CLICK

SILICONES

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By

GILBERT YU, 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 (2008)	McMaster University
(Chemistry)	Hamilton, Ontario
TITLE:	Click Silicones
AUTHOR:	Gilbert Yu, B. Sc. M.Sc. (Ateneo de Manila University)
SUPERVISOR:	Professor Michael A. Brook
NUMBER OF PAGES	xiii, 66

Abstract

Both the thermal and copper(I) catalyzed azide-alkyne Huisgen cycloadditions were explored as strategies to be used for silicone functionalization and crosslinking. The generality of these reactions was demonstrated (Chapter 2) using 1,3-bis(azidopropyl)tetramethyldisiloxane (BAPTMDS) as a model compound. The ligation of this compound with several alkyne-containing molecules, especially the copper(I) catalyzed process or "click" proved to be easy to perform, high yielding, and gave the 1,4-triazole regioisomer as the sole product. Thermal, metal catalyst-free, azide-alkyne cross-linking (Chapter 3) using a poly(azidopropylmethylsiloxane)-co-dimethylsiloxane as the base polymer and several polysubstituted alkyne molecules as crosslinkers was efficient. The reaction of the base polymer with an ethynyl-terminated disiloxane demonstrates that a silicone elastomer can be synthesized by simple heating and that the resulting material is stable, decomposing only at temperatures higher than 230 °C. Finally, direct bioconjugation of silicones to biotin using propargylamide and BAPTMDS was examined (Chapter 4). The result of the copper(I) catalyzed Huisgen ligation of biotin onto silicones was as efficient as the reactions in the previous chapters, revealing that the "click" process can successfully be applied to a broad range of silicones.

Preface

The research work on this master's thesis was carried out by the author and Ferdinand Gonzaga between October 2007 and August 2008. The "click silicone" project was borne out of the unsuccessful experiments on covalently linking biotin moeties and starch molecules onto silicones (which are not described in this thesis). Because of the numerous publications out on "click" chemistry at that time detailing mild reaction conditions that were efficient in chemically immobilizing biological molecules onto several compounds, it was decided that we should give this "click" chemistry on silicones a try. This dissertation was intended to be a sandwich thesis; as such, chapters 2, 3, and 4 are designed and written to be part of or to be the article themselves.

The derivatization of the disiloxane, 1,3-bis(azidopropyl)tetramethyldisiloxane (BAPTMDS) and the polyazide was performed by the author. The "click" ligation of several alkynated compounds with BAPTMDS was carried out by the author whereas the "click" experiments with the polyazide was performed by Ferdinand Gonzaga. Both the author and Ferdinand Gonzaga worked on the thermal crosslinking of azido-and alkynyl-derived silicones.

Acknowledgement

I would like to thank Dr. Mike Brook for giving me the opportunity to work in his laboratory. It is not an ordinary day event that a professor overseas shows interest in your application, contacts you and offers you to do research on his lab—for this I am truly grateful. I consider myself to be truly lucky to have a mentor/supervisor who continually inspires and gives advises not only on his chosen field but much, much more.

I would also like to thank all the professors of whom I had the chance to learn valuable knowledge from, Dr Harald Stöver, Dr. James McNulty, Dr. Heather Sheardown, Dr. Fred Capretta, and Dr. Kalai Saravanamuttu. My special thanks go to Dr. Harald Stöver and Dr. James McNulty for giving their nod to become part of my graduate committee and for giving good advice on those sessions.

I am also grateful to the Brook research group—Rebecca, Dave, Shigui, Lucy, Weian, Yongxin, Renita, Yohan, Neven, Yunping, Ken, Jon, Jordan, Vinodh, Amanda, Helen, and Gongchang—for keeping me company and giving me valuable tips and information on how to go about in the lab and deal with McMaster life in general. Special mention goes to the two titans of ABB-359, Dr. Yang Chen and Dr. Ferdinand Gonzaga who took great pains in patiently guiding me through the experiments, most of which, I was performing for the first time.

To Frank Gibbs, Dr. M. K Green, Dr. Steve Kornic, and Dr. Bob Berno who helped me with the instrumentation/ DSC analysis—thank you. To NSERC—for the much needed funding—thank you.

My appreciation also goes to my friends, both old and new—Teri, Kunal, Jafar, Jeffrey, Lichun, Gregor, Patiguli, and Prio for providing good laughs and banter to keep the TA duties light. Truly, I am blessed to have known you all.

Finally, I would like to give my thanks and my gratitude to my family—my dad, mom, and my sisters—for giving me the support, the encouragement, and the added "push" to carry me throughout this two year endeavor—without which, I think would be impossible.

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List of Abbreviations and Acroynms

ATR	attenuated total reflectance
BAPTMDS	1,3-bis(azidopropyl)dimethyldisiloxane
BCPTMDS	1,3-bis(chloropropyl)dimethyldisiloxane
Boc	*tert*-butyloxycarbonyl
Cbz	carbobenzyloxy
CDI	carbonyldiimidazole
D_4	octamethylcyclotetrasiloxane
DCC	dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DNA	deoxyribonucleic acid
DSC	differential scanning calorimetry
ESI	electron spray ionization
FMO	frontier molecular orbitals
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
LED	light emitting diode
LUMO	lowest unoccupied molecular orbital
MO	molecular orbital

NMR	nuclear magnetic resonance
PDMS	polydimethyldisiloxane
PEO	polyethylene oxide
RTV	room temperature vulcanization
TEOS	tetraethylorthosilicate
TGA	thermal gravimetric analysis

Chapter 1

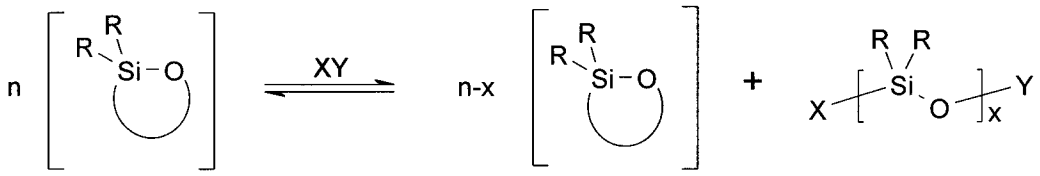
Introduction

Silicones—Brief Description, Uses, and Preparation

A material's importance is determined by its function, and its relevance by the innovation it delivers. Silicones are certainly no exception. Silicones, or polysiloxanes, are polymers with an -(Si-O)- repeating unit where commonly two alkyl or aryl groups (or sometimes other functional groups such as $CH{=}CH_2$, H, Cl, or OH), are attached to the silicon atoms. These materials have interesting properties:[1] good thermal stability, excellent electrical resistance, outstanding hydrophobicity, exceptional flexibility, and remarkable biocompatibility that is generally considered to be superior to other conventional organic polymers. This has led the use of silicones in many wide-ranging applications from kitchen appliances to prosthetic devices.[2]

Silicones are usually prepared using dialkyldichlorosilanes, particularly dichlorodimethylsilane, as starting materials. These are transformed to linear oligomers and low molecular weight cyclic silicones via hydrolysis, usually under excess water or basic conditions.[3] The linear polymers and cyclic oligomers are further processed into more valuable, high molecular weight oils via equilibration catalyzed by either acid or base (Scheme 1).[4] The equilibration procedure is carried out with the use of small amounts of acid or base since their utilization may also lead to siloxane bond cleavage redistribution.[5] Also, the reaction has to be performed under anhydrous conditions to

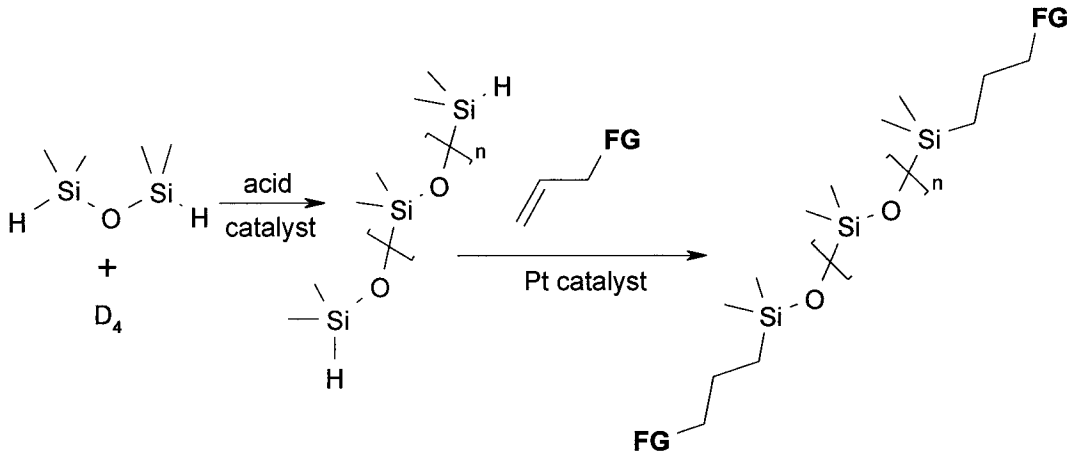
prevent the premature end capping or, in the worst case scenario, depolymerization of the growing silicone polymer chains.



Cyclic Oligomers Cyclic Oligomers High(er) Molecular Weight Linear Polymer

Scheme 1

Added value is imparted to silicones when they are modified with appropriate organic functional groups. When more hydrophilic groups are attached to silicones either as end and/or pendant groups, the resulting material can behave as surface active agents/surfactants, liquid crystals, antifoaming agents, textile finishing agents, and much more.[6] One way of introducing functional groups is through hydrosilylation (use of Pt catalyst), via the addition of functionalized vinyl or allyl groups, $CH{=}CH\text{-}CH_2FG$ onto –Si-H species on the silicone chains resulting in propyl functionalized polymers (FG = functional group, Scheme 2). Another method makes use of the chlorination of methylsilanes ($R_3SiMe \rightarrow R_3SiCH_2Cl \rightarrow R_3SiCH_2FG$) which can undergo further substitution. In this case, the chloroalkyl unit can be substituted before or after the silanes have been transformed into silicones via hydrolysis, producing alpha-functionalized polysiloxanes.[7] In general, for both methods, the functionalization of silicones is usually performed on small silicone or silane molecules, that is, before they undergo hydrolysis and condensation during transformation to high molecular weight silicones.[8]



Scheme 2

Silicone elastomers are also high value silicone-based materials. Silicone rubbers are made by crosslinking silicone chains together, generally via two distinct methods: hydrolysis and condensation of functional silanes with HO-terminated silicones, or reaction of organofunctional polymers.[9] In the first case, trifunctional or tetrafunctional oxygen-based functional silanes, e.g., tetraethylorthosilicate (TEOS) are hydrolyzed and condensed with HO-terminated polymers in the presence of an appropriate catalyst. In the second method, addition across silicon-substituted alkene of i) alkyl radicals (high temperature radical cure), or ii) of SiH groups (platinum catalyzed "addition cure") leads to the generation of crosslinks.

While it is true that methods for both functionalizing and crosslinking silicones have been established and even entrenched for decades, there are a variety of disadvantages of these processes. For instance, the methods involved usually make use of anhydrous conditions and hence, can be moisture sensitive. Also, most of the time, these processes make use of an expensive Pt catalyst to carry out effective transformations. An

alternative process that is relatively easy to perform, gives high yields, and one that operates efficiently under a wide variety of reaction conditions, including the presence of other functional groups, a broad pH range, and moisture would be a welcome development. This thesis is focused on the development of such a process, exploiting "click" chemistry in the silicone world.

"Click" Chemistry—Azide-Alkyne Huisgen Cycloaddition

(A) The Thermal Huisgen Cycloaddition—Brief Description and Regioselectivity

The "click" reaction is a name coined by Sharpless for the 1,3-dipolar cycloaddition reaction between azides and alkynes, made famous by Huisgen[10]: this reaction has been known for decades. The Huisgen cycloaddition is a [4+2]* reaction similar to the Diels-Alder reaction, in that it involves the cyclic addition of 3 pairs of π electrons. In the case of the azide-alkyne "click" (one of the many known 1,3-dipolar cycloaddition reactions[11]), 2 pairs of electrons "4" from the azide (the dipole) and 1 pair "+2" from the alkyne (the dipolarophile) come together to form a 1,2,3 –triazole (a ring structure) with the formation of two sigma bonds as shown in Scheme 3. [12] These reactions are known for their large thermodynamic driving force (large, exothermic ΔH_{rxn})[13] and prior to the discovery of the Cu(I) and other catalyzed versions,[14] have been reported to readily undergo cycloadditions thermally.

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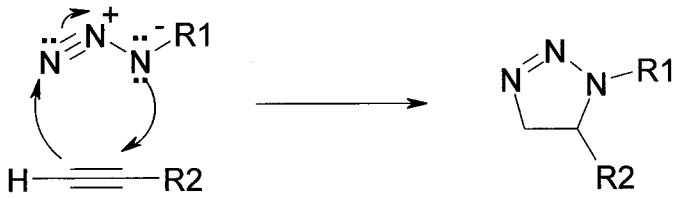
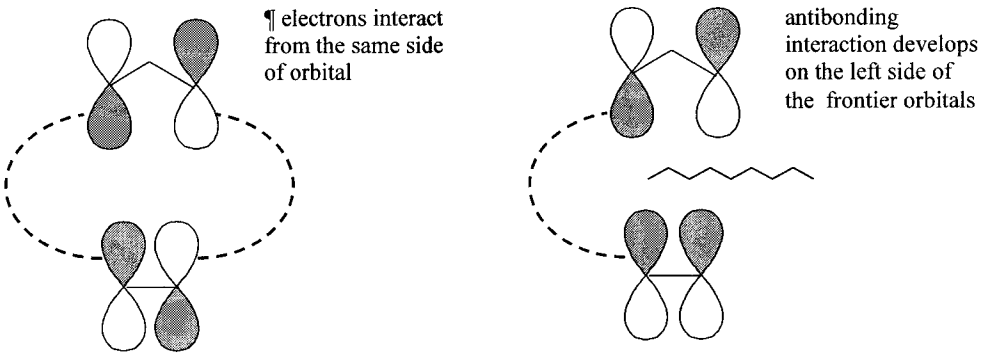
* According to IUPAC guidelines, the braces [] are assigned to the number of π electrons in a cycloaddition reaction, whereas the parenthesis () refers to the number of atoms involved in the formation of the ring; thus the azide-alkyne cycloaddition is a [4+2] and at the same time a (3+2) reaction.



