PHOTOCONJUGATION AND PHOTORELEASE: AN INVESTIGATION INTO THE UTILITY OF NAPHTHOQUINONE METHIDE PHOTOCLICK CHEMISTRY

by

JOSHUA ALLEN VALENCIA

(Under the Direction of Jason Locklin)

ABSTRACT

The fast and effective photogeneration of *o*-naphthoquinone methides (NQM) from a naphthoquinone methide precursor (NQMP) has been well studied for its use in protein labelling and the patterning of surfaces. We have developed a method for using the fast photogeneration of NQM from NQMP derivatives to synthesize an NQMP-photobase derivative. This neutral molecule is capable of releasing a mild organic base under a few minutes of ultraviolet irradiation. Additionally, we have investigated a method of using the fast Diels-Alder reaction of NQM with enamines to conjugate enamines generated *in-situ* from aldehydes or ketones to a surface.

INDEX WORDS: COPPER-FREE CLICK CHEMISTRY, PHOTO-CLICK, NAPHTHOQUINONE METHIDE, PHOTOBASE, DIELS-ALDER, ENAMINE, FUNCTIONAL SURFACES, CLICK CHEMISTRY

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JOSHUA ALLEN VALENCIA

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JOSHUA ALLEN VALENCIA

Major Professor:	Jason Locklin
Committee:	Vladimir V. Popik
	Jin Xie

Electronic Version Approved:

Suzanne Barbour
Dean of the Graduate School
The University of Georgia
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CHAPTER 1

INTRODUCTION

1.1 Click Chemistry

Background

The term “click” chemistry was coined in 1998 by K. Barry Sharpless to refer to chemistry that modular, wide in scope, high-yielding, stereospecific, easily purified, create few or benign byproducts, and use no solvent, or a benign or easily removed solvent.[1]

For many applications, whether in the biomedical or material field, the use of volatile organic solvents, transition metal catalysts, or small molecule byproducts can render an otherwise robust and versatile chemistry commercially useless. To remedy this, recent research has turned to various “click” chemistries to solve some of the more taxing problems in the biomedical and materials field.

While there are many chemistries that have come to be known as “click” chemistries, some of the most studied and useful examples are the various cycloadditions.[2] These most commonly involve an alkyne or strained alkene, and have been utilized for everything from drug discovery to protein tagging to surface modification.[2-5]

Copper(I)-Catalyzed Alkyne-Azide Cycloaddition (CuAAC)

One of the earliest examples of click chemistry is copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC). This reaction takes place between a terminal alkyne and an azide to form a 1,2,3-triazole species (Figure 1.1).

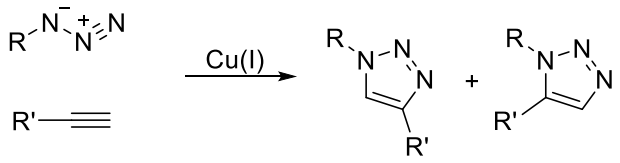

Figure 1.01. General Reaction Scheme of CuAAC

These reactions have been carried out with many variations. Studies have been done involving using a solid support resin for a copper acetylide to react with a terminal azide to yield a mixture 1,4- and 1,5-disubstituted [1,2,3]-triazoles in good yield under mild conditions.[6] It was also found that this cycloaddition could take place in the presence of a copper (II) species and a reducing agent such as sodium ascorbate.[7] Under relatively mild conditions, the reaction between an alkyne and an azide would take place to give predominantly the 1,4-disubstituted [1,2,3]-triazoles in very good yield.[7] One of the biggest drawbacks to this method is its reliance on high catalyst loading and its limited use outside of terminal alkynes. To address this, studies have recently been done to address these issues and have found that 1-iodoalkynes are readily accessible internal alkynes that show an improved reactivity over terminal alkynes, leading to a lowered reliance on copper catalyst loading.[8]

Strain-Promoted Alkyne-Azide Cycloaddition (SPAAC)

Another method of reducing the reliance on copper catalysts involves the use of a strained 8-membered cyclic alkyne. Also known as "copper-free click" chemistry, SPAAC uses the ring strain to increase the reactivity of an internal alkyne to achieve cycloaddition without the use of a cytotoxic copper catalyst. By using a cyclooctyne, it was found that the alkyne-azide cycloaddition could take place under mild conditions without affecting live cell viability.[9]

Further developments in cyclooctynes has led to the creation of dibenzocyclooctynes (DIBO)[10], difluorinated cyclooctynes (DIFO)[11], aza-dibenzocyclooctynes (ADIBO)[12], and oxa-dibenzocyclooctynes (ODIBO)[13]. Each of these derivatives shows increased reactivity and kinetics over the original cyclooctyne moiety when reacting with azides while retaining the same biocompatibility[10-13].

Strain-Promoted Alkyne-Nitrone Cycloaddition (SPANC)

Another example of strain-promoted click cycloaddition is strain-promoted alkyne-nitrone cycloaddition (SPANC). Similar to SPAAC, SPANC does not involve the use of a copper catalyst to perform the cycloaddition. Instead, SPANC relies on the ring strain of the alkyne and the increased reactivity of a nitrone over an azide to achieve a high rate of reaction without the need for a copper catalyst.[14] Several studies have found that it is fairly straightforward to convert various peptides to nitrones, which allow the use of SPANC to quickly and efficiently label various biological materials.[14] Additionally, cyclic nitrones have an even greater reactivity toward strained alkynes, further increasing the rate.[15-17]

Diels-Alder Cycloaddition

In addition to strained alkyne systems, there are several examples of strained alkene click chemistry. The most well-known is perhaps Diels-Alder cycloaddition. Through the use of a diene and an electron-rich dienophile, a [4+2]-cycloaddition can occur with great speed and without any byproducts or cytotoxic catalysts.

Some of the recent advancements in Diels-Alder cycloaddition include the use of tetrazines as a diene to increase the rate of the reaction.[18-19] These reactions can be used for protein tagging,[18] as well as live cell tagging.[19] One advantage that Diels-Alder cycloaddition has over other forms of click chemistry involves the aqueous environments in which most biological applications take place. For biological applications, the low solubility of many of the strained alkynes can limit their usefulness, while the Diels-Alder reaction with tetrazines not only has increased solubility, but increased rate in aqueous systems.[19]

Photoclick

Photochemistry involves using high-energy light to induce a chemical change in a molecule. The use of light allows a researcher to exert spatial and temporal control over a reaction. By choosing when and where the reaction takes place, there are many applications such as in patterning and targeted reaction where photochemistry is the ideal method. However, photochemistry is not without its drawbacks. The major drawback for photochemistry in biological systems is the limited penetration depth of most wavelengths of light. While this limits the usefulness for *in-vivo* tagging, the control gained over the reaction is a reasonable tradeoff.

There have been several studies that have combined photochemistry with click chemistry. By utilizing a photolabile cyclopropenone protecting group, ODIBO can be used in the patterning of surfaces and multifunctional surfaces.[3, 13, 20] Additionally, very reactive Diels-Alder dienes can be prepared photochemically from stable naphthol derivatives.[21]

1.2 Naphthoquinone Methides

Naphthoquinone methides (NQMs) are highly reactive molecules under Diels-Alder and Michael addition conditions. These molecules can be photochemically generated from naphthol derivatives known as "naphthoquinone methide precursors" (NQMP) as shown in Figure 1.02.[21] Once the NQM is generated, it reacts in a rapid manner with vinyl ethers and enamines in a Diels-Alder fashion, or in Michael addition fashion in the presence of thiols.[21-22]

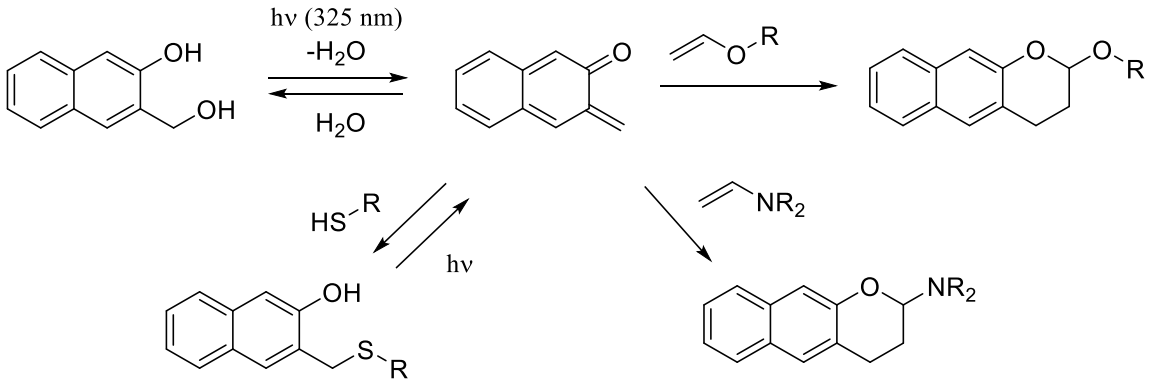

Figure 1.02. Naphthoquinone Methide Photogeneration and Reactions.

