuAAC is not generally applicable in biomaterials applications.

The alternative strategy, which avoids copper completely, is the thermal Huisgen cycloaddition. Although the reaction commonly requires temperatures above 80 °C, we,[13] and others,[14] have shown that electron-deficient alkynes will react at much lower temperatures. Furthermore, we have shown that the offset temperature is affected by the electronic character, which can be manipulated by our choice of substituents.

Previously in our group, we have used both Cu(I) and the non-catalyzed azide-alkyne cycloaddition to functionalize polysiloxanes.[15] With regards to the non-catalyzed Huisgen cycloaddition, it was possible to perform low temperature cycloadditions using electron deficient alkynes due to the rate enhancement given by the narrower HOMO-LUMO gap.[16] By introducing electron deficient alkynes onto polysiloxanes, cyclization would occur at reduced temperatures (just above room temperature) without the need of a catalyst. However, the drawback is that a regioisomeric mixture of the 1,2,3-triazoles was produced.

We were interested in examining the utility of the thermal cycloaddition to create functional silicones modified with both large and small saccharides, and to begin to establish the benefits and detriments of combining silicones with natural materials. In this paper, we examine the click reaction of azide-modified glucose to a small silicone. The surprising ability of this compound to gel diethyl ether will also be discussed.

Experimental

1,3-Bis(trimethylsiloxy)methylsilane and octamethylcyclotetrasiloxane were obtained from Gelest. Sodium azide (95%) was purchased from J.T. Baker. 3-Bromopropylamine hydrobromide (98%), gluconolactone (98%), propiolic acid (95%), triflic acid (98%), 4-

dimethylaminopyridine (99%), dicyclohexylcarbodiimide (99%), allyl alcohol (98%) and (~2% Pt) platinum(0)-1,1,3,3-tetramethyldisiloxane complex in xylenes were obtained from Sigma-Aldrich. All materials were used as received.

^{1}H NMR and ^{13}C NMR were recorded at room temperature on a Bruker AC-200 and AC-600 spectrometer using deuterated solvents ($CDCl_3$ and DMSO-d_6). High-resolution mass spectrometry was performed using a Hi-Res Waters/Micromass Quattro Global Ultima (Q-TOF mass spectrometer). SEM data was acquired using the JEOL 7000F instrument.

3-Azidopropylamine, 1[17]

Sodium azide (4.54 g, 6.99 mmol) was added into a 50 mL round-bottomed flask containing 3-bromopropylamine hydrobromide (5.11 g, 2.33 mmol) in 3:1 THF:H_2O (20 mL). The reaction was left stirring overnight at 50 °C. After the reaction was complete, THF was removed in vacuo. Three pellets of NaOH were dissolved in the reaction mixture. Water (3 mL) was added to the reaction mixture and the product was extracted with 5 portions of dichloromethane (~20 mL). Dichloromethane was removed in vacuo to obtain the product (0.98 g, yield 42%).

^{1}H NMR 200 MHz ($CDCl_3$): 1.99 (m, 2H), 3.14 (t, 2H, *J*= 6.6 Hz), 3.56 (t, 2H, *J*= 6.6 Hz)

^{13}C NMR 600 MHz ($CDCl_3$): 32.55, 39.73, 49.48

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_3H_9N_4$: 101.0827, found 101.0824.

3-Azidopropylgluconamide, 2

3-Azidopropylamine (0.64 g, 6.4 mmol) was added into a 50 mL round-bottomed flask containing gluconolactone (0.92 g, 5.2 mmol) in DMF (20 mL). The reaction was left stirring overnight at room temperature while attached to the N_2 line. After the reaction was complete, DMF was removed in vacuo. The crude product was dissolved in a minimum amount of DMF.

The crude product was added dropwise to acetone (40 mL) to precipitate the product. The solution is filtered and the product **2** was obtained as a beige solid (1.3 g, yield 42%).

^{1}H NMR 600 MHz (DMSO-d_6): 1.67 (m, 2H), 3.15 (m, 2H), 3.37 (m, 3H), 3.47 (s, 2H), 3.58 (m, 1H), 3.91(m, 1H), 3.99 (bs, 1H), 4.33 (m, 1H), 4.41 (bd, 1H, *J*= 6.95 Hz), 4.47 (bd, 1H, *J*= 4.62 Hz), 4.54 (bs, 1H), 5.38 (d, 1H, *J*= 4.62 Hz), 7.76 (t, 1H, *J*= 5.94 Hz).

^{13}C NMR 600 MHz (DMSO-d_6): 28.46, 35.59, 48.41, 63.34, 70.10, 71.47, 72.35, 73.65, 172.60

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_{19}O_6N_4$: 279.1303, found 279.1303.