Scheme 3

The facility with which the Huisgen 1,3-dipolar cycloadditions occurs thermally can be explained by examining some concepts of the Frontier Molecular Orbital Theory (FMO) developed by Fukui.[15] According to this theory, a cycloaddition reaction can occur with thermal energy when there is significant overlap between the frontier orbitals—Highest Occupied Molecular Orbital (HOMO) of the dipole and the Lowest Unoccupied Molecular Orbital (LUMO) of the dipolarophile or vice versa; that is, both HOMO and LUMO orbitals must overlap from the same side of the π system; i.e., HOMO azide-LUMO alkyne must overlap suprafacially (Scheme 4). This hypothesis is consistent for all [4+2] cycloaddition reactions. Since the azide-alkyne pair has the requisite symmetry, ligation via this 1,3-dipolar cycloaddition can proceed thermally.[16]



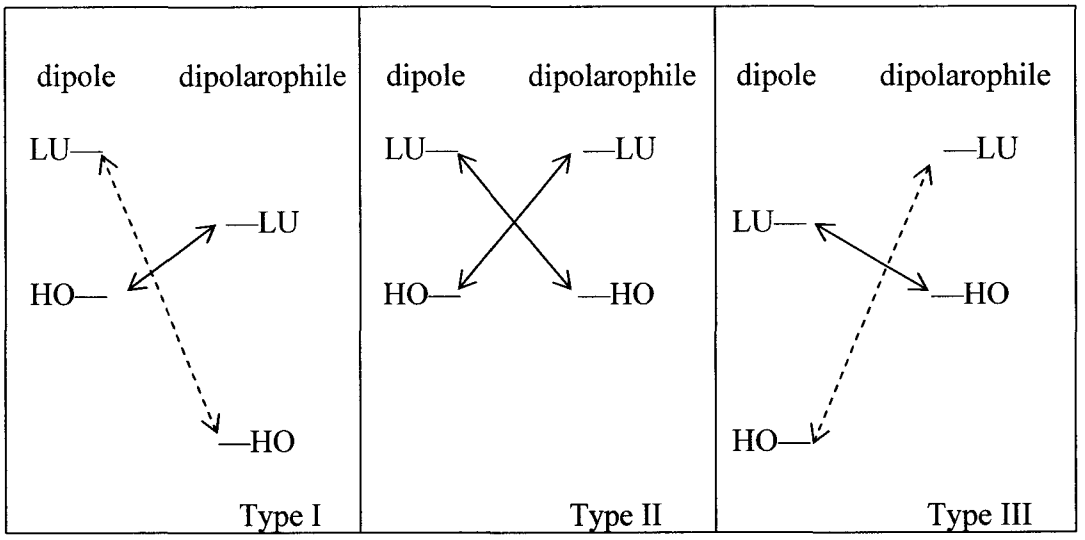
symmetry-allowed overlap

symmetry-forbidden overlap

Scheme 4

Fukui's FMO not only provides elegant description as to why 1,3-dipolar cycloadditions can readily occur thermally, but also provides a simple explanation as to why certain reactions, i.e., azide-alkyne cycloadditions, preferentially form one regioisomer over the other. Huisgen[17] described thermal 1,3-dipolar cycloadditions to be "concerted but asynchronous" reactions—although the formation of the ring occurs as a single step, the formation of the two sigma bonds does not happen at the same time. As stated above, the FMO theory cites two ways by which symmetry-allowed overlap can take place leading to cycloaddition: either via the HOMO dipole—LUMO dipolarophile interaction or through HOMO dipolarophile—LUMO dipole orbital overlap. For certain 1,3-dipolar cycloadditions, one molecular orbital (MO) interaction is favored over the other; for some, either MO overlap occurs quite readily. Regioselectivity arises when a smaller HOMO-LUMO gap is preferred, allowing for maximum overlap between the two orbitals.[18] 1,3-Dipolar cycloaddition reactions biased towards 1,4 regioisomers typically

have smaller HOMO dipole-LUMO dipolarophile gaps and are classified as type I or HOMO dipole-controlled (HOMO controlled) MO interactions. Those that favor the 1,5-regioisomer are classified as type III or LUMO dipole-controlled (LUMO controlled) MO interactions, while those that have similar HOMO-LUMO energy gaps regardless of dipole/dipolarophile assignments are described to be type II or HO, LU-controlled (Scheme 5) and can form both regioisomers in almost equal amounts.[19]



Scheme 5

The chemical natures of both dipoles and dipolarophiles also affect which regioisomer dominates in a particular 1,3-dipolar cycloaddition. When considering ethylene as the "standard" dipolarophile, Sustmann was able to classify dipoles in a similar manner to MO interactions: type 1 dipoles have high lying HOMOs and LUMOs and are considered as "nucleophiles"; cycloadditions with these type I dipoles are generally HOMO-controlled regardless of the chemical nature of the dipolarophile. In type III dipoles, which are considered "electrophilic", the frontier orbitals are low lying

and generally follow a LUMO-controlled cycloaddition. Type II dipoles are described to be "ambiphilic" and can go both ways; therefore substituents on the dipolarophile will determine which regioisomer will be predominantly formed.[20]

For purposes of convenience, the substituents attached to the dipolarophiles can be assigned and classified into Z (electron-withdrawing), X (electron-donating), and C (conjugated) groups and generally have the following effects on the different types of cycloadditions: Z groups decrease the energies of both the LUMO and HOMO orbitals of the dipolarophile and therefore promote type I cycloadditions, retard type III MO interactions, and give predominantly 1,4-regioisomers in type II reactions. The opposite holds true for X groups, which increase both energy levels of the frontier orbitals of the dipolarophiles: type I reactions are decelerated whereas type III reactions are promoted, and 1,5 regioisomers are favored for type II MO interactions. Conjugated substituents on the dipolarophile are much harder to predict than the other two because they decrease the LUMO and increases the HOMO energy at the same time. Which regioisomers predominate depends on the dipole used: type I dipoles will form 1,4 regioisomers, type III will have mostly 1,5-regioisomers; whereas reactions of type II dipoles with conjugated dipolarophiles will contain a mixture of both 1,4 and 1,5-regioisomers.[21] Additionally, electronic substituents on the dipole may affect the regioselectivity of the cycloaddition, but this would have an opposite effect to substituents on the dipolarophile, i.e., whereas electron withdrawing groups on dipolarophiles accelerate type I cycloadditions, electron-donating groups on the dipoles promote this interaction.

Azides are generally accepted to be type II dipoles; hence, in azide-alkyne thermal Huisgen reactions, the regioselectivity of the cycloaddition is dependent on the substituents attached to the alkyne. Electron withdrawing groups give 1,4-regioisomers whereas electron-donating groups favor the 1,5 regioisomer. Conjugated groups give mixed outcomes.[22]

(B) The Cu(I) Catalyzed "Click" Reaction

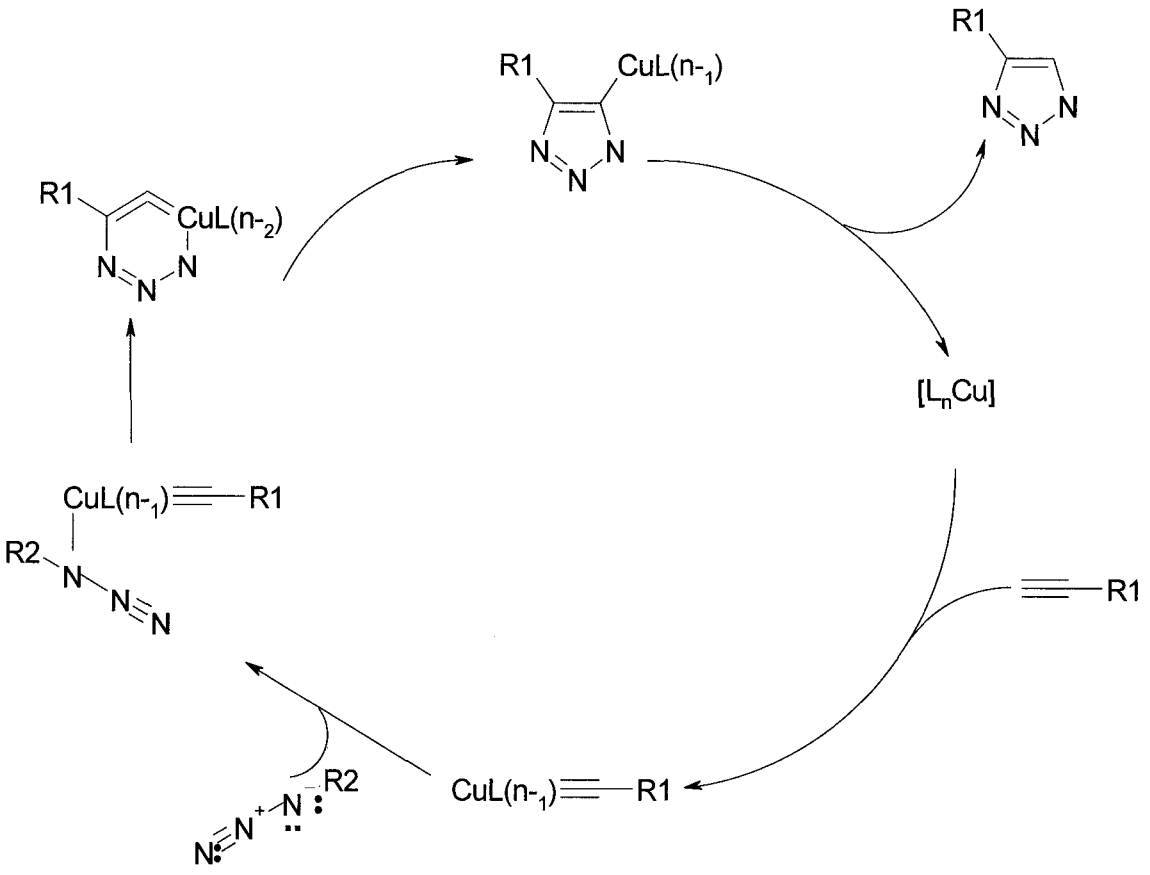
Although the thermal azide-alkyne reaction is a reliable reaction, most of the time high temperatures are required to make the reaction proceed at acceptable rates and with higher yields. Performing these reactions at high temperatures is not without disadvantages. For one, azides, particularly small, inorganic azides, are known to explode upon contact with metal.[23] In addition, most organic molecules, for example biotin, amino acids (which will be relevant to this thesis, see below), tend to decompose upon prolonged contact with heat.

Since Sharpless published the first report of Cu(I) catalyzed azide-alkyne reactions, there has been an exponential growth in publications utilizing "click" applications ranging from advanced materials to biomedical uses.[1,24] There are several copper catalyst systems available but the most common is the Cu(II) sulfate/sodium ascorbate system that generates a Cu(I) catalyst in situ.[25] Unlike most thermal Huisgen cycloadditions, "click" reactions can occur readily at room temperature when catalyzed and can be quite forgiving to a wide variety of reaction conditions, including pHs ranging from 4-12, water and oxygen, and the presence of a broad range of functional groups.

High yields, environmentally friendly conditions (inoffensive by-products, water as co-solvent), and easy isolation further add to its appeal.[26]

The copper catalyzed "click" reaction is comparably faster and more regioselective than its thermal counterpart. This is logical, since faster cycloaddition reactions leads to greater regioselectivity: studies have demonstrated that the catalyzed reaction rates are 7 to 8 magnitude times higher than the thermal process and give the 1,4-regioisomer regardless of the electron demand of the alkyne substituent.[27]

A few proposals have been put forth for the mechanistic details of the "click" reactions. Although there is some divergence of opinion, it is generally agreed that "click" reactions follow a step-wise mechanism rather than a concerted pathway. Also, a copper-acetylene complex is generally considered to be the first step of the reaction process. While there is still debate regarding the specific details of the intermediate complex,[28] a six-membered transition state is thought to form prior to the formation of the triazole ring (Scheme 6).[29]



Scheme 6

Hypothesis, Scope and Limitations

Because of the large thermodynamic driving force associated with azide-alkyne reactions and hence, ease of reaction; we hypothesize that alternative methods of silicone functionalization and even crosslinking can be facilitated either through the thermal or the Cu(I) catalyzed azide-alkyne cycloadditions. Such an achievement would open up opportunities for the development of Pt metal catalyst-free systems (in the case of the thermal reaction) and/or non-moisture sensitive ("click") processes for silicone modification.

We have already explored the use of the thermal and Cu(I) catalyzed Huisgen cycloaddition in silicones, and provided a brief background of silicone modification methods and "click" chemistry is given in this chapter. The remainder of this thesis is divided into 4 parts. Chapter 2 demonstrates the generality of the process of applying the azide-alkyne click reaction to silicones. A model siloxane compound, 1,3-diazidopropyltetramethyldisiloxane (BAPTMDS), was used to effectively demonstrate the ligation of silicones with various alkynated compounds. Both thermal and Cu(I) catalyzed processes were performed. Thermal, catalyst-free azide-alkyne crosslinking is investigated in Chapter 3. The thermal stability of the azide-containing silicones was studied in this chapter. Also, the azide/alkyne ratios of a poly(dimethyldisiloxane-co-(azidopropylmethyl disiloxane)/ethynyl-terminated disiloxane system required to produce silicone rubber monoliths was examined. Chapter 4 examined bioconjugation onto silicones using biotin propargyl amide. In this chapter both thermal and Cu(I) catalyzed processes were similarly explored by the direct ligation of biotin moeties onto BAPTMDS. Lastly, a brief conclusion is provided in chapter 5.