While the Diels-Alder reaction between NQM and enamines and vinyl ethers proceeds in a non-reversible fashion, the Michael addition between the reactive alkene of the NQM and a thiol is reversible. This means that the reaction is highly dependent on the

concentration of thiol relative to the water in the system.[22] Additionally, the NQMP can be derivatized to release a "payload" of sorts under UV irradiation. By taking advantage of the reversibility of the reaction and the rapid hydration of NQM back to NQMP, these derivatives can be used to release a functional molecule or create/remove a pattern from a surface with temporal and spatial control.[21, 23] These reactions allow NQMP to be used as a versatile caging group for the release of alcohols, thiols, or other groups[21, 23], or as a versatile group for the patterning of surfaces.[23-25]

1.3 Conclusion

There has been a boom in the past decade of new chemistries that rely on strained alkynes and alkenes to perform conjugations and surface modifications in a manner that is fast, simple, clean, and effective. These "click" chemistries show particular promise in the fields of bioconjugation and materials science. Particularly when these "click" chemistries are combined with photochemistry, we can begin to achieve a level of control and functionality far beyond what has been seen in the past.

Of particular interest is the naphthoquinone methide precursor molecule. Through the rapid generation of the highly reactive naphthoquinone methide moiety under UV irradiation, we can envision using this molecule for the targeted release of various functionalities into a system or the targeted capture of various molecules onto a surface using the rapid Diels-Alder cycloaddition.

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CHAPTER 2

PREPARATION AND CHARACTERIZATION OF AN NQMP-BASED ORGANIC PHOTOBASE

2.1 Introduction

One of the key strengths of the NQMP photochemistry is the level of spatial and temporal control that is afforded. There are many situations where a particular chemical functionality is desired under specific circumstances in a system. One instance where this may be advantageous involves pH. There are many biological systems that are heavily dependent on the pH of the surrounding environment.

The adhesive plaques of mussels relies on 3,4-dihydroxyphenylalanine (DOPA) residues to adhere to iron on ships and rocks.[1] This DOPA residue relies on the local pH of its surroundings to bind or release from the iron. This biological system has been mimicked to create a hydrogel that can undergo a sol-gel transition based on the pH of the system.[1] To achieve a level of spatial and temporal control over this transition, both a photoacid generator and a photobase generator are needed.

While there are numerous studies involving the synthesis and characterization of photoacid generators[2-4], there are relatively few organic photobase generators.[5] To this end, we have designed a molecule that will take advantage of the fast photogeneration of the NQM from NQMP and its derivatives. By derivatizing NQMP with a carbamate functionality tied into the photocleavage site, we hope to be able to synthesize and

characterize a purely organic photobase that can rapidly alter the pH of a system at our direction (Figure 2.01).

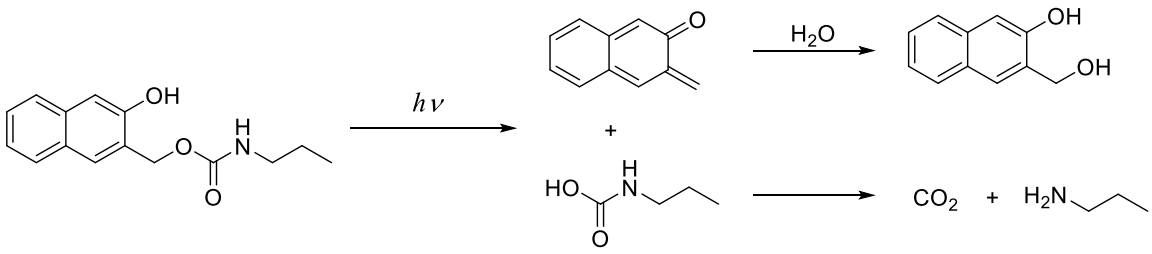
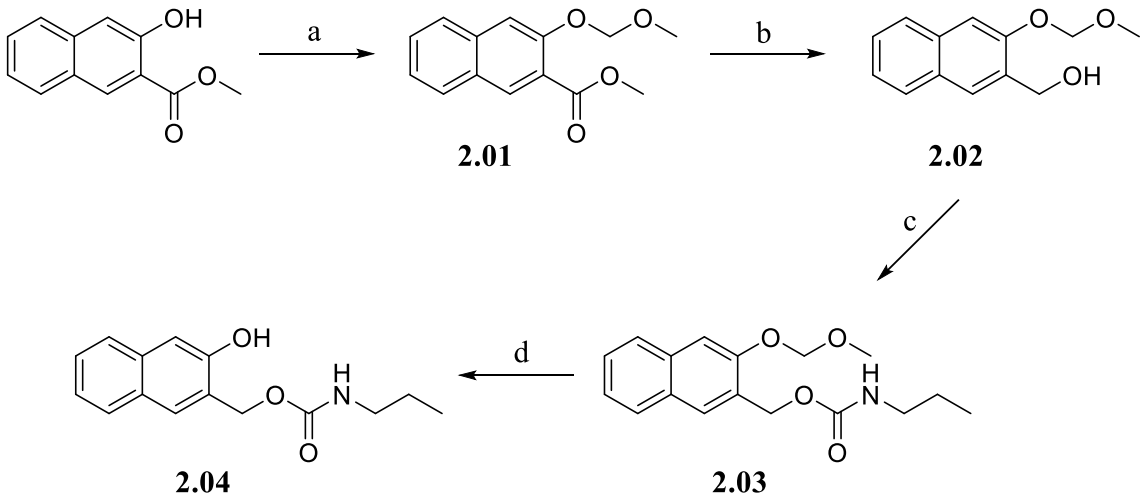


Figure 2.01. NQMP-Photobase Release of Propylamine

2.2 Synthesis of NQMP-Photobase

The target NQMP-photobase **2.04** (Scheme 2.01) was prepared from commercially available methyl 3-hydroxy-2-naphthoate in four steps. The naphthol was reacted in a Williamson ether synthesis with sodium hydride (NaH) and chloromethyl methyl ether in dimethyl formamide to give the protected naphtholic product **2.01**. Next, compound **2.01** was reduced with lithium aluminum hydride (LAH) in tetrahydrofuran to yield **2.02.** Next, compound **2.02** was reacted with propyl isocyanate in dichloromethane to afford compound **2.03.** Finally, compound **2.03** was deprotected with Amberlyst-15 proton exchange resin in 90% methanol in water to give the NQMP-photobase **2.04.** In four steps with a total yield of 53% NQMP-photobase **2.04** can be synthesized in gram-scale quantities.

Scheme 2.01



Reagents and Conditions: a) NaH, chloromethyl methyl ether, DMF, 90%; b) LAH, THF, 94.6%; c) Propyl isocyanate, DMAP, triethylamine, CH_2Cl_2, 78%; d) Amberlyst 15, methanol/water 9:1, 80%.

2.3 Properties of NQMP-Photobase

NQMP-photobase **2.04** is an off-white crystalline compound that is shelf stable for long periods of time if stored away from light. It is stable in water, methanol, and solutions of the two. Prior to irradiation, the molecule is neutral in a 75% methanol/water mixture.

2.4 Characteristics of NQMP-Photobase Release

The efficiency and speed of the NQMP-photobase release was measured by pH probe. NQMP-photobase **2.04** in a tenfold excess was dissolved in a 0.125 mM solution of hydrochloric acid in a 75% methanol/water mixture. The pH of these solutions was monitored before, during, and after irradiation to track the release of propylamine by the neutralization of hydrochloric acid.

While under constant irradiation at 310nm, the pH of the solution was checked every sixty seconds. The solution was initially at pH 4, indicating a fairly acidic solution. During irradiation, the pH of the solution continually rose, reaching a neutral pH within ten minutes, and a pH of 8 within twenty minutes. At this point it is assumed that the released propylamine (pK_b = 3.3) is in a buffered equilibrium with the slightly acidic naphthol on the NQMP (pK_a = 9.01) (Figure 2.02).[6]

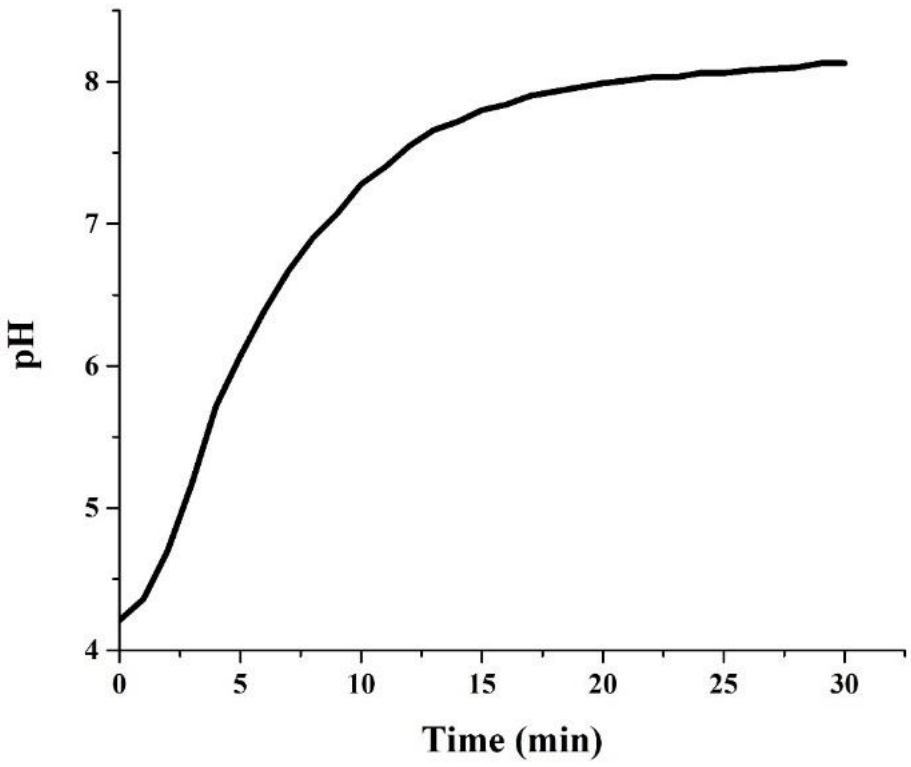


Figure 2.02. Hydrochloric Acid Neutralization by Propylamine Released from NQMP-Photobase under Constant Irradiation.