3-Hydroxylpropylmethylbis(trimethylsiloxy)silane

1,3-Bis(trimethylsiloxy)methylsilane (15 g, 70 mmol) was added into a 150 mL flask containing allyl alcohol (4.76 g, 85 mmol) and toluene (8 mL). Karstedt's catalyst (4 drops) was added and the reaction was flushed with nitrogen and left overnight. Decolorizing charcoal was added into the reaction and, after 30 min, was filtered off. The solvent and excess allyl alcohol were evaporated in vacuo to afford a clear oil (17.18 g, yield 90%).

^{1}H NMR 200 MHz ($CDCl_3$): 0.07 (s, 21H), 0.40 (m, 2H), 1.52 (m, 2H), 3.55 (t, 2H, *J* = 6.72 Hz).

^{13}C NMR 200 MHz ($CDCl_3$): -0.23, 1.97, 13.35, 26.55, 65.60.

HRMS: m/z $[M+H]^+$: calcd for $C_{10}H_{29}O_3Si_3$: 281.63; found 283.0.

Trisiloxane 3

Dicyclohexylcarbodiimide (7.22 g, 35 mmol), dissolved in dichloromethane (5 mL), was added into a 150 mL flask cooled to -35 °C containing dichloromethane (10 mL) and propiolic acid (2.94 g, 42 mmol). 3-Hydroxylpropylmethylbis(trimethylsiloxy)silane (4.45 g, 20 mmol) and 4-dimethylamino-pyridine (50 mg, 0.41 mmol), dissolved in dichloromethane (10 mL), were added portionwise and the reaction was kept at around -35 °C for 3-4 h. The reaction was then cooled to -75 °C and left overnight to warm to room temperature. Dicyclohexylurea was filtered through

Celite using dichloromethane as a solvent. The solvent was removed in vacuo and the crude product was refiltered in diethyl ether. The product was purified using silica gel gravity chromatography (19:1 v/v hexane:ethyl acetate) to produce a clear colorless oil (1.67 g, yield 88%).

^{1}H NMR 200 MHz ($CDCl_3$): -0.06 (s, 3H), 0.00 (s, 18H), 0.38 (m, 2H), 1.60 (m, 2H), 2.76 (s, 1H), 4.05 (t, 2H, *J* = 7.02 Hz).

^{13}C NMR 200 MHz ($CDCl_3$): -0.26, 1.95, 13.42, 22.34, 68.74, 74.49, 74.97, 152.93.

HRMS: m/z $[M+H]^+$ calcd for $C_{13}H_{29}O_4Si_3$: 332.1295; found: 332.1279.

Polysiloxane 4

Triflic acid (20 µL) was added into a vial containing trisiloxane **3** (0.65 g, 2 mmol) and Octamethylcyclotetrasiloxane (2.51 g, 8.5 mmol). The reaction was left stirring at room temperature overnight. Magnesium oxide (~0.5 g) was added and the reaction was left stirring for 30 minutes. Hexane was added to the solution and the magnesium oxide was filtered off. Once the hexane was removed in vacuo, the crude product underwent Kugelrohr distillation to remove the cyclic siloxane byproducts. The product was a clear oil (1.6 g, yield 62%).

^{1}H NMR 600 MHz ($CDCl_3$): 0.02 (s, 9H), 0.05 (s, 118H), 0.52 (m, 2H), 1.71 (m, 2H), 2.83 (m, 1H), 4.14 (t, 2H, *J*= 6.84 Hz).

^{13}C NMR 600 MHz ($CDCl_3$): -0.27, 1.37, 1.41, 2.11, 13.52, 22.43, 68.88, 74.60, 75.16, 153.12

Gelator 5

Trisiloxane **3** (1.10 g, 3.16 mmol) was added into a 50 mL round-bottomed flask containing 3-azidopropylgluconamide (0.8 g, 2.87 mmol) and 1:1 DMF:THF (20 mL). The reaction was left to stir for two d at 50 °C. After the reaction was complete, the solvent was removed in vacuo. The crude product was dissolved in a minimum amount of DMF and purified by silica gel

chromatography using 5% methanol/dichloromethane solvent to obtain a yellow-orange gel-like substance (1.2 g, yield 70%).