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Chapter 2

Highly Efficient Derivatization of Polysiloxanes *via* Click Technology[‡1]

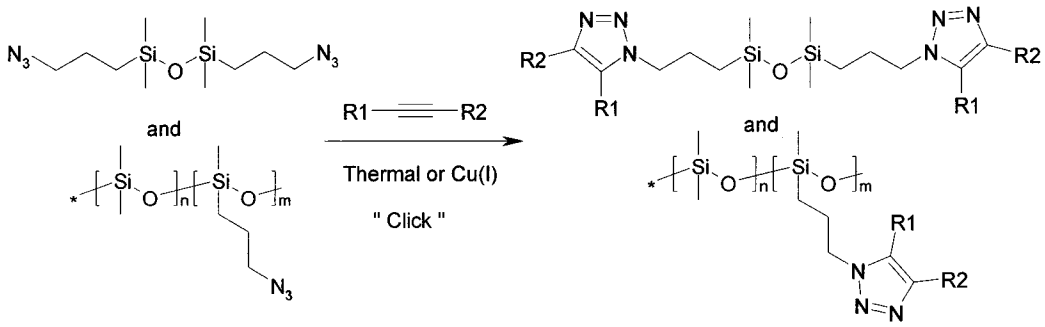
Gilbert Yu, Ferdinand Gonzaga*, Michael A. Brook*

Department of Chemistry, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada, L8S 4M1.

Abstract

The application of click-chemistry to the functionalization of siloxanes is presented. An azide-terminated disiloxane, used as a model compound, undergoes either thermal or copper (I) catalyzed 1,3 dipolar cycloadditions with various alkynes to give the corresponding coupling products in very high yields and, in the case of copper catalysis, with regiospecificity. The generality of the process is illustrated by the use of various alkynes, such as alkyne-terminated amino acids or carbohydrates: the concept has been extended to macromolecular polysiloxanes. The reaction can be performed under heterogeneous conditions, and easily yields products which would be otherwise difficult if not impossible to prepare by traditional methodologies.

‡ Submitted as a communication *J. Am. Chem. Soc.* All derivatizations of the disiloxanes were undertaken and products characterized by Gilbert Yu; polymeric "click" materials were derivatized by Ferdinand Gonzaga.



11 examples including alkynyl-aminoacids or carbohydrates ; yields ranging from 84 to 100%

Introduction

Silicones (polysiloxanes) are a class of polymers known for their extreme hydrophobicity.[2] When functionalized, particularly with hydrophilic species, silicones become more versatile. Small quantities of functional groups attached to the silicone polymer backbone (either as chain ends or pendant groups) can significantly alter their properties: surfactants, liquid crystals, antifoaming agents, and textile finishing agents are some examples of applications of functional polysiloxanes.[3]

One commonly encountered challenge of functionalizing silicones is solubility. Frequently, it is difficult to find convenient solvents to dissolve both the silicone and polar molecule. For example, while methods for the conjugation of polysiloxanes with more polar species such as carbohydrates or even proteins[4] have been established, these processes usually involve an inefficient series of protection and deprotection steps, as in the case of carbohydrate-functionalized silicones.[5] Moreover, the reactions are performed in organic solvents and generally involve the use of expensive platinum (Pt) hydrosilylation catalysts.[1a,6] Thus, there is a need for the development of new synthetic strategies to link silicones with more polar species. An ideal silicone derivatization

strategy would be highly efficient (in terms of yield and selectivity), low cost (avoiding expensive noble metals such as platinum), and easy to perform. In particular, the possibility to create surface active materials using heterogeneous reactions in high yield between silicone chains (only soluble in organic solvents) and, for example, water-soluble carbohydrates or amino acids, would be significant.

The Huisgen 1,3-dipolar cycloaddition of azides to alkynes presents itself as a robust and reliable method for the functionalization of a wide variety of molecules because its sole product – the triazole ring – acts as a stable linker between the two precursors.[7] This reaction can proceed thermally or through a copper (I)-catalyzed cycloaddition process, now commonly known as "click chemistry."[8] These cycloaddition reactions are particularly attractive because they are benign – no side products are generally formed, high yielding, often regiospecific (particularly the copper-catalyzed version), tolerant of a wide variety of functional groups, and also relatively green, as they can be performed using easily removed or innocuous solvents such as water under heterogeneous conditions.[9] For all those reasons, the copper(I) catalyzed Huisgen cycloaddition has become the most well-known and used "click" reaction.[10]

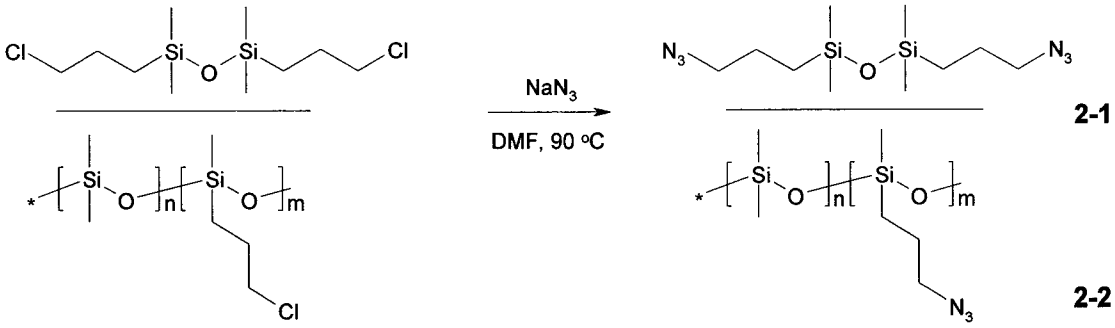
Here, we report the application of click-chemistry to the functionalization of molecular or polymeric siloxanes. We first describe the synthesis of an azide-terminated disiloxane which is used as a model compound, and show that thermal or copper (I) catalyzed 1,3-dipolar cycloadditions with various alkynes yield the corresponding coupling products in very high yields and selectivity. The generality of the process is illustrated by the use of various alkynes, such as alkyne-terminated amino acids or

carbohydrates. Then, we generalize this concept to macromolecular polysiloxanes, and demonstrate that the same methodology can be used to functionalize high-molecular weight silicones. The reaction can be performed in heterogeneous conditions, and easily yields products which would be otherwise difficult if not impossible to prepare with traditional methodologies.

Results and Discussion

A pre-requisite for the click-reaction of silicones is the ability to prepare azide- or alkyne-terminated (or pendant modified) siloxanes. We reasoned that a classical nucleophilic substitution of 1,3-bis-chloropropyl-tetramethyldisiloxane by the azide anion would easily yield the corresponding azidopropyl derivative. Indeed, its reaction with sodium azide in DMF was successful and yielded the corresponding 1,3-bis-azidopropyltetramethyldisiloxane (**2-1**) in 96% yield (Scheme 7). Using the same methodology, a polymeric azido-siloxane **2-2** was also prepared, starting from a commercially available poly(dimethyl)-co-(methyl-chloropropyl)-siloxane (MW: 7500-10000; 14-16% mol chloropropyl units).

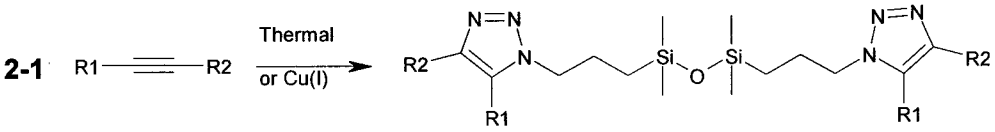
Scheme 7. Synthesis of azidopropyl-modified siloxanes 2-1 and 2-2

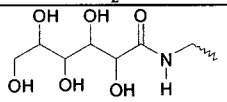
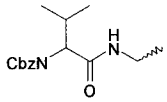
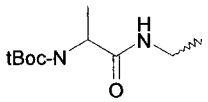
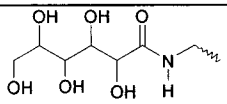


It should be noted here that while most azides can be handled without incident, some members of this class are explosives.[11] However, thermogravimetric analysis (TGA, see Supporting Information) demonstrated that slow thermal decomposition for compound **2-1** started only at 120 °C. The polymeric derivative **2-2** was even more thermally stable, which may be explained by a dilution effect of the azido-groups within the polymeric matrix. In both cases, the slow decomposition occurs at temperatures well above those required to perform thermal cycloadditions, and exhibits no characteristics of explosive behavior, confirming the viability of this synthetic approach.

The click ligation of several alkynes with **2-1** was examined both thermally and using copper-catalysis, as shown in Table 1. The thermal Huisgen cycloaddition reaction was carried out with two common alkynes, propargyl alcohol and phenylacetylene, acting both as solvent and reagent (Table 1, entries 1 and 2), at 90 °C. In both cases, click ligation was successful and quantitatively yielded the corresponding triazole derivative, in only 3 hours for propargyl alcohol (24 hours for phenylacetylene). Neither of these reactions occurred thermally at room temperature, even after 1 day of reaction.

Table 1. Thermal and copper-catalyzed click ligation of alkynes to siloxane-azides.



Entry	Azide	Alkyne		Type	Yield (%)	Selectivity
	2-1	R1	R2			
1	**2-1**	H	CH_2OH	Thermal	100	50:50
2	**2-1**	H	Ph	Thermal	100	50:50
3[§]	**2-1**	$COOCH_3$	$COOCH_3$	Cu(I)*	92	100:0
4	**2-1**	H	$C(CH_3)_2OH$	Cu(I)	95	100:0
5	**2-1**	H	Ph	Cu(I)	96	100:0
6	**2-1**	H	CH_2OH	Cu(I)	94	100:0
7	**2-1**	H		Cu(I)	94	100:0
8	**2-1**	H		Cu(I)	100	100:0
9	**2-1**	H		Cu(I)	95	100:0
10	**2-2**	H	Ph	Thermal	100	Nd
11	**2-2**	H		Cu(I)	84	100:0

* The reaction gave the same products, at room temperature, in the absence of copper catalyst and, thus, is likely a thermal reaction.

Copper-catalyzed reactions were also performed using 2% molar copper (II) catalyst, and 10% molar sodium ascorbate, in binary solvent system such as THF:water (1:1; v:v) or DMF:water (5:1; v:v) at room temperature. Under such conditions Cu(I), the active catalyst, spontaneously forms.[12] As in the case of thermal cycloadditions, the reaction was found to proceed smoothly, yielding the coupling product in very high yields (ranging from 92 to 100%). Moreover, unlike the thermal reactions, the copper-

[§] Performed in Cu(I)-catalyzed conditions but was later found to go cycloaddition at room temperature without the use of catalyst; can be therefore described as a thermal reaction at room temperature.

catalyzed reaction gave only one regioisomer, irrespective of alkyne hydrophilicity or electronic distribution. A particularly interesting result appears in entry 7, where **2-1** was reacted with propargyl-gluconamide. Although these 2 reagents possess very different polarities, their coupling via click technology yielded in 94% a disiloxane-diglucose molecule, without the use of any protecting groups and an extremely simple work-up (a simple precipitation in acetone, see Supporting Information for detailed experimental procedures). For the alkynyl amino acids (entries 8 and 9), a DMF-H_2O binary system was used to facilitate their solubilization. It is interesting to note that the click ligation also performed well with only marginally soluble (precipitated) alkynes, suggesting that this process can occur interfacially, although the process was slow due to low contact surface areas between reagents.

This functionalization strategy can be readily ported to polymeric siloxanes. A polysiloxane-co-polyazidopropyl **2-2** was prepared according to Scheme 7 in quantitative yield from the corresponding, commercially available chloropropyl precursor. When submitted to a thermal cycloaddition with phenylacetylene (Table 1, entry 10), the corresponding phenyl triazolyl-graft-copolymer was obtained quantitatively in 24 hours at 90 °C. The copper-catalyzed click reaction between **2-2** and the most challenging alkyne (with respect to solubility), the propargyl gluconamide, was performed in a mixture of THF and water. The reaction yield was found to be quantitative by ^{1}H NMR after 2 days at room temperature and the corresponding gluconamidetriazolyl-graft-polysiloxane was isolated in an 84% yield (entry 11, Table 1), thus confirming that the

methodology applied for our model diazido-siloxane **2-1** could be extended to high molecular weight, azido-modified siloxanes.

The functionalization of silicone polymers, particularly by hydrophilic groups is normally challenged by poor yields, the need to work with low molecular weight materials, protection/deprotection sequences and/or the use noble metal catalysts that can remain in the product. The simple click chemistry strategy obviates all these problems, leading to the ready incorporation of a wide variety of functional groups in the silicone, including water soluble fragments.

Acknowledgement. We thank the Natural Sciences and Engineering Research Council of Canada for funding this project.

Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Supporting Information

Highly Efficient Derivatization of Polysiloxanes via Click Technology

Gilbert Yu, Ferdinand Gonzaga*, Michael A. Brook*

Department of Chemistry, McMaster University, 1280 Main St. W., Hamilton Ontario, L8S 4M1

* (E-mails: gonzaga@mcmaster.ca; mabrook@mcmaster.ca)

OUTLINE OF SUPPORTING INFORMATION

Experimental Section

1) Materials and methods

1,3-Bis(chloropropyl)tetramethyldisiloxane and (chloropropyl)methylsiloxane-dimethyl-siloxane copolymer (14-16 mole% (chloropropyl)methylsiloxane) were obtained from ABCR and Gelest, respectively. Sodium azide (95%) was purchased from J. T. Baker. Sodium iodide (99%), propargyl alcohol (99%), 3-butyn-2-methyl-2-ol (98%), phenylacetylene (98%), propargyl amine (98%), Boc-L-alanine (98%), Cbz-L-valine (99%) and dimethylacetylene dicarboxylate (99%), gluconolactone (99%) were obtained from Sigma-Aldrich. Triethylamine (99%) was purchased from EMD. Sodium ascorbate (98%) was obtained from Fluka while copper(II) sulfate pentahydrate (99%) was purchased from Fisher Scientific. All materials were used as received.

IR analysis was made using a Bio-Rad Infrared Spectrometer (FTS-40). ^{1}H NMR and ^{13}C NMR were recorded at room temperature on a Bruker AC-200 spectrometer using deuterated solvents ($CDCl_3$, DMSO-d_6, CD_3OD). High-resolution mass spectrometry was performed using a Hi-Res Waters/Micromass Quattro Global Ultima (Q-TOF mass spectrometer). TGA analysis was performed using NETZCH STA 409 PC/PG.

2) Synthesis of azido-terminated siloxanes

Compound **2-1**: Bis(azidopropyl)tetramethyldisiloxane: sodium azide (6.2 g, 96 mmol, 3 equiv.), sodium iodide (9.3 g, 62 mmol, 2 equiv.), and 1,3-bis(chloropropyl)-tetramethyldisiloxane (9.0 g, 31 mmol, 1 equiv.) dissolved in DMF (40 mL). The

mixture was stirred until all reagents dissolved and then heated at 90 °C overnight. The reaction was stopped after ^{1}H NMR showed the absence of the 1,3-bis(chloropropyl)tetramethyldisiloxane starting material. The reaction mixture was then partitioned between water and dichloromethane. The organic phase was separated, dried over sodium sulfate, and then evaporated to give 9.7 g (96%) of the title compound as a light yellow liquid.

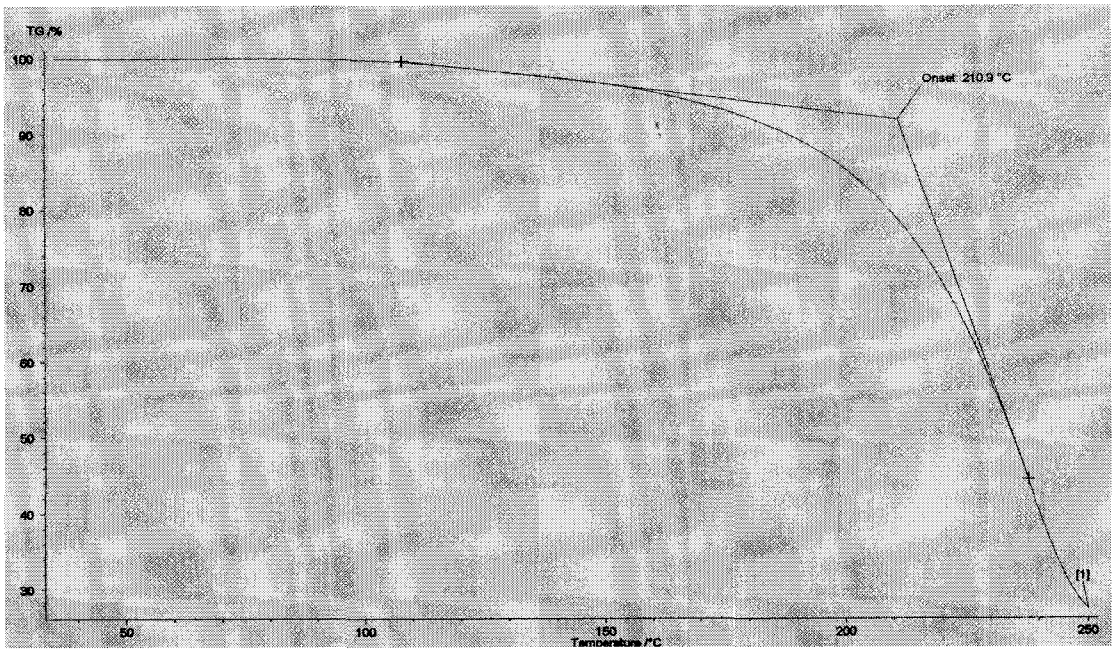
^{1}H NMR ($CDCl_3$): δ = 3.22 (t, J = 7 Hz, 4H), 1.59 (m, 4H), 0.54 (m, 4H), 0.06 (s, 12 H); ^{13}C NMR ($CDCl_3$): δ = 54.1, 22.9, 15.2, 0.3; IR (KBr, cm^{-1}): 2097 (N_3); HRMS (ESI): m/z calculated: $[M+Ag]^+$ = 407.0601, found: $[M+Ag]^+$ = 407.0620

Compound **2-2**: (Azidopropyl)methylsiloxane-dimethylsiloxane copolymer: (Chloropropyl) methylsiloxane-dimethylsiloxane copolymer (14-16 mole% (chloropropyl) methylsiloxane) (10.0 g) was dissolved in 40 ml of a mixture of DMF and THF (2:1; v:v). Sodium azide (1.0 grams, 15 mmol) was then added, and the mixture was heated at 70 °C for 24 h. At this stage, reaction was found incomplete by proton NMR: 1.0 gram of sodium azide (15 mmol) was added, and the mixture was heated at 70 °C until completion (48 additional hours, as indicated by proton NMR). The reaction medium was then cooled, added to 300 mL of water, and extracted twice with 100 mL of a mixture of hexanes and ethyl acetate (1:1; v:v). The combined organic phase was dried over Na_2SO_4. Volatiles were removed in vacuo to yield 9.9 g (99%) of the title compound. ^{1}H NMR ($CDCl_3$): δ = 4.64 (d, J = 2.4 Hz, 18H), 2.44 (m, 2H), 2.32 (m, 2H), 1.66 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 54.2, 22.9, 14.6, 1.2; IR (KBr, cm^{-1}): N_3 stretch = 2097

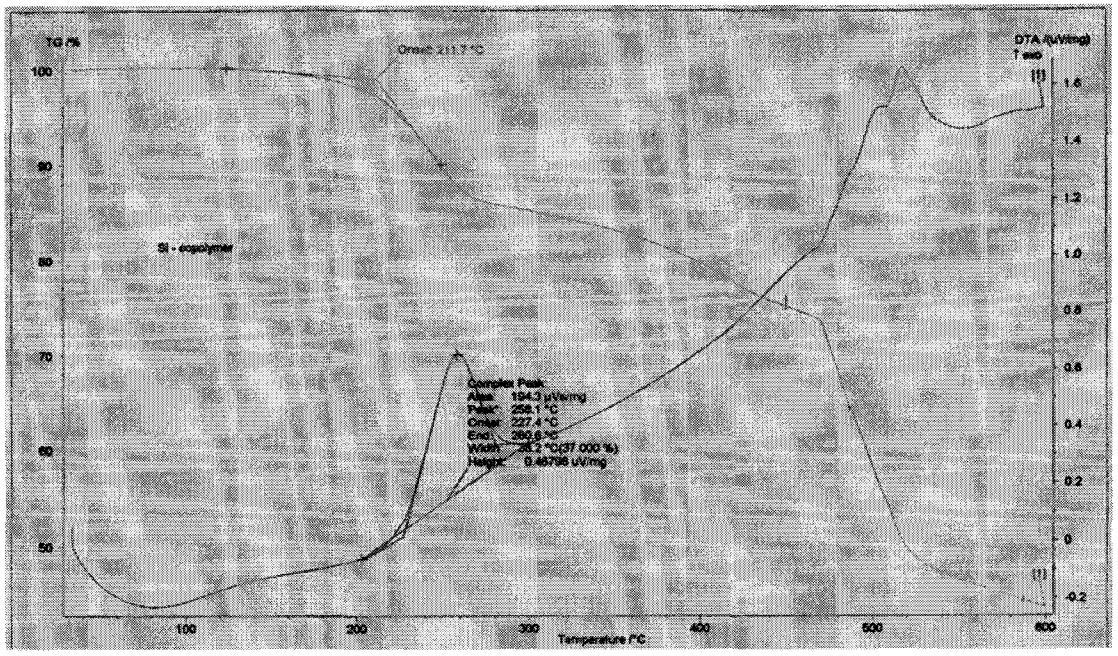
cm^{-1}(s); MS (MALDI-TOF): 6000 (6188-6378), 10000 (10280-10642), 12000 (12318-12872).

3) TGA Analysis of compounds 2-1 and 2-2:

Compound **2-1**:



Compound **2-2**: TGA and DSC



4) Synthesis of alkynyl derivatives

The alkynylgluconamide[13] (Table 1, Entries 7 and 11) and *N*-(*tert*-butoxycarbonyl)-L-alanine-*N*'-propargylamide (Table 1, Entry 9) were prepared as previously described.[14]

The synthesis of *N*-Cbz-L-valine-*N*'-propargylamide (Table 1, Entry 8) was performed using the same procedure as for the propargyl alanine derivative (Table 1, Entry 9) (Yield: 76%).

^{1}H NMR ($CDCl_3$): δ = 8.40 (t, *J* = 5.0 Hz, 1H), 7.35 (s, 5H), 4.95 (s, 2H), 3.85 (m, 2H), 3.10 (s, 1H), 1.91 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ = 171.1, 156.1, 137.1, 128.3, 127.7, 81.0, 72.9, 65.4, 60.1, 30.3, 27.8, 19.1, 18.3; IR (KBr, cm^{-1}) = 3314 (≡C-H stretch), 3275 (NH), 1685 (CONH), 1650 (Ar stretching); HRMS (ESI): m/z $[M+H]^+$ calculated = 289.1552 $[M+H]^+$ found: 289.1552.

5) General procedures for thermal Huisgen cycloadditions

The general procedure is illustrated by the thermal reaction of compound **2-1** with propargyl alcohol (Table 1, entry 1): in a 5 mL round-bottomed flask, 1,3-bis(azidopropyl)-tetramethyldisiloxane (300 mg, 1.00 mmol) and propargyl alcohol (1.0 mL, 17.18 mmol) were stirred at 90 °C under a nitrogen atmosphere. Proton NMR indicated that the reaction was complete within 3 h. The resulting mixture was then subjected to vacuum to remove the excess volatile alkyne to yield 412 mg of the product (quantitative). This product was composed of 3 regioisomers (bis-1,4 click addition; bis-

1,5 click addition; mixed 1,4-and 1,5-click additions). No attempts were made to separate these regioisomers.

^{1}H NMR ($CDCl_3$): δ = 7.57 (s, 1.1H), 7.50 and 7.48 (2 singlets, 0.9H). The first signal at 7.57 ppm is attributed to the regioisomer having the 2 hydroxymethyl in position 4 of the triazolyl ring (55% of the addition), while the 2 other singlets correspond to the bis (5-hydroxymethyl) or mixed (4-and 5-hydroxymethyl) regioisomers (45%). 4.75 (br s, 4H), 4.43 (br s, 2H), 4.28 (m, 4H), 1.92 (m, 4H), 0.47 (m, 4H), 0.03 (br s, 12H); ^{13}C NMR ($CDCl_3$): δ = 147.9, 136.4, 132.7, 122.1, 122.0, 56.2, 53.1, 52.9, 51.1, 24.8, 24.7, 24.4, 15.2, 15.1 -0.3 ; HRMS (ESI): $[M+H]^+$ calculated = 413.2153, $[M+H]^+$ found: 413.2147. NMR spectra of the pure 1,3-bis((4-hydroxymethyl-1,2,3-triazol-1-yl)propyl)tetramethyldisiloxane, prepared using the copper(I)-catalyzed procedure, are reported below.

Table 1, Entry 2: mixture of 3 regioisomers:1,3-bis((4-phenyl-1,2,3-triazol-1-yl)propyl)tetramethyldisiloxane, 1,3-bis((5-phenyl-1,2,3-triazol-1-l)propyl)tetramethyl disiloxane and 1-((4-phenyl-1,2,3-triazol-1-yl)propyl)-3-((5-phenyl-1,2,3-triazol-1-yl)propyl)-tetra-methyl disiloxane.

^{1}H NMR ($CDCl_3$): δ = 8.09 to 7.25 (m, 12H), 4.30 (m, 4H), 2.05 to 1.65 (m, 4H), 0.60 to 0.30 (m, 4H), 0.05 - 0.02 (m, 12); ^{13}C NMR ($CDCl_3$): δ = 147.7, 137.8, 133.1, 130.8, 129.5, 129.2, 128.9, 128.8, 128.3, 128.1, 127.4, 125.7, 119.8, 119.7, 53.2, 51.1, 24.8, 24.4, 15.2, 15.1, 0.3, 0.2; HRMS (ESI): m/z $[M+H]^+$ calculated = 505.2567, $[M+H]^+$ found: 505.2559.

6) General procedures for copper(I)-catalyzed click cycloadditions

The general procedure is illustrated by the thermal reaction between compound **2-1** with propargyl alcohol (Table 1, entry 3): 1,3-bis(azidopropyl)tetramethyldisiloxane (300 mg, 1.0 mmol) and propargyl alcohol (168 mg, 3.0 mmol, 1.5 equiv. for each azide) were solubilized in 2 mL of THF. Sodium ascorbate (49 mg, 0.25 mmol, in 1.00 mL of water) was added, followed by copper(II) sulfate pentahydrate (13 mg, 0.05 mmoles, in 1.00 mL of water). The mixture was stirred vigorously for two days, at which stage ^{1}H NMR indicated the complete consumption of the starting materials. The reaction mixture was fractionated between water and dichloromethane. The aqueous phase was extracted three times with dichloromethane. The combined organic phase was dried over sodium sulfate, filtered, evaporated then passed through a short pad of neutral alumina to afford 94% of the click adduct.