To determine whether the photorelease of the carbamate from the NQMP or the degradation of the carbamic acid was the rate-limiting factor in the neutralization of acid, a solution of 1.25 mM NQMP-photobase **2.04** was dissolved in a 0.125 mM solution of hydrochloric acid in 75% methanol/water. The solution was subjected to one-minute pulses of irradiation at 310 nm, then the pH was monitored for five minutes. After the first minute of irradiation, the pH climbed from 4.5 to 5.2. The rate of change of the pH was found to slow over the five minutes of monitoring after the first minute of irradiation. After the second minute of irradiation, the pH climbed at a much faster rate, and reached a pH of 6.6 after five minutes. Unlike the initial irradiation, there was no observable slowing of the rate of pH change. Subsequent irradiation cycles followed a similar smooth curve to a final pH of 8.3 after five irradiation cycles (a total of five minutes of irradiation)(Figure 2.03).

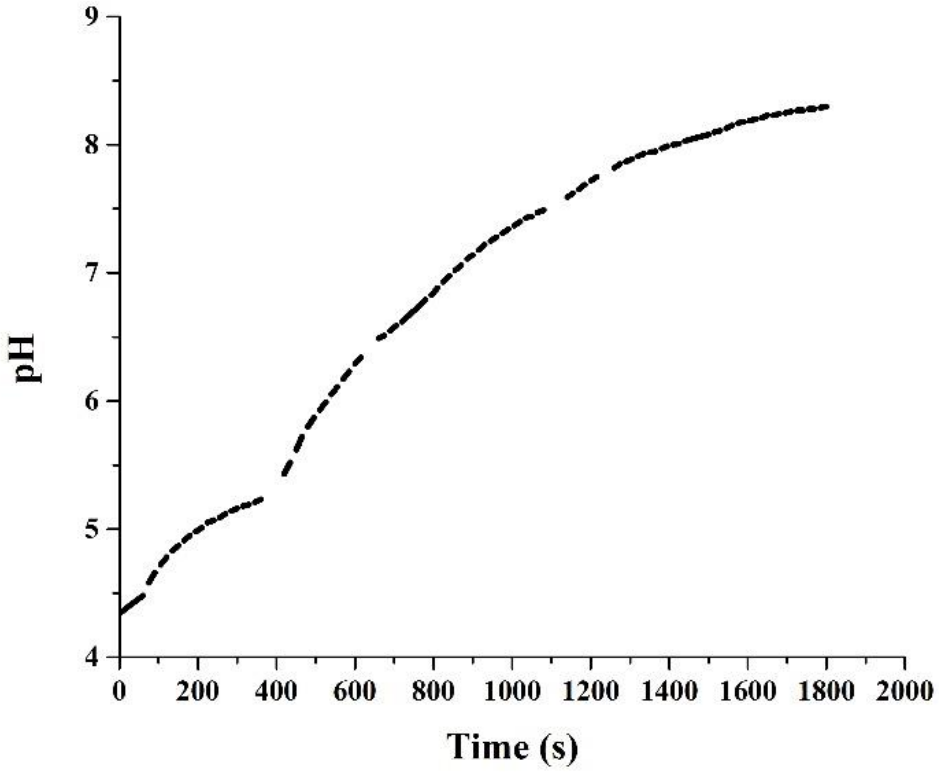


Figure 2.03. Hydrochloric Acid Neutralization by Propylamine Released from NQMP-Photobase under Pulsed Irradiation.

This change in the rate of pH change leads to the conclusion that the degradation of the carbamic acid is a slower process than the photorelease of the carbamic acid. Additionally, the steady rate of pH change after two minutes of irradiation suggests that only two minutes of irradiation is needed to fully convert the NQMP-photobase to NQMP and carbamic acid. The carbamic acid then degrades into CO_2 and propylamine over the course of twenty minutes.

Further investigation into this phenomenon indicates that this is most likely the case. Studies have indicated that the degradation of carbamic acids into linear

alkylamines takes place on the order of 10^2-10^3 $M^{-1}s^{-1}$.[7] The photochemical conversion of NQMP derivatives into NQM occurs on the order of 10^4-10^5 $M^{-1}s^{-1}$.[8] These rates support the conclusion that the initial release of the carbamic acid from the NQMP-photobase takes place rapidly under only a few minutes of irradiation, while the degradation of the released carbamic acid into CO_2 and propylamine is a much slower process that takes several minutes to reach an equilibrium.

2.5 Conclusion

The development of a purely organic photobase using a naphthoquinone methide photocore was achieved. The NQMP-photobase could be prepared quickly and in high yields and quantities. The NQMP-photobase is remarkably stable, remaining pure by NMR after three years of storage on a shelf away from light. The NQMP-photobase reacts very quickly under 310 nm UV light to release a propyl carbamic acid which degrades into CO_2 and propylamine over a short period of time. The future goals of this work will be to prepare NQMP-photobase with a synthetic handle that will allow its integration into materials and surfaces. Additionally, there may be other "payloads" that can be delivered using this system of photocleavage from an NQMP derivative.

2.6 Experimental

Synthetic Methodology. All syntheses were carried out under an inert atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. Unless otherwise noted, all data was worked up using Origin 9.0.0 SR2 software from OriginLab.

NMR spectroscopy. NMR spectra were recorded using a Varian Mercury 400 NMR working at 400 MHz for proton spectra and 100 MHz for carbon spectra. Chemical shifts

are reported relative to an internal tetramethylsilane standard. The data was worked up using MNova 10.0.2 software from Mestrelab Research S. L.

UV-Vis measurements. UV-vis spectra were obtained on a Cary 50 Bio UV-vis spectrophotometer from Varian.

PH measurements. PH measurements were taken on a FiveEasy FE20 pH probe from Mettler Toledo that was calibrated by two-point calibration using 4.00 and 10.00 buffer solutions from VWR.

Synthesis of methyl 3-(methoxymethoxy)-2-naphthoate. In a dry round-bottom flask under positive N_2 pressure containing 15 mL dry DMF at 0 °C was added sodium hydride (NaH) (1.48 g, 37 mmol). To this was added a solution of methyl 3-hydroxy-2-napthoate (5g, 24.73 mmol) in 10 mL dry DMF dropwise. The solution was allowed to stir under N_2 at 0 °C for one hour. While stirring, chloromethyl methyl ether (2.81 mL, 37 mmol) was added dropwise. The solution was allowed to come to room temperature and stir for five hours. The solution was then cooled to 0 °C and quenched with water (30 mL) and the product was extracted with diethyl ether. The organic layer was then washed with water, brine, and dried over $MgSO_4$. The crude mixture was purified by silica column using 20% ethyl acetate in hexanes mixture. ^{1}H NMR analysis indicated a pure product (5.48 g, 22.25 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$)

Synthesis of (3-(methoxymethoxy)naphthalen-2-yl)methanol. In a dry round-bottom flask under positive N_2 pressure containing 50 mL dry THF at 0 °C was added lithium aluminum hydride (LAH) (0.927 g, 24.4 mmol). To this was added a solution of methyl 3-(methoxymethoxy)-2-naphthoate (5.47 g, 22.21 mmol) in 20 mL dry THF. The solution was allowed to come to room temperature and react for three hours while stirring. The

solution was then returned to 0 °C and quenched with ethyl acetate (20 mL). The crude product was filtered through celite with dichloromethane, and the solvent was reduced under vacuum. The crude product was purified through a silica column with a dichloromethane/methanol solution (9:1 to 8:2). The solvent was removed under vacuum to give (3-(methoxymethoxy)naphthalen-2-yl)methanol as a yellow oil (4.583 g, 21.01 mmol, 94.6%). 1H NMR (400 MHz, CDCl3) δ 7.76-7.72 (m, 3H), 7.45-7.42 (t, 1H), 7.40 (s, 1H), 7.38-7.34 (t, 1H), 5.33 (s, 2H), 4.85 (s, 2H), 3.51 (s, 3H).