^{1}H NMR 600 MHz (DMSO-d_6): -0.05 (bs,18H), 0.00 (m, 3H), 0.43 (m, 2H), 1.61 (m, 2H), 1.91 (m, 2H), 2.98 (m, 1H), 3.07 (m, 2H), 3.29 (m, 1H), 3.40 (m, 2H), 3.49 (m, 1H), 3.85 (m, 1H), 3.93 (m, 1H), 4.13 (t, 2H, *J*= 7.02 Hz), 4.24 (t, 2H, *J*= 5.70 Hz), 4.32 (m, 2H), 4.38 (d, 1H, *J*= 7.26 Hz), 4.41 (d, 1H, *J*= 5.64 Hz), 4.46 (d, 1H, *J*= 1.56 Hz), 5.35 (d, 1H, *J*= 4.92 Hz), 7.78 (t, 1H, *J*= 5.94 Hz), 8.71 (s, 1H).

^{13}C NMR 600 MHz (DMSO-d_6): -0.38, 2.00, 12.84, 22.09, 29.76, 35.10, 47.40, 63.29, 66.40, 70.11, 71.46, 72.29, 73.61, 129.24, 138.58, 160.36, 172.87.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{47}N_4O_{10}Si_3$: 611.2607; found 611.2600.

Gelation Experiments

Solvent (500 µL) was added into a small vial containing gelator **5** (10-15 mg). The vial was sealed with paraffin and placed into a oil bath heating at 50 °C for 30 min, at which point the vial was removed from the oil bath and allowed to cool down for 30 min prior to any observations to be taken. The ungelled solvent, in the case of diethyl ether, was decanted, and the remaining gel weighed.

Scanning Electron Microscopy

A small quantity of gel was poured onto a aluminum plate and placed into a dessicator and allowed to dry for 24 h under nitrogen. The gel collapsed into a residue that was coated with a thin-layer of gold using a sputtering machine and directly imaged with the instrument.

Results

Azides

The click reaction was used to functionalize the prototypical low molecular weight saccharide, glucose, with polysiloxanes, which necessitated the introduction of alkynes and azides on the reaction partners. A bifunctional linker was required to bridge the sugar onto alkyne-functionalized siloxanes or polysiloxanes. 3-Azidopropylamine **1**, the chosen linker, was prepared by the S_N2 substitution of 3-bromopropylamine hydrobromide with sodium azide after basic workup.[17] The amino functional group is available to be coupled to the sugar, while the azide can form a triazole with the alkyne-functionalized polysiloxane. Gluconolactone was opened using 3-azidopropylamine to produce the azido-functionalized carbohydrate **2** that was bound to the sugar via a hydrolytically stable amide linkage (Figure 16).

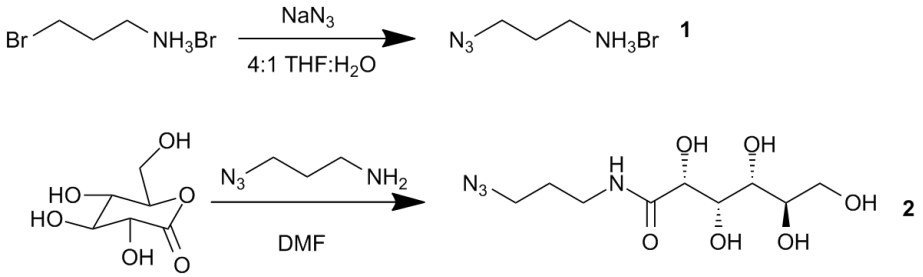


Figure 16: Preparation of 3-azidopropylamine **1** and azide-functionalized carbohydrate **2**

Alkynes

Trisiloxane **3** was prepared in two steps from allyl alcohol (Figure 17). Hydrosilylation of unprotected allyl alcohol was, surprisingly, not compromised by reaction of the silane with the alcohol,[18] and was followed by esterification with propiolic acid.[19]

Polysiloxanes undergo metathesis under acidic and basic conditions.[20] This process is frequently used to create high molecular weight silicones from functional silanes and, normally, cyclic monomers such as D_4 ($(Me_2SiO)_4$). This strategy was used to introduce unfunctionalized and propiolate-terminated side chains onto the siloxane backbone. That is, we performed acid-

catalyzed siloxane equilibration polymerization using trisiloxane **3** and D_4 to prepare polysiloxane **4** with an M_n of 1800 g/mol (Figure 17).