1,3-Bis((4-hydroxymethyl-1,2,3-triazol-1-yl)propyl)tetramethyldisiloxane

^{1}H NMR ($CDCl_3$): δ = 7.56 (s, 2H), 4.78 (d, J = 6 Hz, 2H), 4.28 (t, J = 7.2 Hz, 4H), 3.88 (s, 2H), 1.87 (m, 4H), 0.48 (m, 4H), 0.05 (s, 12); ^{13}C NMR ($CDCl_3$): δ = 148.2, 122.4, 56.2, 53.3, 24.9, 15.2, 0.7; MS (ESI): m/z $[M+H]^+$ calculated = 413.2153, $[M+H]^+$ found: 413.2155.

Table 1, Entry 4: 1,3-Bis((4-(1,1-dimethyl)hydroxymethyl-1,2,3-triazol-1-yl)propyl)tetra-methyldisiloxane: ^{1}H NMR ($CDCl_3$): δ = 7.50 (s, 2H), 4.26 (t, J = 7.4 Hz, 4H), 3.49 (s, 2H), 1.89 (m, 4H), 1.64 (s, 12), 0.509 (m, 4H), 0.04 (s, 12); ^{13}C NMR

($CDCl_3$): δ = 155.8, 119.4, 68.5, 53.0, 30.5, 24.7, 15.2, 0.3 ; MS (ESI): m/z $[M+H]^+$ calculated = 469.2779, $[M+H]^+$ found: 469.2770.

Table 1, Entry 5: 1,3-Bis((4-phenyl-1,2,3-triazol-1-yl)propyl)tetramethyldisiloxane: ^1H NMR ($CDCl_3$): δ = 7.82 (m, 6H), 7.37 (m, 6H), 4.36 (t, *J* = 7.2 Hz, 4H), 1.94 (m, 4H), 0.52 (m, 4H), 0.06 (s, 12) ; ^{13}C NMR ($CDCl_3$): δ = 147.6, 130.8, 128.9, 128.1, 125.7, 119.8, 53.1, 24.8, 15.2, 0.3; MS (ESI): m/z $[M+H]^+$ calculated = 505.2567, $[M+H]^+$ found: 505.2559.

Table 1, Entry 6: 1,3-Bis((4,5 dimethylcarboxy-1,2,3-triazol-1-yl)propyl)tetramethyl disiloxane: ^1H NMR ($CDCl_3$): δ = 4.56 (t, *J* = 7.2 Hz, 4H), 3.99 (s, 6H), 3.97 (s, 6H), 1.90 (m, 4H), 0.48 (m, 4H), 0.03 (s, 12); ^{13}C NMR ($CDCl_3$): δ = 160.6, 159.1, 139.9, 129.9, 53.5, 53.2, 24.6, 15.0, 0.2; MS (ESI): m/z $[M+H]^+$ calculated = 585.2161, $[M]^+$ found: 585.2158.

Table 1, Entry 7: 1,3-Bis((4-*N*-methylenegluconamide-1,2,3-triazol-1-yl)propyl)tetramethyl disiloxane: ^1H NMR ($CDCl_3$): δ = 8.10 (t, J = 5.6 Hz, 2H), 7.86 (s, 2H), 5.46 (d, *J* = 4 Hz, 2H), 4.23 (t, *J* = 7.2 Hz, 4H), 3.34 to 4.57 (m, 20H), 1.77 (m, 4H), 0.43 (m, 4H), 0.025 (s, 12); ^{13}C NMR ($CDCl_3$): δ = 173.1, 145.4, 123.2, 74.1, 72.7, 71. 9, 70.6, 63.7, 52.4, 34.6, 24.6, 14.9, 0.7 ; MS (ESI): m/z $[M+H]^+$ calculated = 767.3427, $[M+H]^+$ found: 767.3421.

Table 1, Entry 8: 1,3-Bis((4-N-methylene-Cbz-valineamide-1,2,3-triazol-1-yl)propyl)tetra methyldisiloxane: ^1H NMR ($CDCl_3$): δ = 8.43 (t, *J* = 5.6 Hz, 2H), 7.85

(s, 2H), 7.27 (m, 12H), 5.09 (s, 4H), 4.30 (t, J = 7.2 Hz), 4.23 to 4.40 (m, 4H), 3.82 (t, J = 7.4 Hz, 2H), 1.87 (m, 2H), 1.74 (m, 4H), 0.78 (d, J = 6.6 Hz, 12H), 0.39 (m, 4H), 0.004 (s, 12); ^{13}C NMR ($CDCl_3$): δ = 171.7, 156.7, 145.1, 137.6, 128.8, 128.1, 123.3, 65.9, 60.7, 52.4, 34.7, 30.8, 24.7, 19.7, 18.8, 14.9, 0.7; MS (ESI): m/z $[M+]^+$ calculated = 877.4616, $[M]^+$ found: 877.4630.

Table 1, Entry 9: 1,3-Bis((4-N-methylene-Boc-alanineamide-1,2,3-triazol-1-yl)propyl)tetra methyldisiloxane: ^1H NMR ($CDCl_3$): δ = 8.27 (t, J = 5.0, 2H), 7.83 (s, 2H), 6.95 (d, J = 7.0, 2H), 4.27 (t, J = 7.2 Hz, 4H), 4.23 to 4.30 (*m*, 4H), 3.93 (m, 2H), 1.72 (m, 4H), 1.36 (s, 24H), 1.12 (d, J = 7.6, 6H), 0.41 (m, 4H), 0.017 (s, 12H); ^{13}C NMR ($CDCl_3$): δ = 172.9, 169.7, 145.0, 122.6, 78.0, 52.0, 49.8, 34.4, 28.0, 24.2, 18.1, 14.5, 0.2; MS (ESI): m/z $[M+H]^+$ calculated = 753.4263, $[M+H]^+$ found: 753.4241.

7) Polymeric derivatives: synthesis and characterizations

Thermal reaction between polyazide silicone and phenylacetylene (Table 1, entry 10)

In a 5 mL round-bottomed flask, poly(azidopropyl)-co-poly(dimethyl)siloxane **2-2** (0.706 g; 1.2 mmol of repeating unit) and phenylacetylene (1.0 g; 9.8 mmol) were stirred at 90 °C under a nitrogen atmosphere for 24 h. Volatiles were then removed in vacuo to yield 0.860 g (quantitative yield) of poly(phenyl-triazolyl) derivatives as a viscous yellow-orange oil.

^{1}H NMR ($CDCl_3$): δ = 7.93 to 7.25 (m, 6 H), 4.35 (m, 2H), 1.90 (m, 2H), 2.05 to 1.80 (m, 2H), 0.65 to 0.35 (m, 2H), 0.08 (br s, 36H**); ^{13}C NMR ($CDCl_3$): δ = 147.6, 137.6, 132.9, 132.6, 130.8, 130.0, 129.4, 128.8, 128.7, 128.2, 128.0, 127.6, 127.3, 127.2, 126.9, 126.0, 125.6, 125.3, 119.5, 52.8, 50.9, 24.4, 24.1, 15.0, 14.2, 13.8, 1.8, 1.0, 0.3, -0.6, -0.7.

Copper-catalyzed reaction between polyazide silicone and ethynyl-gluconamide (Table 1, Entry 11)

In a 5mL round-bottomed flask, poly(azidopropyl)-co-poly(dimethyl)siloxane (0.723 g, 1.2 mmol of repeating unit) was dissolved in 1mL of THF. Ethynylgluconamide (500 mg, 2.1 mmol) dissolved in water (3mL) was added. Sodium ascorbate (49 mg, 0.25 mmol) was then added, followed by copper(II) sulfate pentahydrate (13 mg, 0.05 mmol). The mixture was stirred vigorously for 2 d. It was then slowly added to water (100 mL), which resulted in precipitation of a fluffy solid. The solid was filtered, dissolved again in a minimum amount of water/THF (1:1, vol:vol), and precipitated again in 100mL of water. The solid was filtrated, and dried in vacuo to yield 0.848 g (84%) of the click-adduct.

^{1}H NMR ($CDCl_3$): δ = 8.10 (s, 1H), 7.86 (s, 1H), 5.43 (s, 1H), 4.23 (t, J = 7.2 Hz, 2H) 3.48 to 4.58 (m, 10H), 1.79 (m, 2H), 0.43 (m, 2H), 0.055 to -0.025 (m, 42§); ^{13}C NMR ($CDCl_3$): δ = 172.7, 145.3 , 123.0, 73.8, 72.4, 71..6, 70.2, 63.4, 51.8, 34.2, 23.9, 13.7, 0.7

** The ratio of the protons were calculated based on the average mole% chloropropylsiloxane vs Me_2SiO monomers in the starting material. NMR of the starting material demonstrated there was ~1 chloropropylmethylsiloxane group for each 6 dimethylsiloxane units in the polymer chain, although the chloropropylsiloxane units are randomly distributed throughout the silicone.

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Chapter 3

Polysiloxanes Elastomers and Composites via Click Technology[††]

Gilbert Yu, Ferdinand Gonzaga, Michael A. Brook*

Department of Chemistry, McMaster University, 1280 Main St. W., Hamilton Ontario, L8S 4M1

Abstract

Functional silicone elastomers were efficiently prepared using a poly(dimethylsiloxane)-co-(azidopropyl methyl disiloxane) as the base polymer with an di-ethynyl terminated disiloxane as crosslinker. A study on the relative azide/alkyne ratios of this system revealed a stoichiometric range between 3:1 and 1:3 was necessary to give effective elastomers. TGA analysis of the rubber samples showed good stability, showing only minimal decomposition below 230 °C. Furthermore, the wide range of relative ratios between the azide and the crosslinker with which efficient reactions occur opens up new synthetic strategies for simple silicone elastomers and, additionally, provides the possibility of both crosslinking and functional derivatization in a single step.

[††] To be submitted as an article in *Macromolecules*. Derivatization of the polyazide and the dipropargyl adipate and characterization were done by Gilbert Yu. Ethynyl terminated siloxane and the propargyl terminated PEO were derivatized by Ferdinand Gonzaga. Gilbert Yu and Ferdinand Gonzaga both did the thermal crosslinking experiments.

Introduction

Silicones or polysiloxanes are polymers with wide-ranging applications.[1] This is largely due to their many interesting properties, which frequently cannot be met by other organic polymers. These include: hydrophobicity, surface activity, thermal and electrical stability, and biocompatibility among others.[2] One particularly important form of silicones in commerce are elastomers – crosslinked silicone rubbers – which carry with them the desirable qualities of their starting silicone polymers. The high thermal stability of silicones, for example, allows them to be used as cake and baking molds and together with their excellent optical transparency, have found use as LED covers.[3] Their electrical stability permits them to be used as sealants that protect a variety of sensitive components in electronic devices, and high tension devices such as spark plug wires.[4]

The crosslinking of silicones is performed principally via two approaches: by the condensation of functional silanes with silicones to give Si-O bonds between the silicone chains, or through the use of organic side groups such as end-functionalized vinyl or propylene moieties. Commercially, the three most common routes used to create silicone elastomers are platinum catalyzed addition cure, tin or titanium catalyzed room temperature vulcanization (RTV, moisture cure), or radical cure, which is frequently performed at higher temperatures. Although these 3 methods are very well established, they do suffer from some disadvantages, which include the use of expensive metals such as platinum, the formation of elastomers that contain metal residues which can leach from the elastomer, and/or difficulties in processing the elastomer during and after cure.[5] There is, therefore, a need for a general, simple, efficient, catalyst-free system to prepare both

functional and/or crosslinked silicones. In addition, it would be beneficial to be able to functionalize or crosslink silicones neat, in organic solvents, or in water-based solvent systems as these various media allow the incorporation of a wide variety of organic constituents into hydrophobic silicone polymers.

The use of cycloaddition reactions, such as the Diels-Alder reaction, to manipulate polymers, including silicones, has previously been demonstrated. This process, for example, has been used to functionalize polymeric materials, including the modification of small silicones with amino acids.[6] More recently, there has been utilization of the Huisgen 1,3-dipolar cycloaddition of azides to alkynes to functionalize organic molecules and polymers.[7] The reaction, a "click" reaction, is a robust and reliable method for the functionalization of a wide variety of molecules because its sole product, the triazole ring, acts as a stable linker between the two precursors.[8] This reaction can proceed thermally or through a copper (I) catalyzed process.

We describe the preparation of elastomeric polysiloxanes via "click" chemistry. The synthesis of alkyne- and azide-functionalized polysiloxanes,[9] is first examined, followed by a description of thermal crosslinking. As shall be demonstrated, it is facile using this approach to prepare "pure" elastomeric polysiloxanes, or to extend the method to the synthesis of various functionalized composite materials, including polyalkyl-, aryl-, or ethylene oxide-modified silicone polymers.

Results and Discussion

To make an essentially "pure" silicone elastomer via "click" chemistry, it is first necessary to synthesize azide- or alkyne-functionalized silicones; the crosslinker must

have the complementary functionality. Azides, including organic azides, may be explosive materials. Empirical studies have demonstrated that for an organic azide to be considered "safe to handle" the C and O atoms vs. N atom ratio should be greater than three.[10] Pentaerythrityl tetraazide, for example, is extremely shock-sensitive and can explode simply upon contact with a metal spatula.[11] It is possible when making silicone elastomers to have the azido constituent as part either of the crosslinker or the base silicone polymer. Clearly, small tri- or tetra- azido-functionalized small molecule crosslinkers are likely to pose a potential risk for shock sensitivity and, because of safety concerns, we decided to derivatize longer silicone chains with azido units and use alkynyl-terminated crosslinkers.