Synthesis of (3-(methoxymethoxy)naphthalen-2-yl)methyl propylcarbamate. A 15 mL solution of (3-(methoxymethoxy)naphthalen-2-yl)methanol (4.58 g, 21 mmol) in dichloromethane at 0 °C was added 4-dimethylaminopyridine (0.051 g, 0.42 mmol) and triethylamine (9 mL, 63 mmol). The solution was allowed to stir for 30 minutes at 0 °C. To this solution was then added propyl isocyanate (2 mL, 25.2 mmol) dropwise. The solution was allowed to come to room temperature and stir for four hours. The solution was then washed with 1M hydrochloric acid, sodium bicarbonate, water, and brine, passed through celite, and dried under $MgSO_4$ and the solvent was reduced under vacuum. The crude product mixture was purified through silica with a 75% ethyl acetate/hexanes solution. The solvent was reduced under vacuum to give (3-(methoxymethoxy)naphthalen-2-yl)methyl propylcarbamate as a yellow oil (4.985 g, 16.44 mmol, 78 %). 1H NMR (400 MHz, cdcl3) δ 7.79 (s, 1H), 7.75-7.70 (m, 2H), 7.43-7.39 (m, 2H), 7.35-7.32 (t, 2H), 5.31 (s, 4H), 4.97 (s, 1H), 3.50 (s, 3H), 3.20-3.15 (m, 2H), 1.57-1.48 (m, 2H), 0.94-0.90 (t, 3H). 13C NMR (101 MHz, CDCl3) δ 156.57, 153.00, 134.17, 129.00, 128.46, 127.68, 126.94, 126.80, 126.47, 124.26, 108.85, 94.35, 62.35, 56.17, 42.88, 23.27, 11.27.

Synthesis of (3-hydroxynahthalen-2-yl)methyl propylcarbamate. To a round-bottom flask containing (3-(methoxymethoxy)naphthalen-2-yl)methyl propylcarbamate (4.01 g, 13.22 mmol) in 90% methanol/water (50 mL) was added amberlyst-15 exchange resin (12 g). The solution was stirred for 48 hours under reflux. The solution was passed through a paper filter to remove the remaining resin, then extracted with diethyl ether, washed with water, dried under $NaSO_4$, and the solvent was reduced under vacuum. The crude product was purified through silica with an ethyl acetate/hexanes solvent system (60% to 100% EtOAc) and the solvent was removed under vacuum. The remaining orange semisolid was recrystallized in hot dichloromethane to give (3-hydroxynaphthalen-2-yl)methyl propylcarbamate as off-white crystals (2.74 g, 10.58 mmol, 80%). 1H NMR (400 MHz, dmso) δ 10.06 (s, 1H), 7.76-7.73 (m, 2H), 7.69-7.67 (d, 1H), 7.40-7.36 (t, 1H), 7.33-7.30 (t, 1H), 7.28-7.25 (t, 1H), 7.18 (s, 1H), 5.16 (s, 2H), 3.02-2.97 (m, 2H), 1.49-1.40 (m, 2H), 0.87-0.84 (t, 3H). 13C NMR (101 MHz, dmso) δ 156.69, 153.86, 134.46, 128.13, 127.86, 127.00, 126.51, 126.08, 123.36, 108.98, 61.59, 42.56, 23.12, 11.66. ESI HRMS: calcd. ($M+H^+$): $C_{15}H_{18}NO_3$ 260.1281, found 260.1291.

UV photorelease general sample preparation. To a 0.125 mM solution of hydrochloric acid in 75% methanol/water (6 mL) in a quartz cell was added (3-hydroxynaphthalen-2-yl)methyl propylcarbamate (1.9 mg, 0.0075 mmol) to give a 1.25 mM solution of photobase.

UV photorelease of propylamine. The solution was stirred and irradiated with a hand lamp equipped with a 300 nm bulb (~1.00 mW/cm^2) at a distance of one inch above the surface of the solution. The pH of the solution was measured prior to the addition of the photobase, after the addition of the photobase, and every sixty seconds during irradiation.

Pulsed UV photorelease of propylamine. The solution was stirred and irradiated in a UV reactor equipped with eight 300 nm bulbs (~1.00 mW/cm^2). The solution was irradiated for one minute, then removed from the reactor and the pH was monitored for five minutes before repeating this process for a total of five minutes irradiation. The pH data was collected prior to irradiation and every fifteen seconds following each irradiation cycle.

2.7 References

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CHAPTER 3

USING SURFACE-TETHERED NQMP TO CONJUGATE ALDEHYDES AND KETONES

3.1 Introduction

One of the most common goals in materials science and surface chemistry is the fast and versatile conjugation of materials to a surface. NQMP has been shown to be a powerful tool for conjugating thiols and vinyl ethers to a surface in the past.[1-3] However, the fast Diels-Alder reaction with enamines has not been studied in-depth in the past (Figure 3.01).[4] This is partially due to the relative instability of enamines. They are very reactive molecules, and their method of preparation is reversible, so they often can rapidly hydrolize to an inactive state.

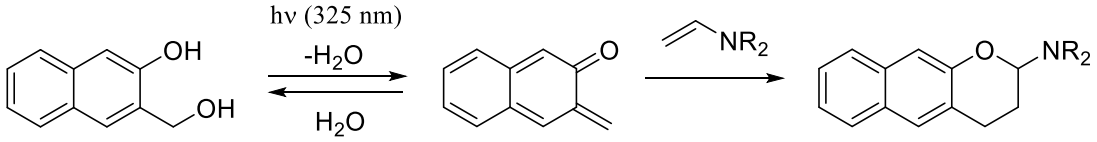


Figure 3.01. NQMP Reaction with Enamines.

The standard method of preparing enamines involves reacting an aldehyde or ketone with an amine (typically a secondary cyclic amine) in the presence of an acid catalyst (Figure 3.02).[5] While this method can give good product yield, the molecule is not necessarily stable, and preparing and storing large amounts of it may be troublesome. However, if we were to perform the preparation of an enamine from an aldehyde or

ketone *in situ* while irradiating an NQMP-functionalized surface, we may be able to "trap" the molecule in its reactive enamine state with our highly reactive NQM. In this manner, we hope to be able to use the high relative concentration of NQM on a surface to rapidly and easily conjugate any aldehyde or ketone to a surface using an *in situ* enamine generation.

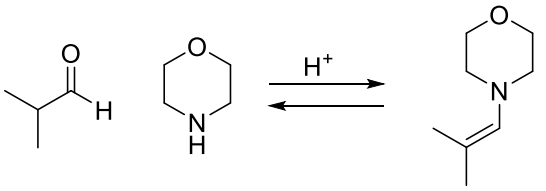


Figure 3.02. Preparation of an Enamine from an Aldehyde.

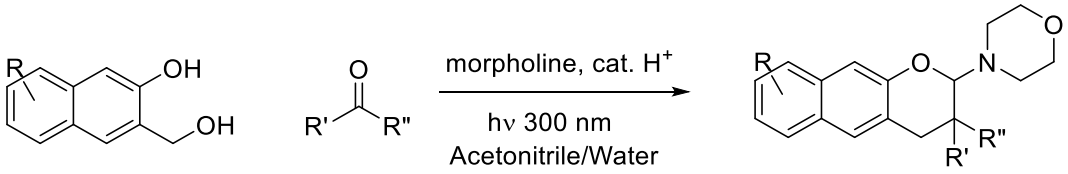
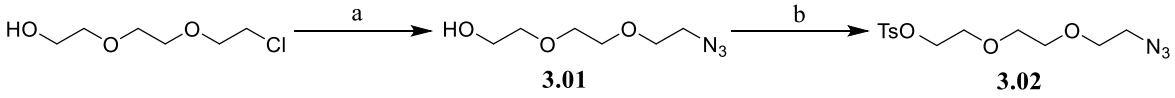


Figure 3.03. *In Situ* Formation and Conjugation of an Enamine onto NQMP.

3.2 Synthesis of Photoactive Surfaces

The target azide-terminated triethylene glycol linker was prepared from commercially available 2-(2-(2-chloroethoxy)ethoxy)ethanol in two steps with a total yield of 56%. The 2-(2-(2-chloroethoxy)ethoxy)ethanol was reacted with sodium azide in dimethylformamide to give the azide-terminated triethylene glycol product **3.01**. Next, compound **3.01** was reacted with *p*-toluenesulfonyl chloride and pyridine in dichloromethane to give the tosylated triethylene glycol azide product **3.02**.

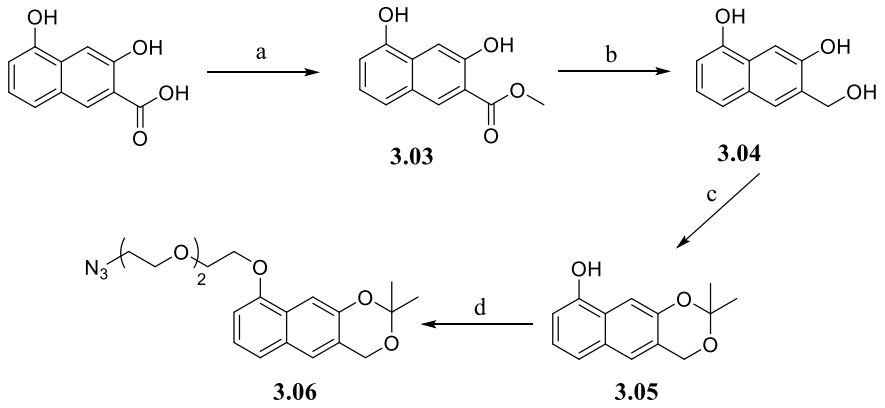
Scheme 3.01



Reagents and Conditions: a) NaN_3, DMF, 68%; b) *p*-toluenesulfonyl chloride, pyridine, CH_2Cl_2, 82%.