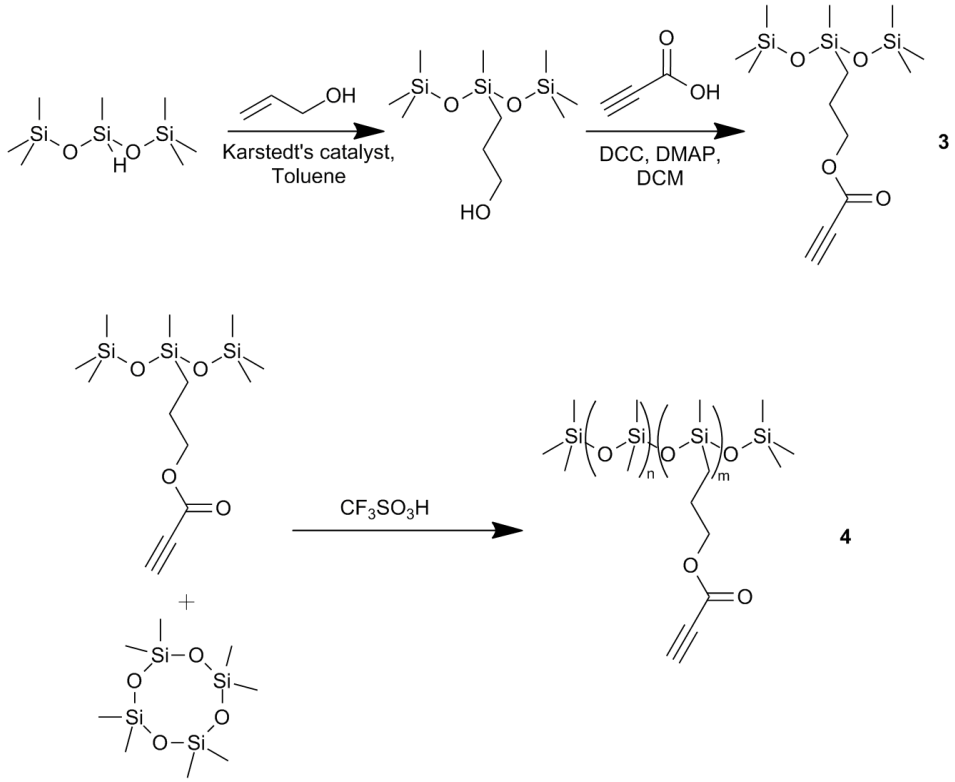


Figure 17: Preparation of propiolate-functionalized trisiloxane and polysiloxane

Cyclization

Siloxane **3** was directly modified with **2** in the absence of a catalyst by simply heating in 1:1 DMF:THF at 50 °C. Note that there is no need to protect/deprotect the saccharide unlike most syntheses of silicone-modified saccharides.[4] As expected from previous syntheses of such materials, challenges were presented by the large difference in solubility of the two reagents. However, the reaction reached completion after three days, leading to **5** (Figure 18). The resulting products were characterized primarily by NMR, which clearly showed triazole product formation. Interestingly, during an attempt to recrystallize **5** in diethyl ether, the solvent gelled.