Previously, we have demonstrated the ability to prepare azidofunctional silicones by the nucleophilic substitution reaction azide with 1,3–chloropropyldisiloxanes.[9] Therefore, the same reaction was attempted on a polymeric derivative. Using a mixed solvent, THF/DMF, it was possible to modify a commercially available poly(dimethylsiloxane-co-chloropropylmethylsiloxane) (MW: 7500-10000; 14-16% mol chloropropyl units) with sodium azide to give the corresponding poly(dimethyl)-co(methyl-azidopropyl) disiloxane (**3-1**) in high yield (Scheme ; see Experimental Section for detailed experimental procedures). As the stability of this material (**3-1**) needed to be established, the TGA was examined, and showed slow thermal decomposition starting at 210 °C, a temperature much below the intended temperature for the thermal Huisgen cycloaddition procedure.

Initially, two commercially available, small, alkyne-terminated molecules were utilized as cross-linkers to test the viability of this method: tripropargylamine and dipropargyl adipate. One to two drops of the crosslinker were placed in small glass vials together with the 200 mg of the azidopropyl substituted polymer and the mixture was heated at 90 °C. After 10 minutes, clear, transparent materials were produced. The "rubbers" made, however, were quite brittle. Because these preliminary results suggested the crosslink density was too high, longer alkynylated molecules were subsequently used as crosslinkers to lead to more flexible elastomers. To test this hypothesis, both alkynyl-derivatized siloxanes and PEO molecules were made.

Alkyne-terminated PEO

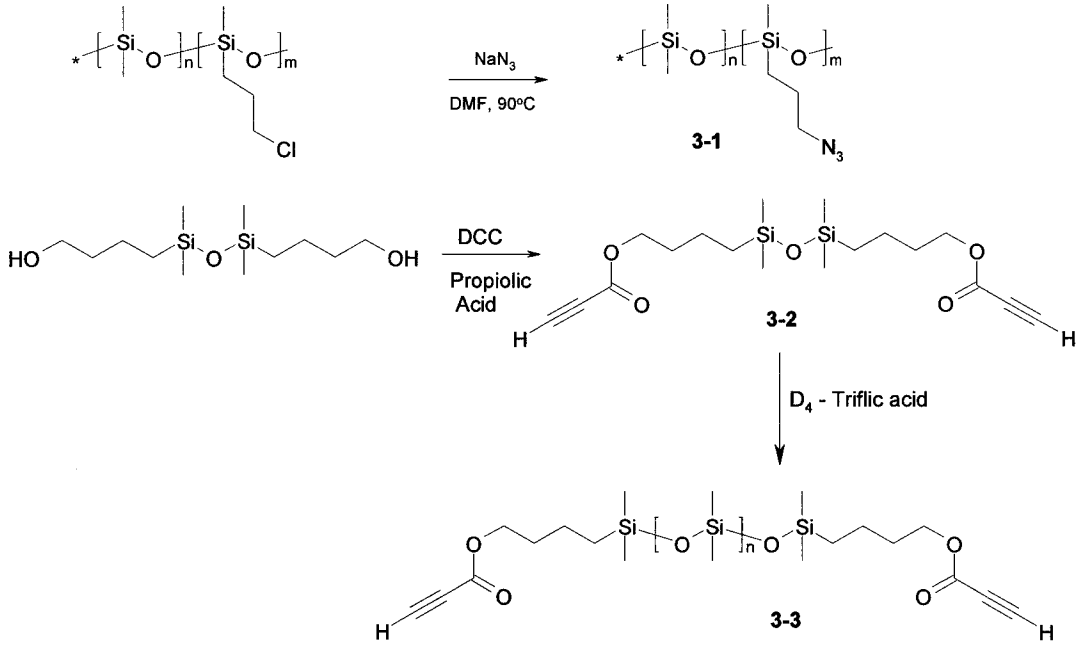
Dialkynyl-terminated PEO units were utilized to crosslink the base polyazide **3-1**. The PEO moieties were not miscible with the azido-derived polymer. To remedy this dioxane was used to homogenize the mixture. The resulting solution was then placed in the oven at 90 °C and was observed for 1 day. Contrary to expectations based on the previous use of alkyne-terminated cross-linkers, this system did not produce elastomers. NMR spectra of the sample showed the starting materials to be intact; almost no hydrogen peaks attributable to the triazole was observed in the resulting mixture. Rather than focus on the origins of the difficulty with this experiment, we examined alternative alkyne-terminated crosslinkers.

Alkyne-terminated Silicone

In the desire to produce "pure" silicone elastomers, both alkyne and azido-terminated silicones were synthesized. Alkynyl-silicones were prepared by the double

esterification of bis(hydroxybutyl)-tetramethyl disiloxane with propiolic acid to obtain the ethynyl-terminated disiloxane **3-2** (Scheme 8). An acid equilibration/redistribution reaction of **3-2** with octamethylcyclotetrasiloxane (D_4) yielded the ethynyl-terminated polysiloxane **3-3** in a 60% yield. Compound **3-3** readily formed elastomers upon heating with the azido-derived polymer **3-1**. Because the equilibration process of silicone used in the formation of **3-3** can be contaminated with water, leading to SiOH end groups, it was difficult to ensure that all chains of **3-3** had the desired ethynyl ends.

Scheme 8 Synthesis of azidopropyl- and alkynyl-modified siloxanes 3-1, 3-2 and 3-3



The crosslinking efficiency of the thermal cycloaddition., as a function of azide/alkyne ratios, was established using compound **3-2**, which had a much lower molecular weight distribution than compound **3-3**. A uniform amount (200 mg) of the polyazide-siloxane polymer **3-1** was placed in 12 different scintillation vials to react with

the alkyne crosslinker. To ensure homogeneity of the system, dioxane (1 mL) was added to the reaction mixture, various amounts of **3-2** were added to the 12 vials, and the entire solution was placed in the oven at 90 °C. The alkyne/azide ratios of each sample as well as their respective products are outlined in Table 2.

Table 2: Outcomes of thermal click crosslinking reactions after 3.5 hours.

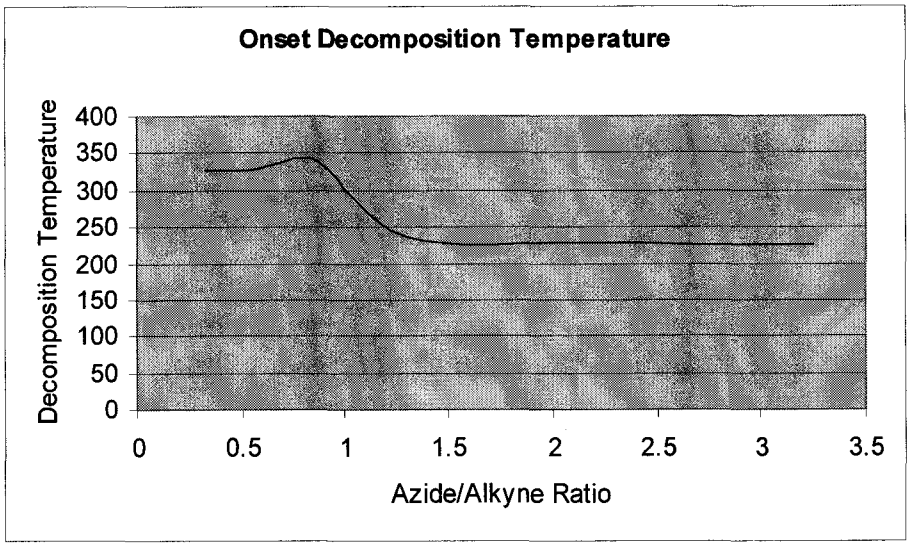
Sample Number	Amount of crosslinker **3-2** (in mg)	Estimated Molar ratio (azide/alkyne)	Type of product
1	5	13.0	Viscous oil
2	10	6.50	Viscous oil
3	20	3.25	Monolithic elastomer
4	30	2.17	Monolithic elastomer
5	50	1.30	Monolithic elastomer
6	75	0.87	Monolithic elastomer
7	100	0.65	Monolithic elastomer
8	125	0.52	Monolithic elastomer
9	150	0.43	Monolithic elastomer
10	200	0.32	Monolithic elastomer
11	400	0.16	Viscous gel
12	800	0.08	Viscous oil

A solid elastomeric material was obtained for most systems after 10 minutes of reaction. The results of this study indicate that azide/alkyne ratios of 3: 1 to 1: 3 are effective in producing monolith silicone elastomers. Although no specific hardness test was performed on the elastomers, the resulting materials displayed increasing rigidity with increasing ethynyl-terminated siloxane concentrations. This is likely due to the increase in crosslink density brought about by the increasing concentration of **3-2** within the material. The samples were then placed into the oven at 90 °C and monitored for 3.5 hours more to ensure that the observations taken to ensure that no further crosslinking

occurred. All the materials were then placed in the oven at 90 °C to dry overnight. In order to demonstrate that the samples were effectively crosslinked, they were soaked and swelled for 24 hours using THF: no apparent dissolution after subsequent drying occurred, indicating that rubbers were obtained through covalent chain-crosslinking.

The thermal stability of the materials remained a source of great concern, especially with the elastomers containing residual azides after crosslinking. Therefore, all the silicone monoliths were subjected to TGA analysis. Results of this study showed that the materials were very stable; i.e. no degradative (much less explosive) behaviour was observed for any of the samples until the temperature was in excess of 230 °C, at which point weight loss began. Furthermore, the rubber sample with 1: 1 azide/alkyne ratio was shown to have the most stable temperature with the onset of decomposition at 337°C (Scheme 9).

Scheme 9. Decomposition Temperature of Silicone Rubbers with Variable Azide/Alkyne Ratios



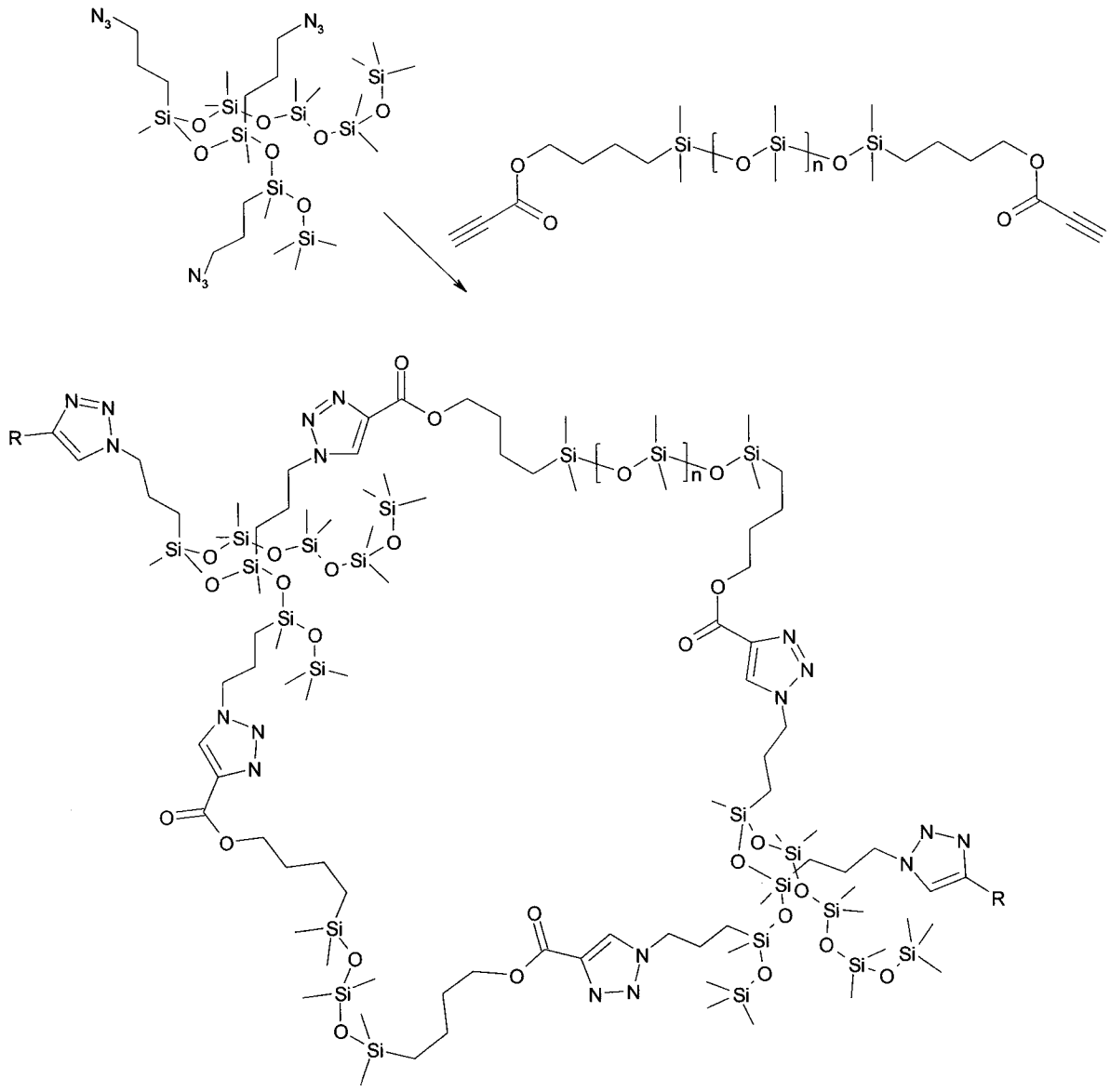
To test whether residual azide and alkyne groups were present in the elastomers two samples, elastomers from entries 3 and 10 (see Table 2) were immersed and swelled in hexane for 2 hours to remove any ungrafted material from the surface of the elastomer. The samples were then oven dried for 30 minutes and ATR was undertaken for both materials. ATR analysis showed the presence of the azide functional groups (N_3, ν = 2095 cm^{-1}) for sample entry 3 and alkynyl moeties (C≡C, ν = 2116 cm^{-1}) for sample entry10. This shows that further modification with these elastomeric systems is possible.