The target azide-terminated protected NQMP derivative was prepared from commercially available 5-dihydroxy-2-naphthoic acid in four steps with a total yield of 46%. The naphthoic acid was reacted in a Fischer esterification with sulfuric acid (H_2SO_4) and methanol to give the methyl ester **3.03**. Next, compound **3.03** was reduced by diisobutylaluminum hydride (DIBAL) in tetrahydrofuran to yield the diol **3.04**. Next, compound **3.04** was reacted with 2,2-dimethyoxypropane and *p*-toluenesulfonic acid in acetone to yield the protected diol **3.05**. Finally, compound **3.05** was reacted with **3.02** and potassium carbonate in dimethyl formamide to give the azide-termined protected NQMP derivative **3.06**.

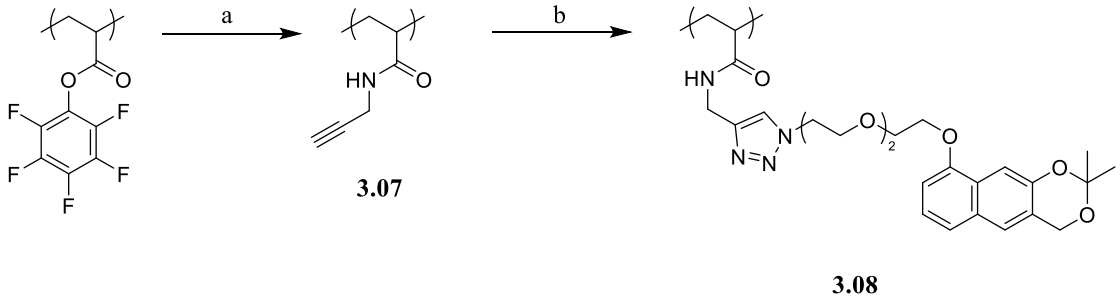
Scheme 3.02



Reagents and Conditions: a) H_2SO_4, methanol, 97%; b) DIBAL, THF, 91%; c) 2,2-dimethoxypropane, p-toluenesulfonic acid, acetone, 95%; d) **3.02**, K_2CO_3, DMF, 55%.

The protected NQMP-derivatized slides were prepared in two steps from previously prepared grafted-from films of poly(pentafluorophenyl acrylate) (pPFPA) on quartz, glass, and silicon slides in two steps. The poly(propargyl acrylamide) slides were prepared by reacting the pPFPA slides with propargyl amine and triethylamine in dimethylformamide to give the slides functionalized with **3.07**. The functionalized slides **3.07** were then reacted with copper (i) bromide, *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA), and **3.06** in dimethylformamide to give slides functionalized with **3.08**.

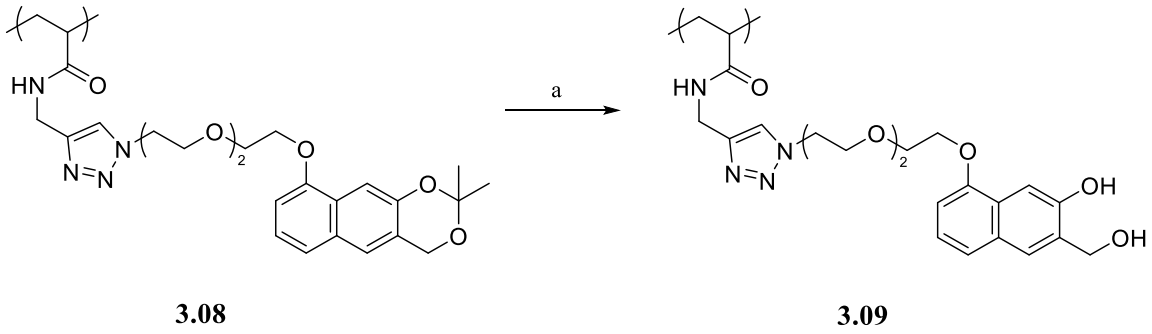
Scheme 3.03



Reagents and Conditions: a) propargyl amine, triethylamine, DMF; b)CuBr, PMDETA, **3.06**, DMF.

The deprotected surface-bound NQMP slides **3.09** were prepared in one step. The surface-bound protected NQMP slides **3.08** were reacted with hydrochloric acid in methanol to give the deprotected surface-bound NQMP slides **3.09**.

Scheme 3.04



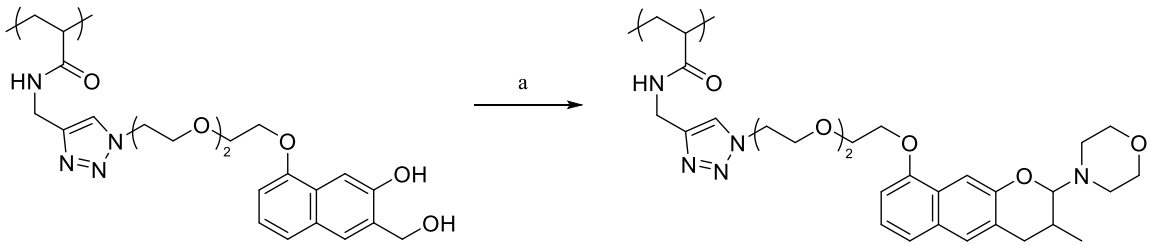
Reagents and Conditions: a) HCl, MeOH.

3.3 Photoconjugation with Aldehydes and Ketones

The conjugation of isobutyraldehyde to the surface-bound NQMP slides was perfomed in one step. The surface-bound NQMP slides **3.09** were reacted with

isobutyraldehyde, morpholine, and *p*-toluenesulfonic acid in a 50:50 solution of acetonitrile and water to give conjugate **3.10**.

Scheme 3.05



3.09 **3.10**

Reagents and Conditions: a) isobutyraldehyde, morpholine, *p*-toluenesulfonic acid, 310nm hν, acetonitrile/water 1:1.

3.4 Characterization of Surfaces

The functionalized surfaces were characterized by spectroscopic ellipsometry, drop-shape analysis (DSA), and FTIR. When looking at the change in film thickness and contact angle (Table 3.01) the initial pPFPA brushes were 44 nm in thickness, and relatively hydrophobic with a contact angle of 91° as measured by DSA. After conversion to **3.07**, the thickness decreased by 17.5 nm to 26.5 nm. This is expected due to the much smaller size of the propargyl group compared to the pentafluorophenyl group. The contact angle also decreased by 22° to 73°, indicating a more hydrophilic surface. After the reaction with **3.06**, the thickness increased by 75.5 nm to 102 nm. This is due to the much larger size of the tethered protected NQMP compared to the relatively small propargyl group. The contact angle slightly increased by 10° to 83°, in accordance with previously published data.[1] After deprotection to yield **3.09**, the thickness decreased

by 19.5 nm to 81.5 nm and the contact angle decreased by 6° to 77°. While these changes are in the proper direction, they are not as significant as previously reported data.[1] This is likely due to the thickness of the brushes. While the previously reported data was collected on slides with a thickness of approximately 65 nm, the films used in this study were 30% thicker at 81 nm.[1] This could lead to a drastic change in the degree of functionalization that is possible under these conditions. After the *in-situ* conjugation with isobutyraldehyde, the thickness of the films increased by 6.5 nm to 88 nm, and the contact angle slightly increased by 2° to 79°. This is expected, as the loss of the alcohol groups on the NQMP molecule should lead to a more hydrophobic surface.

Table 3.01. Thickness and Contact Angle Measurements for Functionalized Slides.

Brush	**Thickness**	**Thickness Change**	**Contact Angle**	**Contact Angle Change**
Poly(PFPA)	43.97 nm		91°	
3.07	26.40 nm	-17.57 nm	73°	-22°
3.08	101.81 nm	+75.41 nm	83°	+10°
3.09	81.32 nm	-19.5 nm	77°	-6°
3.10	87.83 nm	+6.51 nm	79°	+2°

When examining the FTIR of the substrates (Figure 3.04), we can see the initial pPFPA brushes have the characteristic C=C aromatic stretches at 1518 cm^{-1} and C-F stretches at 1000 cm^{-1}. After reaction with propargylamine, the aromatic peaks and C-F peaks are lost, and there is the appearance of a C=O amide I stretch at 1656 cm^{-1}, as well as an sp C-H bend at 3019 cm^{-1} from the newly added propargyl group. After the protected NQMP is conjugated to the surface, we see a loss of the sp C-H bend, as well as a strong peak at 1261 cm^{-1}. While it is not entirely clear, it is possible that this peak

corresponds to the C-O stretch from the acetonide protecting group on the NQMP. The deprotection of the NQMP is also difficult to trace by FTIR. While there is a loss of the C-O stretch at 1261 cm^{-1}, it cannot be definitively stated whether this corresponds to a successful deprotection. After the *in-situ* conjugation with isobutyraldehye, there is virtually no change in the FTIR of the substrates. The primary difficulty with using FTIR for this characterization is the thickness of the films. Since the GATR attachment for the FTIR requires intimate contact with the surface films, very thick films (more than 75 nm) can be very difficult to analyze using FTIR.