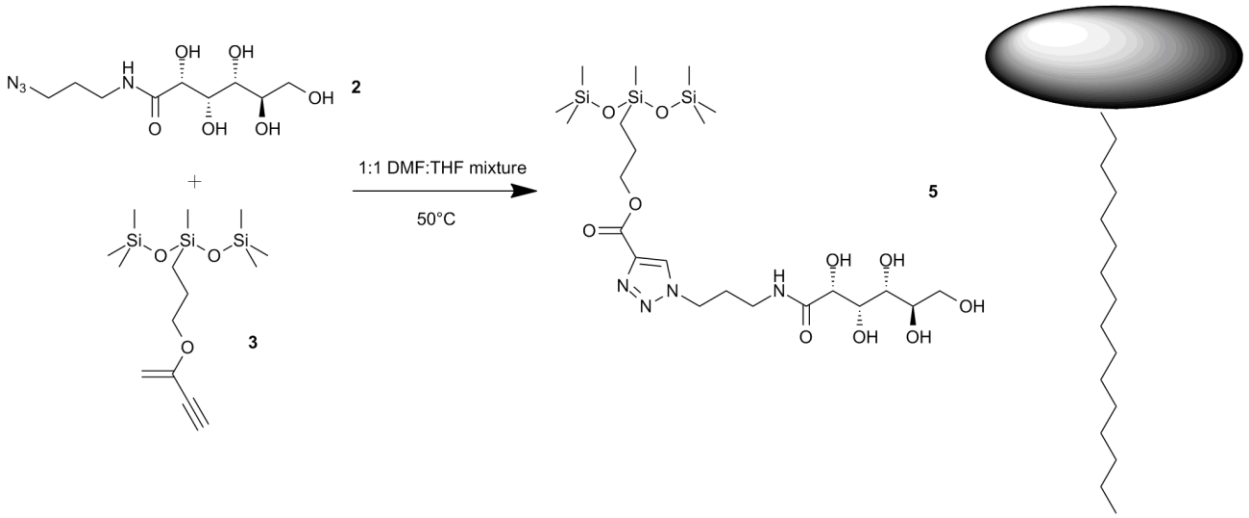


Figure 18: Synthesis of siloxane-sugar gelator **5**

We studied the gelation ability of **5** using the heating/cooling method that is described in the experimental section.[21] Survey experiments were first completed to provide a rough guide of an adequate gelator/solvent volume ratio to use for gelation experiments. In most examples the necessary ratio was found to be between 1-5%.[22] Based on a gelation study with diethyl ether, the sample with a ratio of 2.8-3.0% produced the most compact gel compared to the other samples with different gelator/solvent volume ratios. Therefore, for future gelation studies, a gelator/solvent volume ratio of 3% was used. In addition to ether, attempts were made to gel numerous other solvents, both non-polar and polar. As shown on Table 8, **5** was only able to gel diethyl ether; in nonpolar solvents the compound was completely soluble, and in more polar solvents the compound was insoluble.

An attempt was made to establish the structure of the saccharide that is responsible for the formation of a gel. A small (3 cm x 2 cm) sample of the silicone **5**/ether complex was allowed to dry at ambient temperature on an SEM stub. Scanning electron micrographs are shown in Figure 19. Figure 19A shows a relatively homogenous morphology with different sizes of large pores within the structure. The surface itself initially appears to be smooth with no indication of being

produced by fibrous strands like those that have been reported for other molecular gels. However, when an expanded view is utilized (Figure 19B), it is clear that such fibrous structures are present. The pore channels seem to be comprised of a 'wrinkled' pattern of assembled fibrous strands together (Figure 19C and 19D). It has not yet been possible to establish if these structures are representative of the swollen gel, or an artifact of the evaporation process. Compound **5** demonstrated that it can gel ether more than once. Under vacuum, within 5 min, the gel collapses as diethyl ether evaporates leaving only **5** left over. By adding fresh ether and repeating the gelation procedure, the gel is easily reformed.

Table 8: Gelation Studies using **5**

Solvent	Physical State
Tetrahydrofuran	Soluble
Diethyl Ether	Gel
Hexane	Insoluble
Ethyl Acetate	Soluble
Chloroform	Soluble
Dichloromethane	Soluble
Methanol	Soluble
Toluene	Soluble
Acetonitrile	Insoluble
Water	Insoluble