Residual functional groups present, both azides and alkynes, have potential utility for additional chemistry. Further "click" reactions may be performed on exposed silicone surfaces, including with amino acids, sugars, and other biologically relevant molecules such as biotin. Alternatively, lightly crosslinked materials can be formed out of these materials where gels of one silicone in excess of azide groups can be combined with another where alkyne groups are in abundance to formed an instant crosslinked silicone seal upon Cu(I) catalyst and/or heating.

Conclusion

Azide-alkyne thermal crosslinking presents an attractive alternative to conventional methods that require expensive metal catalysts and can be quite moisture-sensitive. The elastomers from a base azido-derivatized polysiloxane and an di-ethynyl terminated siloxane system lead to predominantly silicone materials that were stable at temperatures higher than 200 °C. Furthermore, the wide-range of alkyne-azide ratio offers the possibility for further functionalization as ATR analysis revealed the presence

of such groups on the surfaces. In addition, any excess azide or alkyne units in the elastomers are biologically inert and therefore makes it suitable for use in biomedical applications.



Scheme 10: Network formation *via* thermal click reactions between **3-1** and **3-2** or **3-3**.

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Supporting Information

Polysiloxanes Elastomers and Composites via Click Technology.

Gilbert Yu, Ferdinand Gonzaga*, Michael A. Brook*

Department of Chemistry, McMaster University, 1280 Main St. W., Hamilton Ontario, L8S 4M1

* (E-mails: gonzaga@mcmaster.ca; mabrook@mcmaster.ca)

OUTLINE OF SUPPORTING INFORMATION

Experimental Section

Materials and Methods

(Chloropropyl)methylsiloxane-dimethylsiloxane copolymer (14-16 mole% (chloropropyl)methylsiloxane), octamethylcyclotetrasiloxane (D_4), and bis(hydroxybutyl)-tetramethyldisiloxane were obtained from Gelest. Sodium azide (95%) was purchased from J.T. Baker. Propargyl alcohol (99%), propargyl bromide (80% weight solution in toluene), propiolic acid (95%), DCC, DMAP, and adipoyl chloride (97%) were obtained from Sigma-Aldrich. Triethylamine (99%) was purchased from EMD. Sodium ascorbate (98%) was obtained from Fluka, while copper(II) sulfate pentahydrate (99%) was purchased from Fisher Scientific. All materials were used as received.

IR analyses were made using a Bio-Rad Infrared Spectrometer (FTS-40). ^{1}H NMR and ^{13}C NMR was recorded at room temperature on a Bruker AC-200 spectrometer using $CDCl_3$ or DMSO as solvent. High-resolution mass spectrometry was performed using a Hi-Res Waters/Micromass Quattro Global Ultima (Q-TOF mass spectrometer). TGA analysis was performed using NETZCH STA 409 PC/PG.

Synthesis of Azido-terminated Polysiloxanes

(Chloropropyl)methylsiloxane-dimethylsiloxane copolymer (14-16 mole% (chloropropyl)methylsiloxane)(10.0 g) was dissolved in 40 ml of a mixture of DMF and THF (1:1; v:v). Then, sodium azide (1.0 gram, 15 mmol) was added, and the mixture was heated at 70 °C for 24 h. At this stage, reaction was found to be incomplete by

proton NMR. Therefore, additional sodium azide (1.0 g, 15 mmol) was added, and the mixture was again heated at 70 °C until completion (48 additional hours, as indicated by proton NMR). The reaction medium was then cooled, added to 300 mL of water, and extracted twice with 100 mL of a mixture of hexanes and ethyl acetate (1:1; v:v). The combined organic phase was dried over Na_2SO_4. Volatiles were removed in vacuo to yield 9.9 grams (99%) of the title compound.

^{1}H NMR ($CDCl_3$): δ = 4.64 (d, J = 2.4 Hz, 18H), 2.44 (m, 2H), 2.32 (m, 2H), 1.66 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 54.2, 22.9, 14.6, 1.2; IR (KBr, cm^{-1}): N_3 stretch = 2097 cm^{-1}(s); MS (MALDI-TOF): 6000 (6188-6378), 10000 (10280-10642), 12000 (12318-12872).

Synthesis of Dipropargyl Adipate

In a round-bottomed flask under nitrogen, adipoyl chloride (3.6 g, 20 mmol, 1 equiv.) was dissolved in THF (20 mL). The solution was cooled in an ice bath, and pyridine (4 mL) was added. Then, propargyl alcohol (2.2 g, 40 mmol, 2.2 equiv.) was slowly added to the mixture, with vigorous stirring. The reaction was slowly allowed to return to room temperature, and was stirred overnight. The resulting material was partitioned between dichloromethane and 2M aqueous HCl. The organic phase was dried over sodium sulfate, evaporated, and subjected to chromatography over silica gel (elution with hexane:ethyl acetate, 9:1, v:v) to yield the title compound as a clear oil (4.62 g; 96%).

^{1}H NMR ($CDCl_3$): δ = 8.40 (t, J = 5.0 Hz, 1H), 7.35 (s, 5H), 4.95 (s, 2H), 3.85 (m, 2H), 3.10 (s, 1H), 1.91 (m, 1H), 0.82 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ = 172.3, 77.7, 74.9, 51.8, 33.5, 24.1; IR (KBr, cm^{-1}): 2129 (C≡C), 1739 (C=O), MS (ESI): m/z $[M+Na]^+$ calculated = 245.0790, $[M+Na]^+$ found: 245.0787.

Synthesis of Ethynyl-terminated Silicone

To a cooled (-77 °C; dry ice in acetone) solution of bis(hydroxybutyl)tetramethyl-disiloxane (2.79 g, 10mmol) and propiolic acid (1.75g, 25 mmol) in dichloromethane (25mL) was added a combined solution of DCC (4.13 g, 20 mmol) and DMAP (0.024 g, 0.2 mmol) over a period of 1 h. The reaction was stirred at -77 °C for an additional 8 hrs. Then, dry ether was added (100 mL), and the solution was filtered. Following evaporation of the solvents, the crude product was purified by silica gel chromatography (from 95/5 to 75/25 hexanes/ethyl acetate as eluent) to yield 3.09g (81%) of the dipropionic ester product.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.03 (s, 12H); 0.51 (t, 4H, J = 8.4Hz); 1.37 (m, 4H); 1.69 (m, 4H); 2.88 (s, 2H); 4.18 (t, 4H, J = 6.6Hz).

MS (ES-positive mode): m/z $[M+H^+]$ calculated = 382.61, $[M+H^+]$ found : 382.00

Equilibration Reaction of Ethynyl-terminated Silicone

To a 50mL 1-neck round bottomed flask fitted with a drying tube was added the dipropionic disiloxane product just described (0.50g, 1.31 mmole) and octamethylcyclotetrsiloxane (D_4, 3.00 g, 100 mmoles). The mixture was agitated with a magnetic stirrer, and then triflic acid (0.20 μL) was added. The mixture was stirred for 3

d at room temperature. Then, magnesium oxide (0.40 g) followed by dry hexanes (40 mL) were added. The slurry was stirred for one h, then filtered through a short pad of Celite. Volatiles were removed in vacuo to yield 3.10g of crude product. This crude product was purified by Kugelrohr distillation (1 h at 120 °C, 2 h at 150 °C) to yield 2.28 g of a clear transparent viscous oil. Proton NMR indicates that the polysiloxane chain was now constituted of 21 dimethyl siloxane units (relative integration *vs* 2H (alkynyl proton), 4H (CH_2 ester)), which correspond to a molecular weight of 1788 (Yield: 65%).

Chapter 4

Silicone-Biotin Click Chemistry[‡‡]

Abstract

Biotin is broadly used to link, through streptavidin, molecules of biological interest. Few examples of biotin-modified silicone compounds exist. A simple, high yielding, approach is described that allows the direct conjugation of propargyl-functionalized biotin to alkynyl-functionalized silicones (Huisgen 1,3-dipolar cycloadditions). Both thermal and the copper(I) catalyzed methods efficiently coupled diazido-terminated siloxane, 1,3-bisazidopropyltetramethyldisiloxane and alkynyl-derived biotin. Although the thermal reaction was extremely slow, the copper(I) catalyzed process was surprisingly efficient given the differences in solubility of the two reagents: the reaction was finished in one day and had an isolated yield of 94%.

Introduction

Silicones are well known for their biocompatibility, and are used in a variety of prosthetic devices, including breast implants, contact lenses and intraocular lenses.[1] Some of the attractions of these polymers are resistance to degradation by biological processes, and very low toxicity and immunogenicity.[2] The low degree of biological activity can be beneficial especially when dealing with tissues and cells, such as when used in bioassays/bioanalytical devices[3] and injectable materials.[4] Other properties possessed by

[‡‡] To be submitted as a communication to *Macromolecules*, coauthors M. A. Brook and G. Yu. All derivatization and characterization were performed by Gilbert Yu.

silicones, such as cost and structural versatility, make them attractive candidates for use in the screening and analysis of certain biomolecules such as proteins, for example in microfluidic devices. In particular, polydimethylsiloxanes (PDMS) have been actively researched and tested as substrates for such devices because conventional materials like silicon or glass are expensive to fabricate into devices using expensive and time-consuming fabrication procedures,[5] whereas silicones are flexible and can be readily molded into complex structures including active films and microfluidic devices.[6]

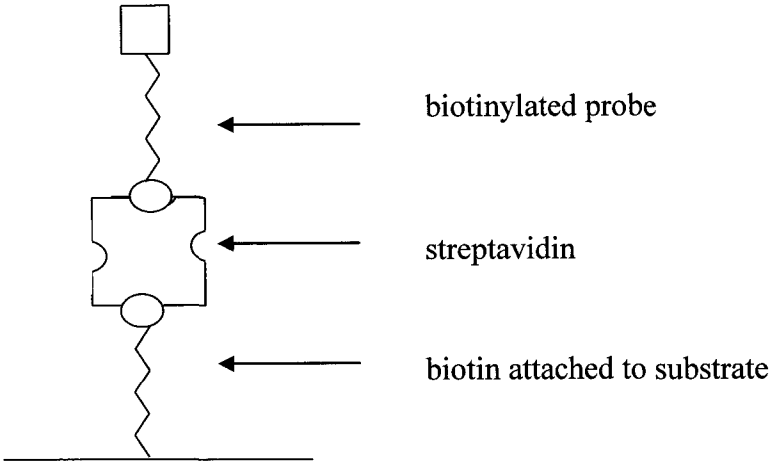
In biological applications, there is one important challenge presented by silicones. They are extremely hydrophobic and thus prone to protein adsorption. In some circumstances, adsorption is followed by protein denaturation which can be detrimental to their biocompatibility, and can impact on their utility in bioassays.[7] Several methods have been devised to resolve this problem,[8] including tethering hydrophilic moeties such as PEO on silicones surfaces to reduce non-specific protein adsorption.[9] Alternatively, silicone surfaces can be modified with biological molecules including proteins.[10]

A key molecule to modify biomaterials' surfaces is biotin,[11] which is one of the most widely used tagging agents because of its high affinity for streptavidin and avidin:[12] the binding strength between biotin and streptavidin is enormous ($Ka = 10^{15}\ M^{-1}$).[13] This complex is unaffected by extreme pH, temperature, organic solvents, and other denaturing agents, making it a popular choice for almost all biological applications concerning protein-protein interactions.[14]

Streptavidin, a tetramer, has four sites unto which biotin or biotin-tagged substance (biotinylated materials) can bind. Thus, binding two or more biotin-modified

substances through avidin is the basis of a strategy broadly employed in biochemistry.[15] For example, the biotin-streptavidin complex is widely employed in a variety of bioanalytical and diagnostic applications: affinity chromatography, immunoassays, bioassays, biosensors, receptor purification, etc.[16] In addition to this, it is also used for in vivo cell-imaging and has been utilized in cancer cell diagnosis and therapy research.[17] For instance, an antibody such as the human Nectin-4 specific IgG can be tethered via biotin/avidin complex to identify the presence of soluble Nectin-4, a cancer disease marker produced in the supernatant of infected cells: such processes lead to the identification of breast carcinoma[18], as long as the biotinylated probe maintains or surpasses the activity of its parent structure (Scheme 11)[19]

Scheme 11: "Molecular sandwiching" utilizing a biotinylated molecule attached to a biotin-strepavidin complex.



The unique behaviour of biotin has not been extensively exploited in conjunction with silicones. In some instances, the two have been brought together using the non-covalent, non-direct attachment of biotin to a silicone substrate. In microfluidics, for

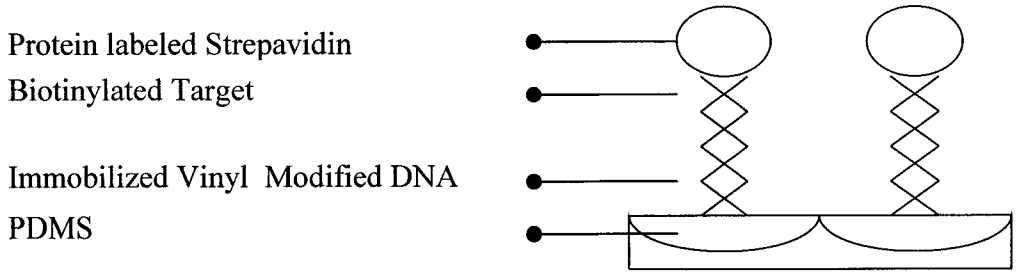
example, the biotin-streptavidin complex is applied separately as a coating in order to effect changes to the biospecificity of the substrate.[20] In another method developed by Huang *et. al.*, a biotinylated phospholipid bilayer was added to the PDMS prepolymer before curing leading to the biotin molecule being interspersed on the PDMS surface. Although both methods lead to surfaces that exhibit significant reduction of non-specific protein adsorption, concerns were raised with regards to the stability of the biotin moeties in these environments over time. For long term stability of materials destined for bioanalysis, it will be necessary to covalently link biotin onto PDMS surfaces.