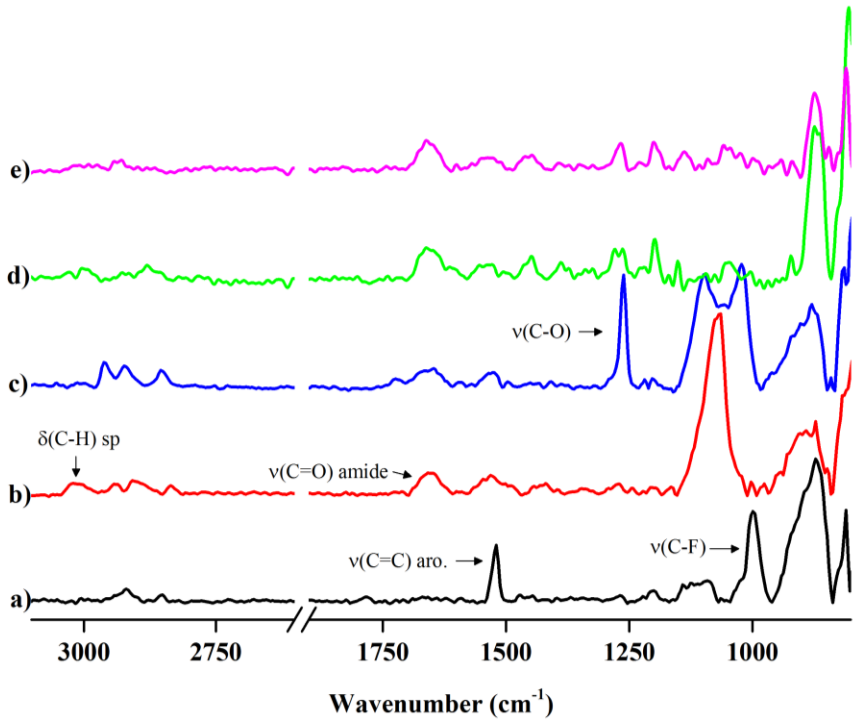


Figure 3.04. FTIR Spectra of Silicon Substrates with a) Poly(PFPA), b) Poly(Propargyl Acrylamide), c) Surface-Tethered Protected NQMP, d) Surface-Tethered NQMP, e) Surface-Tethered NQMP after Isobutyraldehyde Conjugation.

The glass and quartz substrates that were prepared according to the previously mentioned procedure were analyzed by UV-Vis spectroscopy to determine the extent of functionalization with NQMP. Since NQMP has a strong absorbance at 323 nm, it was expected that this could be used to track the attachment of NQMP to the surface as well as the extent of conjugation with isobutyraldehyde. Unfortunately, there was little change in the UV spectrum for either reaction. Again, this is likely due to the thickness of the films. Since the NQMP moiety is only a fraction of the bulk material on the surface of the substrates, it is difficult to tease out any small changes in the spectra.

3.5 Conclusion

The development of a new method of conjugating aldehydes and ketones to surfaces using *in-situ* enamine formation and trapping via Diels-Alder reaction with NQM experienced several setbacks. While the protected NQMP could successfully be attached to the surface, we were unable to determine the success of the deprotection step, as well as the subsequent conjugation with isobutyraldehyde.

There are several methods that can be used to overcome these difficulties. Thinner pPFPA films prepared via grafting-to method may make it easier to see the changes in our substrates by FTIR and UV-Vis. Additionally, other aldehydes or ketones can be used to determine the success of the conjugation to the deprotected NQMP. An aldehyde with a long alkyl chain should impart a significant hydrophobicity and increase in contact angle when it conjugates to the surface. Conversely, a hydrophilic aldehyde or ketone, such as one based on polyethylene glycol, should show a strong decrease in contact angle upon conjugation. While the idea of attaching an aldehyde or ketone dye to the surface

using this chemistry is an enticing proposition, unfortunately most dyes have a strong enough absorbance that they may hinder the photoconversion of NQMP to NQM.

If the conjugation of simple aldehydes and ketones onto the NQMP surface can be performed simply under UV light with mildly acidic conditions, it is not unreasonable to assume that we can use this method to conjugate several aldehydes or ketones to a surface using a photomask. With this method, we may be able to have a single surface that is capable of reacting with a very common functional group, and we can control when and where these common groups are conjugated to the surface.

3.6 Experimental

Synthetic Methodology. All syntheses were carried out under an inert atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. Unless otherwise noted, all data was worked up using Origin 9.0.0 SR2 software from OriginLab.

NMR spectroscopy. ^{1}H NMR spectra were recorded using a Varian Mercury 300 NMR working at 300 MHz. ^{13}C NMR spectra were recorded using a [MODEL] 500 NMR operating at 120 MHz. Chemical shifts are reported relative to an internal tetramethylsilane standard. The data was worked up using MNova 10.0.2 software from Mestrelab Research S. L.

Thickness measurements. The film thickness was measured using a J. A. Woolam M-2000V spectroscopic ellipsometer with a white light source at three angles of incidence (65°, 70°, and 75°) to the slide normal. The film thickness was fit using a Cauchy model.

Contact angle measurements. The contact angle measurements were obtained using a Krüss DSA 100 using a 1 μL drop of deionized water. For each measurement, three drops were recorded and the readings were averaged.

UV-Vis measurements. UV-vis spectra were obtained on a Cary 50 Bio UV-vis spectrophotometer from Varian.

FTIR spectroscopy. Infrared spectra of the surfaces were obtained from a Thermo-Nicolet Model 6700 spectrometer equipped with a variable angle grazing angle attenuated total reflection (GATR-ATR) accessory and processed using the Omnic 8.0 software suite.

Synthesis of 2-(2-(2-azidoethoxy)ethoxy)ethanol. In a round-bottom flask containing 2-(2-(2-chloroethoxy)ethoxy)ethanol (2.27 mL, 15 mmol) in 50 mL dry DMF was sodium azide (1.463 g, 22.5 mmol) slowly added. The reaction was heated slowly to 100 °C and stirred for twelve hours. The reaction was cooled to 25 °C, diluted with 100 mL water and extracted with ethyl acetate. The organic layer was washed with brine, dried with sodium sulfate, and concentrated under vacuum to give 2-(2-(2-azidoethoxy)ethoxy)ethanol (1.79 g, 10.2 mmol, 68%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl3) δ 3.73-3.70 (t, 2H), 3.68-3.65 (m, 6H), 3.61-3.58 (t, 2H), 3.39-3.36 (t, 2H), 2.45 (s, 1H).

Synthesis of 2-(2-(2-azidoethoxy)ethoxy)ethyl 4-methylbenzenesulfonate. To a round bottom flask containing 2-(2-(2-azidoethoxy)ethoxy)ethanol (0.5 g, 2.85 mmol) in 12 mL dichloromethane was added p-toluenesulfonyl chloride (0.653 g, 3.42 mmol) and pyridine (0.460 mL, 5.71 mmol). The reaction was allowed to stir at room temperature for 8 hours. The solution was diluted with 20 mL dichloromethane, washed with water, washed with 10% copper sulfate solution, dried over magnesium sulfate, and concentrated under vacuum. The residue was purified through a silica column with 50% ethyl acetate in hexanes to give 2-(2-(2-azidoethoxy)ethoxy)ethyl 4-

methylbenzenesulfonate as a colorless oil (0.770 g, 2.34 mmol, 82%). ^{1}H NMR (300 MHz, CDCl3) δ 7.80-7.77 (d, 2H), 7.35-7.32 (d, 2H), 4.17-4.14 (t, 2H), 3.71-3.67 (t, 2H) 3.65-3.61 (t, 2H), 3.59 (s, 4H), 3.37-3.34 (t, 2H), 2.44 (s, 3H).

Synthesis of methyl 3,5-dihydroxy-2-naphthoate. In a dry round-bottom flask containing 50 mL methanol was added 5-dihydroxy-2-naphthoic acid (3g, 14.69 mmol). To this was added concentrated sulfuric acid (0.1 mL, 1.876 mmol). The solution was allowed to stir under reflux at 67 °C for sixteen hours. The reaction was quenched in 100 mL ice water and extracted with ethyl acetate. The organic layers were dried with magnesium sulfate and the solvent was removed under vacuum. The remaining dark yellow solid was dried under vacuum for twelve hours to yield methyl 3,4-dihydroxy-2-naphthoate (3.12 g, 14.30 mmol, 97%) ^{1}HNMR (300 MHz, CDCl3) δ 10.43 (s, 1H), 8.47 (s, 1H), 7.63 (s, 1H), 7.43-7.40 (d, 1H), 7.19-7.13 (t, 1H), 6.86-6.84 (d, 1H), 5.22 (s, 1H), 3.98, (s, 3H).