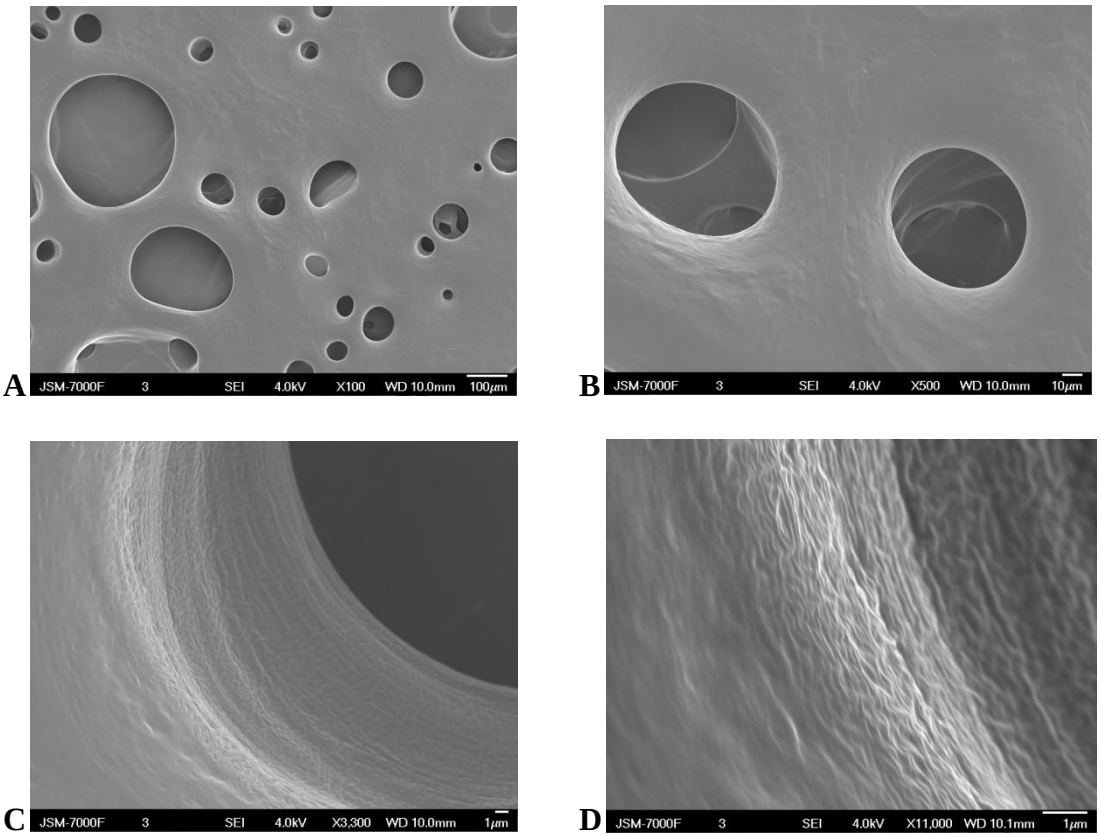


Figure 19: SEM micrographs of the gel of **5** and diethyl ether after evaporation. Sample measured at magnifications of: A: 100 x (10.0 µm scale bar); B: 500 x (10.0 µm scale bar); C: 3,300 x (1 µm scale bar); D: 11,000 x (1 µm scale bar).

A variety of gelators have been previously reported comprising of hydrophobe-modified saccharides including anomeric amidoalklyaryl ethers **6**[23], arylacetals **7**[24], and mannitol diacetals **8**[21] (Figure 20). In all cases, self-supporting optically transparent gels show, after evaporation, filamentous or fibrous assemblies that are postulated to provide the structural elements within the gel. Gelator **5** shows obvious molecular similarities to these structures and the compound constitutes the first member of this class of materials – gelators – based on silicones.

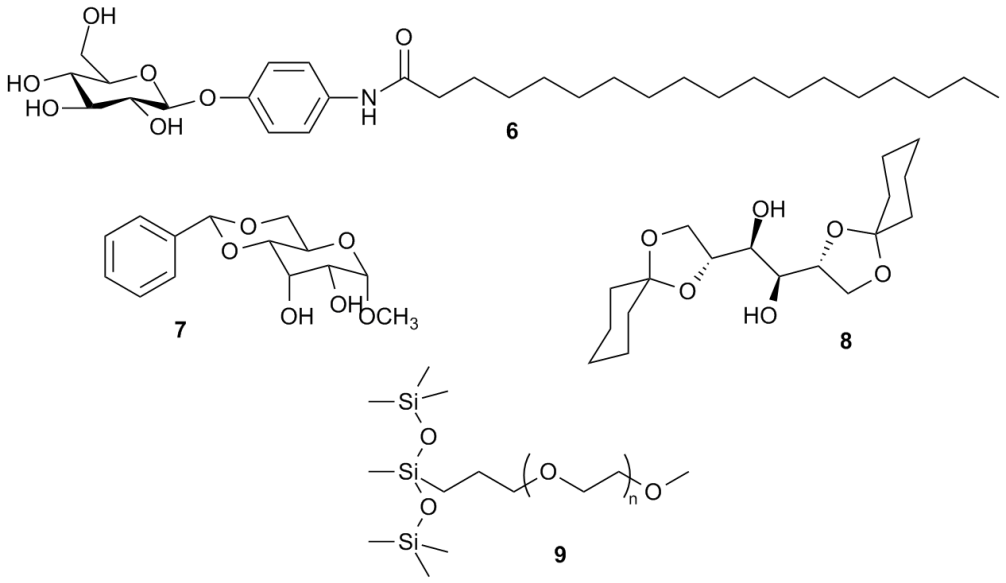


Figure 20: Examples of saccharidic gelators **6**-**8** and superwetter **9**.

Trisiloxane **3** contains the key hydrophobic residue that is present in commercially important silicone surfactants, the so-called 'superwetters' **9** (Figure 20).[1] This hydrophobic moiety has a hydrophobicity comparable to a C12 hydrocarbon.[25] However, its hammer-like shape means that it assembles very differently at air/water interfaces than either analogous silicones, or hydrocarbons. Frequently, surfactants based on this structure pack into lipid bilayers, creating extended three dimensional structures.[23] We infer, as with the related sugar-based gelators (Figure 21), that the phase separation of the triazole-sugar moieties from the silicones, to give lipid bilayers, is further assembled into fibrous structures that holds the ether in place by capillary forces. The affinity of the saccharidic residues, which are required for the self-assembly, may be attributed to a combination of hydrogen bonding and, possibly, π-π interactions between the triazoles of neighboring molecules. The affinity is a delicate balance, however. Only with ether was the balance between solubility/insolubility appropriate to give three dimensional networks: in other solvents, **5** formed a homogenous solution or is insoluble.

Gelator **5** is an attractive substrate as it is comprised of a natural hydrophilic constituent. The ability to stabilize interfaces of this, and of related glycosilicones that we are preparing by the same metal-free click methodology is currently under investigation.