Marquette *et al.* were able to exploit vinyl-termini of biotin-terminated oligonucleotides and employed hydrosilylation to immobilize biotin molecules onto PDMS (Scheme 12). Vinyl-terminated oligonucleotides were added to the PDMS pre-polymer using hydrosilylation prior to curing that involved a two step process, oxidative addition of the silane with the vinyl function (both the DNA and silicones) followed by reductive amination to regenerate the Pt catalyst.[21] Complememtary biotinylated targets were then allowed to interact with the DNA moeties attached to the PDMS cured surface from which subsequent biotin-stepavidin interactions can be further carried out, e.g., chemiluminescent labeling.

Although fluorescence spectroscopy did show specificity with regards to areas where the vinyl-terminated DNA were immobilized, there was no concrete evidence of covalent linking between the modified DNA strands and the PDMS surface. Furthermore, there seems to be a debate as to whether the integration of modified DNA into the PDMS surface is a result of entrapment of these molecules in/on the elastomer, through a

chemical ligation process or both[22]; unmodified DNA molecules were also found to be immobilized onto PDMS surfaces in a control experiment.

Scheme 12: Linkage of oligonucleotides to silicones using biotin/avidin bridges



The group of Meier *et al* has demonstrated it is possible to conjugate biotin to PDMS. They were able to a use hydrophilic polymers, poly(2-methyloxazoline) initially bound to PDMS as a spacer between silicone and biotin,[23] to form nanocontainers intended for drug delivery. However, this procedure utilizes a biotin conjugation step through the use of a coupling agent, DCC, which can be moisture-sensitive. Although they were able to show the presence of biotin with their materials by fluorescence spectroscopy, the viability of the biotin conjugation step is quite unclear – no yields were given.

Recently, our group was able to successfully link several functional groups, including hydrophilic moieties groups such as sugars, onto silicones through the use of "click" chemistry[24]. Specifically, azide terminated-siloxanes were reacted with alkynyl-terminated functional group moeties to form stable triazoles both thermally and with the use of a copper(I) catalyst. Although biotin is not new to "click" chemistry,[25] the Huisgen 1,3-dipolar cycloaddition reaction between biotin and silicones has not yet been reported.

We hypothesized that the marked difference in the hydrophilicities of biotin and PDMS can be overcome during a ligation process, resulting in an easy, efficient, successful direct conjugation of biotin to silicones.

Results and Discussion

Prior to the "click" ligation experiments of biotin onto silicones, several trials of covalent linkage between the two moeties were explored using PEO as spacer.[26] To increase the hydrophilicity of the silicones and hence, make them more compatible with biotin, a Pt hydrosilylation reaction was carried out linking hydride terminated silicones (average mol. weight: 1200 g/mole) with vinyl-terminated PEO (mol. weight: 550 g/mole). Attempts to conjugate the resulting material with biotin using coupling agents such as carbonyldiimidazole (CDI) failed: free biotin was obtained from the samples after running the reaction. Apparently, the PEO chains on the silicones were not sufficiently hydrophilic to permit contact between the biotin and the OH group of the silicone-PEO copolymer. Because of the poor results of these trials, this procedure was abandoned and an alternate methodology had to be developed.

Huisgen cycloaddition reactions between biotin and silicones require both species to be first functionalized with azido- or alkynyl- ends, respectively. It was arbitrarily decided to place the azides on the terminal positions of silicone polymers, as has been previously described in the thesis, and to modify the biotin with alkynyl functional groups. There may be a potential advantage to this assignation of alkynyl groups to biotin: it has been reported that better cycloaddition yields arise when alkynyl-containing

molecules are smaller than their azide-terminated counterparts[27] and thus it may be possible to modify silicone elastomer surfaces using this methodology.

To demonstrate the viability of the "click" reaction of biotin onto silicones, a diazido-terminated disiloxane was used as a model compound. Commercially available, 1,3-bischloropropyltetramethyldisiloxane (BCPTMDS) was transformed to the target molecule via a simple nucleophilic substitution of the chloro groups with azido moeties (see Experimental Section for details) to give 1,3-bisazidopropyltetramethyldisiloxane (BAPTMDS) in high yield. As for the derivatization of biotin, propargylamine was reacted and coupled to the said compound with the aid of dicyclohexyldicarbodimmide (DCC). Although several coupling agents were examined, it was found that DCC was the easiest to work with because the by-product of the reaction, dicyclohexylurea, precipitates out of the reaction mixture readily. The pure biotin propargylamide was obtained after passing it through a silica column twice with a 90/10 CH_2Cl_2: MeOH eluent in 71% yield.

Initially, the thermal process linking BAPTMS with biotin propargylamide was carried out at 60 °C to prevent decomposition of the biotin moeties. No triazole was evident after 24 hours of reaction (^{1}H NMR). The reaction temperature was then increased to 75 °C and the reaction was monitored for four days. NMR spectra of the crude reaction mixture revealed that less than 10% of the starting materials were converted to the product over this time. Because of the slow rate of the thermal cycloaddition process, this method was discontinued and the copper(I) catalyzed reaction was then examined.

The procedure of the copper(I)-catalyzed silicone-biotin "click" was patterned after the silicone-amino acids "click" reactions from our previous report.[28] Compared to the alkynyl amino acids used which were less polar, biotin propargylamide required less solvent to be fully dissolved; a total of 2 mL DMF/H_2O (1:1) solution was enough to make the system (0.1-M) completely miscible. At first, a combination of heating and the copper(II) sulfate/sodium ascorbate catalyst system was designed to drive the reaction to completion since the thermal process was extremely slow. To our surprise, the room temperature "click" reaction of BAPTMDS with biotin propargylamide was efficient and went to completion within one day of reaction. In addition, work-up of this particular "click" adduct was easier because it was significantly less soluble (e.g., in water, CH_2Cl_2) than other triazoles we had previously prepared.. This facilitated its easy isolation: the product was initially washed with hexane/ethyl acetate 1:1 mixture to remove the excess BAPTMDS and was subsequently filtered with water to remove the copper(II) sulfate/sodium ascorbate catalyst. This led to an isolated yield of 94% comparable with the other silicone "clicks" we had synthesized. With this and related biotin-modified silicones in hand, it should be possible to explore conjugation of various silicones with other biological entities through a streptavidin bridge. This will form the basis of future communications.

Conclusion

The Cu(I) catalyzed "click" reaction presents itself as an attractive method for the direct functionalization of biotin onto silicones. Reactions of propargylamides of biotin with alkynylsilanes are: easy to perform, occur in high yields, and compared to the

thermal process, are faster. This opens a lot of possibilities for expanding the uses of silicones in biomedical applications.

Material and Methods

1,3-Bis(chloropropyl)tetramethyldisiloxane was obtained from both ABCR and Gelest. Sodium azide (95%) was purchased from J.T. Baker. Sodium iodide (99%), propargyl amine (98%), D-biotin (99%), 1-hydroxybenzotriazole hydrate (97%) and 1,3 – dicyclohexylcarbodiimide (1.0-M solution in dichloromethane) were obtained from Sigma-Aldrich. Sodium ascorbate (98%) was obtained from Fluka while copper(II) sulfate pentahydrate (99%) was purchased from Fisher Scientific. All materials were used as received.

IR analysis was made using a Bio-Rad Infrared Spectrometer (FTS-40). ^{1}H NMR and ^{13}C NMR were recorded at room temperature on a Bruker AC-200 spectrometer using deuterated solvents ($CDCl_3$, DMSO-d_6, CD_3OD). High-resolution mass spectrometry was performed using a Hi-Res Waters/Micromass Quattro Global Ultima (Q-TOF mass spectrometer). TGA analysis was performed using NETZCH STA 409 PC/PG.

Synthesis of Bis(azidopropyl)tetramethyldisiloxane (BAPTMDS)

Sodium azide (6.2 g, 96 mmol, 3 equiv.), sodium iodide (9.3 g, 62 mmol, 2 equiv.), and 1,3-bis(chloropropyl)tetramethyldisiloxane (9.0 g, 31 mmol, 1 equiv.) dissolved in DMF (40 mL). The mixture was stirred until all reagents dissolved and then heated at 90 °C overnight. The reaction was stopped after ^{1}H NMR showed the absence

of the 1,3-bis(chloropropyl)tetramethyldisiloxane starting material. The reaction mixture was then partitioned between water and dichloromethane. The organic phase was separated, dried over sodium sulfate, and then evaporated to give 9.7 g (96%) of the title compound as a light yellow liquid.

^{1}H NMR ($CDCl_3$): δ = 3.22 (t, J = 7 Hz, 4H), 1.59 (m, 4H), 0.54 (m, 4H), 0.06 (s, 12 H); ^{13}C NMR ($CDCl_3$): δ = 54.1, 22.9, 15.2, 0.3; IR (KBr, cm^{-1}): 2097 (N_3); HRMS (ESI): m/z calculated: $[M+Ag]^+$ = 407.0601, found: $[M+Ag]^+$ = 407.0620.

Synthesis of Biotin propargylamide

Biotin propargyl amide was prepared as previously described.[29]

Synthesis of "Click" Biotin

BAPTMDS (200 mg, 0.67 mmol) and biotin propargylamide (110 mg, 0.39 mmol, 1.5 equiv. for each azide) were solubilized in 1 mL of DMF. Sodium ascorbate (25 mg, 0.13 mmol, in 0.50 mL of water) was added, followed by copper(II) sulfate pentahydrate (6.5 mg, 0.025 mmoles, in 0.50 mL of water). The mixture was stirred vigorously for one day. At that stage, ^{1}H NMR of the sample indicated the complete consumption of the biotin propargylamide. The reaction mixture was washed with both hexane/ethyl acetate 50:50 to remove excess BAPTMDS and water to remove the catalyst. The material was then dried in the oven overnight to afford 287mg (94%) of the click product.

1,3-Bis((4-hydroxymethyl-1,2,3-triazol-1-yl)propyl)tetramethyldisiloxane

^{1}H NMR ($CDCl_3$): δ = 8.28 (t, J = 5.4 Hz, 2H),7.87 (s, 2H), 6.37 (d, J = 11.6 Hz, 4H), 4.28 (broad s, 10 H), 4.13 (m, 2H), 3.34[§§] (2H), 3.10 (broad s, 2H), 2.88 (m, 2H), 2.09 (t, J = 6.4 Hz, 4H), 1.77 (m, 4H), 1.55-1.29 (m, 12H), 0.39 (m, 4H), 0.20 (s, 12H); ^{13}C NMR ($CDCl_3$): δ = 172.2, 162.9, 145.0, 122.8, 61.1, 59.3, 55.5, 52.0, 40.1, 35.1, 34.2, 28.30, 25.3, 24.3, 14.5, 0.3; HRMS (ESI): m/z $[M+H]^+$ calculated = 863.4024, $[M+H]^+$ found: 863.4005.

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[§§] NMR calculation show that there should be a peak associated with 2 protons at 3.34 ppm. This peak was obscured by the absorbance for water at the same position.

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Chapter 5

Conclusion

This thesis demonstrates that the azide-alkyne Huisgen cycloaddition can be effectively employed in the functionalization and crosslinking of silicones. Chapter 2 used a model siloxane compound, 1,3-bis(azidopropyl) tetramethyldisiloxane (BAPTMDS) to show the easy and effective ligation of several alkyne-terminated moeties using both the copper(I) catalyzed and thermal methods. This was readily extended to azido-terminated polymers as well; poly(azidopropylmethyldisiloxane)-co-poly(dimethylsiloxane) was derivatized with two readily available alkynyl-terminated compounds, propargyl alcohol and phenylacetylene, giving good yields. Chapter 3 presented the possibility of creating silicone elastomers using both azido- and alkynyl-terminated silicones. The resulting rubbers were stable even at high temperatures (200 °C). Furthermore, the flexibility of the formulation in terms of the azide/alkyne ratios of the elastomers allows for further derivatization of the elastomers. Chapter 4 introduced the possibility of linking biotin moeties directly to silicones. BAPTMDS was again used as the model compound and was ligated with propargyl-terminated biotin molecules. Although the thermal reaction performed poorly, the Cu(I) catalyzed version was efficient and the divergent hydrophocities of the reactants were not a deterrent in giving reaction yields as high as 94%.

While this document shows the tremendous potential of the azide-alkyne "click" chemistry – be it thermal or Cu(I) catalyzed – several studies have still yet to be undertaken. For one, the materials created need to be further improved for their intended usage, for example, what is the appropriate number of silicone *vs.* OH units needed in a silicone-sugar "click" to effectively create a superior surfactant system? There are some additional questions posed by the results in the preceding chapters that still need to be investigated: is it possible to further derivatize the azide-containing elastomers with propargyl-terminated biotin molecules to make microfluidic devices? are there any consequences in placing a triazole ring in the molecule which could affect the material's property? will the streptavidin bind to these biotinylated "click" silicones? will the rigid structure of the ring be a problem leading to insolubility of the polymer and hence difficulty of processing or will the same structure be beneficial? can liquid crystals be made out of these materials? The exciting results that have led to these and other questions only verify one thing, that silicone modification using the azide-alkyne cycloaddition is an effective synthetic strategy that will lend itself to a variety of applications.