Synthesis of 6-(hydroxymethyl)naphthalene-1,7-diol. In a round-bottom flask containing dry THF at 0 °C was dissolved methyl 3,4-dihydroxy-2-naphthoate (1.09 g, 5 mmol). To this was added dropwise a 1M solution of diisobutyl aluminum hydride (30 mL, 30 mmol) over one hour. The reaction was heated slowly to 45 °C and stirred for sixteen hours. The reaction was quenched with 50 mL ethyl acetate dropwise at 0 °C. To remove the remaining aluminum salts, a 300 mg/mL solution of potassium tartrate (150 mL) was added to the flask and the reaction was stirred at 25 °C for fifteen minutes. The product was extracted with ethyl acetate, washed with water, dried with magnesium sulfate, and concentrated under vacuum. The residue was recrystallized in chloroform to yield 6-(hydroxymethyl)naphthalene-1,7-diol as a white solid (0.862 g, 4.5 mmol, 90.6%)

^{1}HNMR (300 MHz, DMSO-d_6) δ 9.71 (s, 1H), 9.64 (s, 1H), 7.70 (s, 1H), 7.36 (s, 1H), 7.21-7.18 (d, 1H), 7.05-7.00 (t, 1H), 6.72-6.70 (d, 1H), 5.12-5.08 (t, 1H), 4.61 (d, 2H).

Synthesis of 2,2-dimethyl-4H-naphtho[2,3-d][1,3]dioxin-9-ol. In a round-bottom flask containing 6-(hydroxymethyl)naphthalene-1,7-diol (0.25 g, 1.31 mmol) in 50 mL dry acetone was added 2,2-dimethoxypropane (0.0.484 mL, 3.94 mmol). To this solution was added p-toluenesulfonic acid monohydrate (0.011 g, 0.066 mmol) and the reaction was heated to 50 °C and stirred for five hours. The reaction was quenched with water, extracted with dichloromethane, washed with water, dried with sodium sulfate, and concentrated under vacuum to yield 2,2-dimethyl-4H-naphtho[2,3-d][1,3]dioxin-9-ol as a dark oil (0.302 g, 1.24 mmol, 95%) ^{1}HNMR (300 MHz, CDCl3) δ 7.58 (s, 1H), 7.41 (s, 1H), 7.28-7.25 (d, 1H), 7.14-7.09 (t, 1H), 6.76-6.74 (d, 1H), 5.05 (s, 2H), 1.59, (s, 6H).

Synthesis of 9-(2-(3-(2—azidoethoxy)propoxy)ethoxy)-2,2-dimethyl-4H-naphtho[2,3-d][1,3]-dioxine. To a round bottom flask containing 2,2-dimethyl-4H-naphtho[2,3-d][1,3]dioxin-9-ol (0.175 g, 0.76 mmol) and potassium carbonate (0.252 g, 1.824 mmol) in 3 mL DMF was added a solution of 2-(2-(2-azidoethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (0.30 g, 0.91 mmol) in 2 mL DMF. The reaction was heated to 60 °C and stirred overnight. The solution was then cooled to room temperature, diluted with 20 mL diethyl ether, washed with water, dried with magnesium sulfate, and concentrated under vacuum. The residue was purified through an alumina column with 50% ethyl acetate in hexanes to give 9-(2-(3-(2—azidoethoxy)propoxy)ethoxy)-2,2-dimethyl-4H-naphtho[2,3-d][1,3]-dioxine as a yellow oil (0.162 g, 0.418 mmol, 55%). ^{1}H NMR (300 MHz, CDCl3) δ 7.66 (s, 1H), 7.42 (s, 1H), 7.31-7.29 (d, 1H), 7.22-7.17 (t,

1H), 6.74-6.72 (d, 1H), 5.06 (s, 2H), 4.29-4.26 (t, 2H), 4.00-3.96 (t, 2H), 3.82-3.79 (t, 2H), 3.72-3.69 (m, 4H), 3.41-3.37 (t, 2H), 1.60 (s, 6H).

Preparation of alkyne functionalized slides. Quartz, glass, and silicon substrates with a 44 nm film of grafted-from poly(pentafluorophenyl acrylate) were reacted overnight into a solution of 40 mM propargyl amine and 80 mM triethylamine in DMF (2mL). After reaction the thickness of the film decreased to 29 nm, and infrared spectroscopy indicated the disappearance of the PFPA peaks and the appearance of two amide peaks. The contact angle of the slides decreased from 91° to 73°, indicating a slightly more hydrophilic surface.

Preparation of protected-NQMP-functionalized slides. To a dry, air-free Schlenk flask containing alkyne-functionalized slides and 16.7 mg CuBr was added a degassed solution of 13 mM 9-(2-(3-(2—azidoethoxy)propoxy)ethoxy)-2,2-dimethyl-4H-naphtho[2,3-d][1,3]-dioxine and 24.4 μL PMDETA in DMF. The solution was allowed to stir overnight at room temperature. The thickness of the films increased to 102 nm, and infrared spectroscopy indicated the loss of the alkyne peak. The contact angle of the slides increased to 83°, indicating a slightly more hydrophobic surface.

Deprotection of NQMP-functionalized slides. To a Schlenk flask containing 0.1 M hydrochloric acid in methanol was placed the protected NQMP-functionalized slides. The flask was allowed to stir for twelve hours. The thickness of the films decreased to 82 nm. There was no significant change on the infrared spectrum. The contact angle of the slides decreased to 77°, indicating a slightly more hydrophilic surface.

Photoconjugation of isobutyraldehyde onto NQMP-functionalized slides. To a solution of 40 mM isobutyraldehyde, 40 mM morpholine, and 40 mM p-toluenesulfonic

acid in 50% acetonitrile in water was placed a glass slide functionalized with NQMP. The solution was stirred and irradiated under 300 nm light for 20 minutes. The thickness of the films increased slightly to 88 nm. There was no significant change on the infrared spectrum. UV-Vis indicated no significant difference in the slide. Contact angle measurements also indicated no significant difference in the hydrophilicity of the surfaces.

3.7 References

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APPENDIX A

^{1}H AND ^{13}C NMR SPECTRA OF ESSENTIAL COMPOUNDS

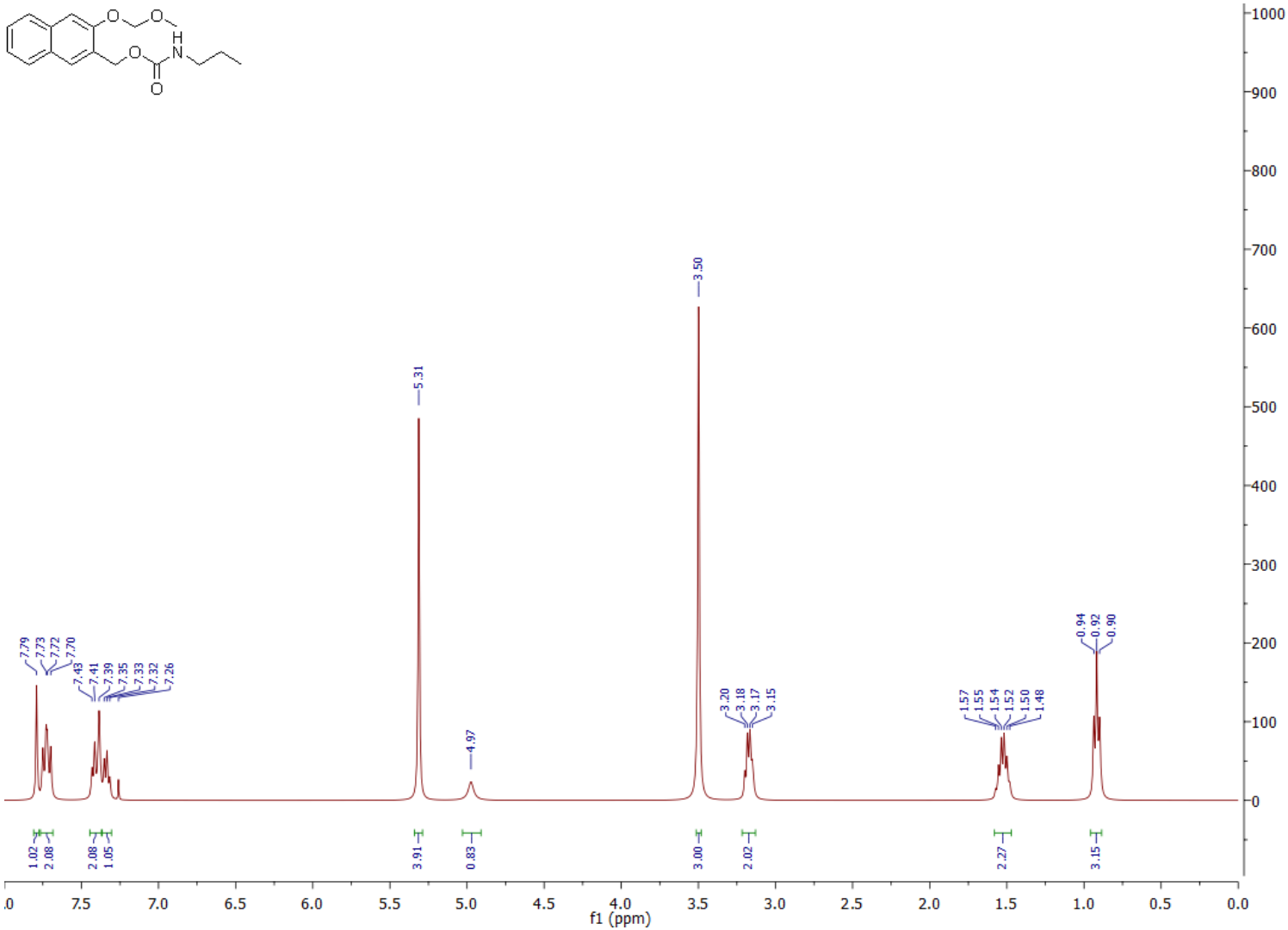

Figure A-1. [1]HNMR of (3-(methoxymethoxy)naphthalen-2-yl)methyl propylcarbamate.