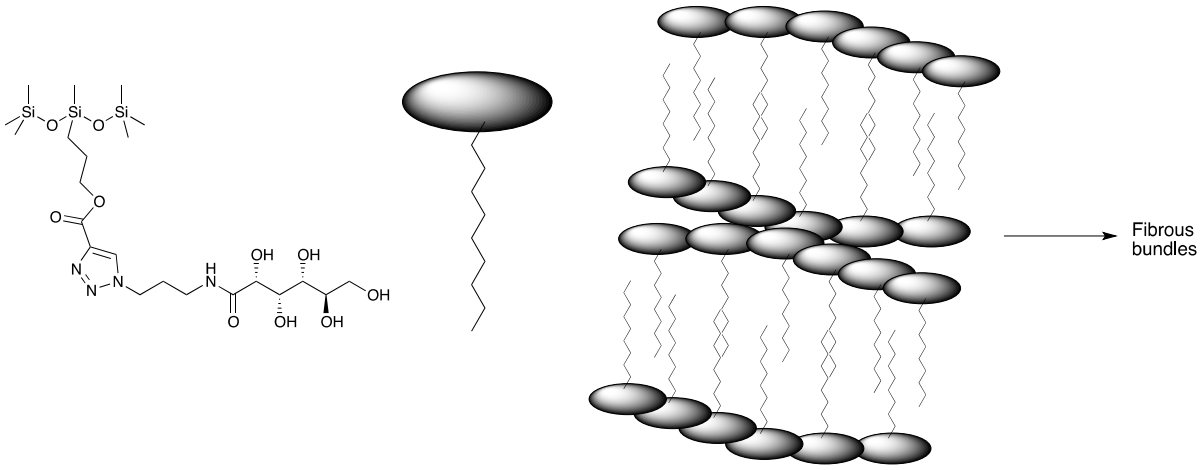


Figure 21: Model assembly of **5** leading to gelating structures.

Conclusion

Previous methods to create carbohydrate-functionalized polysiloxanes require protecting groups, a process that is inherently inefficient. The process described above allows the rapid assembly of azido-modified glucose which, in turn undergoes an efficient, catalyst free Huisgen cyclization to give saccharide-functionalized siloxanes. The bifunctional linker, 3-azidopropylamine, was used to introduce the azide onto a carbohydrate – gluconic acid – using a lactone ring-opening reaction. The introduction of alkynes onto polysiloxanes was achieved by acid-catalyzed siloxane polymerization using an alkyne-functionalized siloxane monomer. Despite the differences in solubility, **2** and **3** reacted at low temperatures to produce **5** without the addition of a catalyst or protection/deprotection steps. Furthermore, **5** was able to gel diethyl ether at 3% gelator/solvent (mg/µL) ratio. The available data is consistent with gelation arising from the

interaction between ether and fibrous structures derived from the self-assembly of the silicone gelator in ether.

Acknowledgements

We gratefully acknowledge the financial support of the Natural Sciences and Engineering Council of Canada and Dr. Ferdinand Gonzaga for helpful advice.

References

[1] Hill, R.M.; Fey, K.C. *Silicone Surfactants, Surfactant Science Series 86*, Marcel Dekker: New York, 1999.
[2] Gonzaga, F.; Grande, J. B.; Brook, M. A. *Chem. Eur. J.* **2012**, *18*, 1536-1541.
[3] Fitremann, J.; Moukarzel, W.; Mauzac, M. *Silicon Based Polymers*,in *Glycosilicones*, Boileau, S.; Boury, B.; Ganachaud, F. Eds.; Springer, **2008**, 181-202.
[4] Thompson, D. B.; Gonzaga, F.; Fawcett, A.S.; Brook, M. A. *Silicon Chem.* **2008**, *3*, 327–334.
[5] a) Braunmuhl, V.; Jonas, G.; Stadler, R. *Macromolecules* **1995**, *28*, 17-24. b) Henkensmeier, D.; Abele, B. C.; Candussio, A.; Thiem, *J. Macromol. Chem. Phys.* **2004**, *205*, 1851-1857. c) Wagner, R.; Richter, L.; Wesig, R.; Schmaucks, G.; Weiland, B.; Weissmuller, J.; Reiners, *J. Appl. Organomet. Chem.* **1996**, *10*, 421-435.
[6] Wagner, R.; Richter, L.; Wu, Y.; Weissmuller, J.; Reiners, J.; Hengge, E.; Kleewein, A.; Hassler, K. *Appl. Oganometal. Chem.* **1997**, *11*, 645-657.
[7] Sahoo, B.; Brandstadt, K.F.; Lane, T.H.; Gross, R.A. *Org. Lett.* **2005**, *7*, 3857-3860.
[8] Ogawa, T. *Polymer Sci., Part A: Polym. Chem.* **2003**, *41*, 3336-3345.
[9] a) Kocienski, P. J. *Protecting Groups*; Thieme: New York, New York, 1994; Chapter 2, pp 28. b) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer* Chemistry; John Wiley & Sons, Inc.: New York, NY, 2000; Chapter 8, pp 198-203. c) Ogilvie, K. K.; Thompson, E. A.; Quilliam, M. A.; Westmore, J. B. *Tetrahedron Lett.* **1974**, *15*, 2865-2868.
[10] Jonas, G.; Stadler, R. *Makromol. Chem., Rapid Comm.* **1991**, *12*, 625-632.
[11] Gonzaga, F.; Yu, G.; Brook, M. A. *Chem. Comm.* **2009**, 1730-1732.
[12] Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Nat. Acad. Sci.* **2007**, *104*, 16793-16797.
[13] Pascoal, M. *Application of Thermally Enhanced Huisgen Cycloaddition on Polysiloxane Functionalization*, in *Application of Thermally Enhanced Huisgen Cycloaddition on Polysiloxane Functionalization*, McMaster University, **2012**.
[14] Jewett, J. C.; Sletten, E. M.; Bertozzi, C. R. *Chem. Comm.* **2010**, 3688-3690.
[15] Gonzaga, F.; Yu, G.; Brook, M. *Macromol.* **2009**, *42*, 9220-9224.
[16] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley & Sons Inc.: New York, 1977.
[17] Jin, J.; Wu, D.; Sun, P.; Liu, L.; Zhao, H. *Macromol.* **2011**, *44*, 2016-2024.
[18] Brook, M. A.; Baklnt, S.; Mohamed, M.; Gottardo, C. *Tetrahedron* **1999**, *55*, 10027-10040.
[19] Kobayashi, H.; Friggeri, A.; Koumoto, K.; Amaike, M.; Shinkai, S.; Reinhoudt, D. N. *Org. Lett.* **2002**, *4*, 1423-1426.

[20] Brook, M., A. *Silicon in Organic, Organometallic, and Polymer* Chemistry; John Wiley & Sons, Inc.: New York, NY, 2000; Chapter 9.
[21] Vidyasagar, A.; Handore, K.; Sureshan, K. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8021-8024.
[22] Jadhav, S. R.; Vemula, P. K.; Kumar, R.; Raghavan, S. R.; John, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 7695-7698.
[23] Gonzaga, F.; Singh, S.; Brook, M. A. *Small* **2008**, *4*, 1390-1398.

Chapter 4

Conclusion

This thesis demonstrates that catalyst-free cycloaddition can be used for controlled functionalization of siloxanes and polysiloxanes with both non-polar and polar substrates. Chapter 2 demonstrates controlled polysiloxane functionalization of more reactive alkynes in preference to less reactive ones. We showed that propiolates reacted faster than propiolamides or propargyl groups. Using these results, we prepared polysiloxanes with at least two electronically different alkynes to show selective reactivity. Polysiloxane **15**, with pendant propiolates and terminal propargyl groups, showed complete selectivity where the propiolates were consumed while the propargyl groups remained untouched. Complete selectivity was further proven with difunctionalization of polysiloxane **15** where propiolates were consumed with benzyl azide followed by chain extension with 1,3-bis(azidopropyl)tetramethyldisiloxane. Chapter 3 demonstrated that azide-functionalized carbohydrates can be introduced onto propiolate-functionalized siloxanes to prepare **5** without metal catalysts or additives or protection/deprotection steps. Furthermore, **5** was able to display surface activity by gelling diethyl ether with a gelator/solvent volume ratio of 3.0%.

As we have shown, we can selectively functionalize electronically different alkynes on polysiloxanes by changing the temperature or by adding the Cu(I) catalyst. However, as good as this result was for our polysiloxane functionalization study, there are still questions and studies that need to be answered and explored. Can we use selective functionalizations to perform selective crosslinking experiments to make materials with different physical properties just by changing the order of functionalization? Can we use other materials besides polysiloxanes such as PEG or carbohydrate-based materials? Herein, we have described a new procedure of

preparing carbohydrate-functionalized siloxanes using the Huisgen cycloaddition. Furthermore, trisiloxane-functionalized carbohydrate **5** gelled diethyl ether. This ability needs to be explored more thoroughly. Are intermolecular interactions from the carbohydrate responsible for the gelation? Does the triazole play a role in gelation? Can we expand the process in functionalizing polysiloxanes with azide-functionalized carbohydrates? Is the process suitable for the larger carbohydrate materials like Gum Guar? The results obtained so far show that the Huisgen cycloaddition involving electron deficient alkynes is a suitable method for functionalizing siloxanes and polysiloxanes with a variety of materials from non-polar siloxanes to polar carbohydrates.