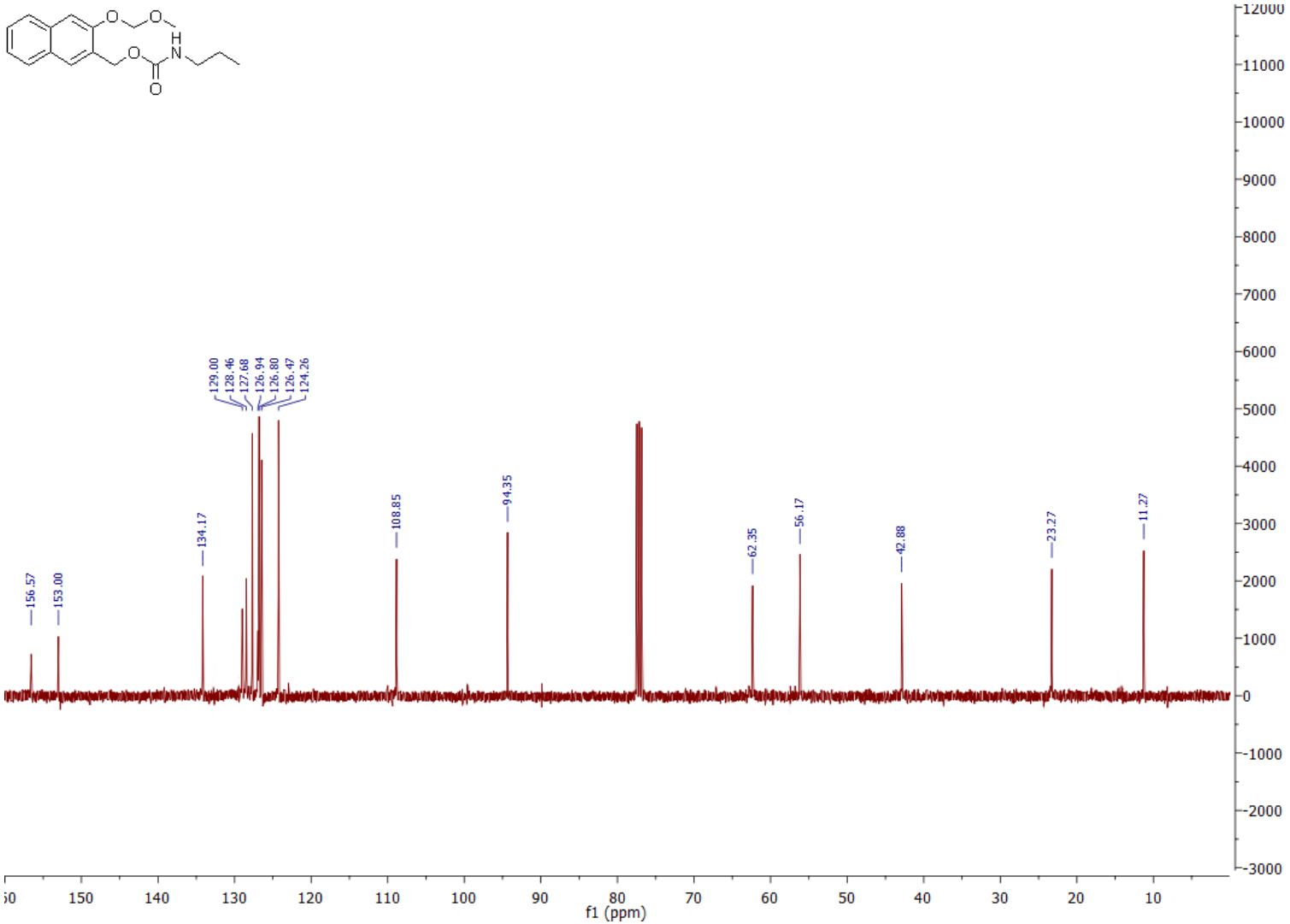

Figure A-2. ^{13}CNMR of (3-(methoxymethoxy)naphthalen-2-yl)methyl propylcarbamate.

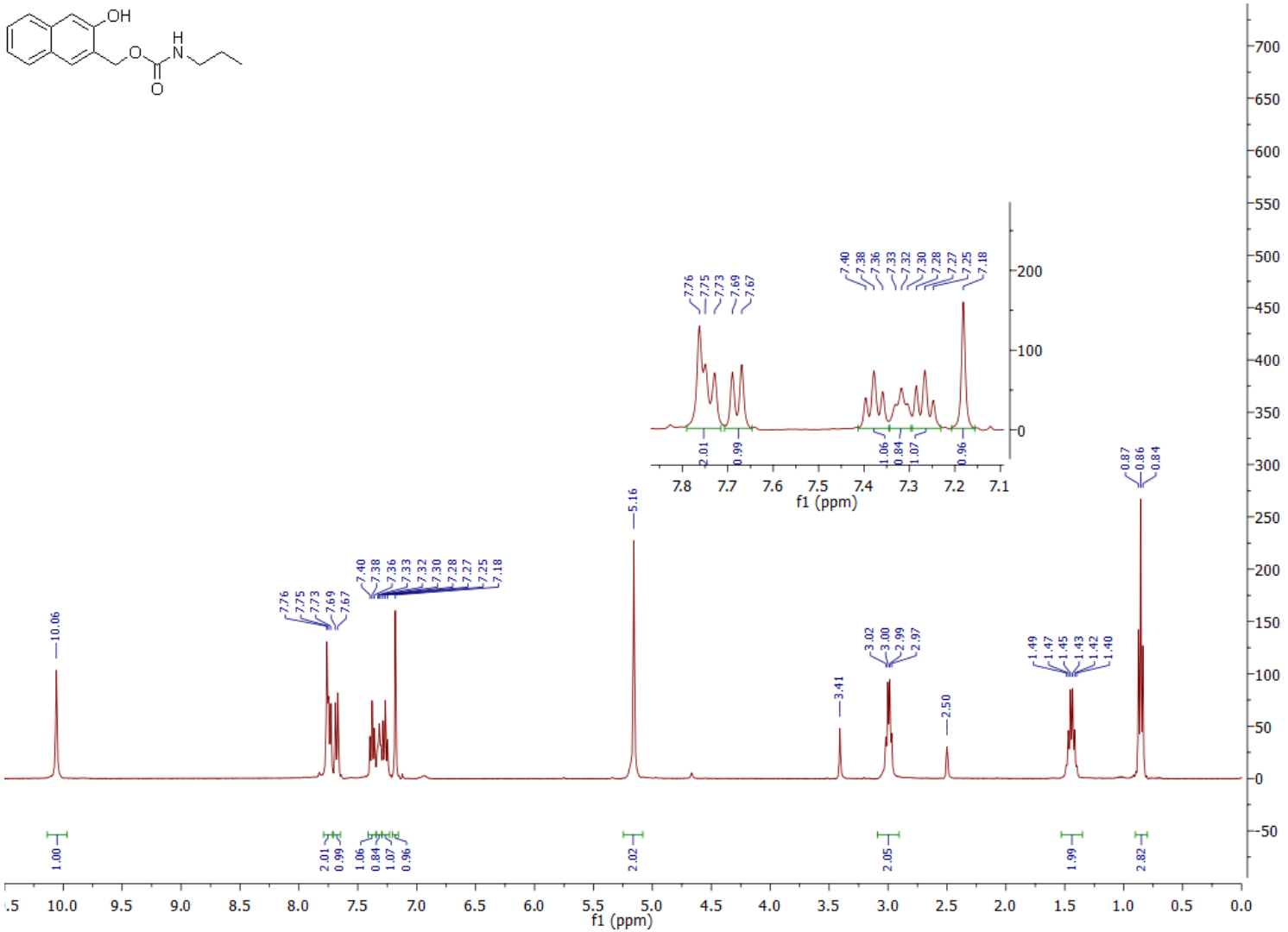

Figure A-3. [1]HNMR of (3-hydroxynaphthalen-2-yl)methyl propylcarbamate.

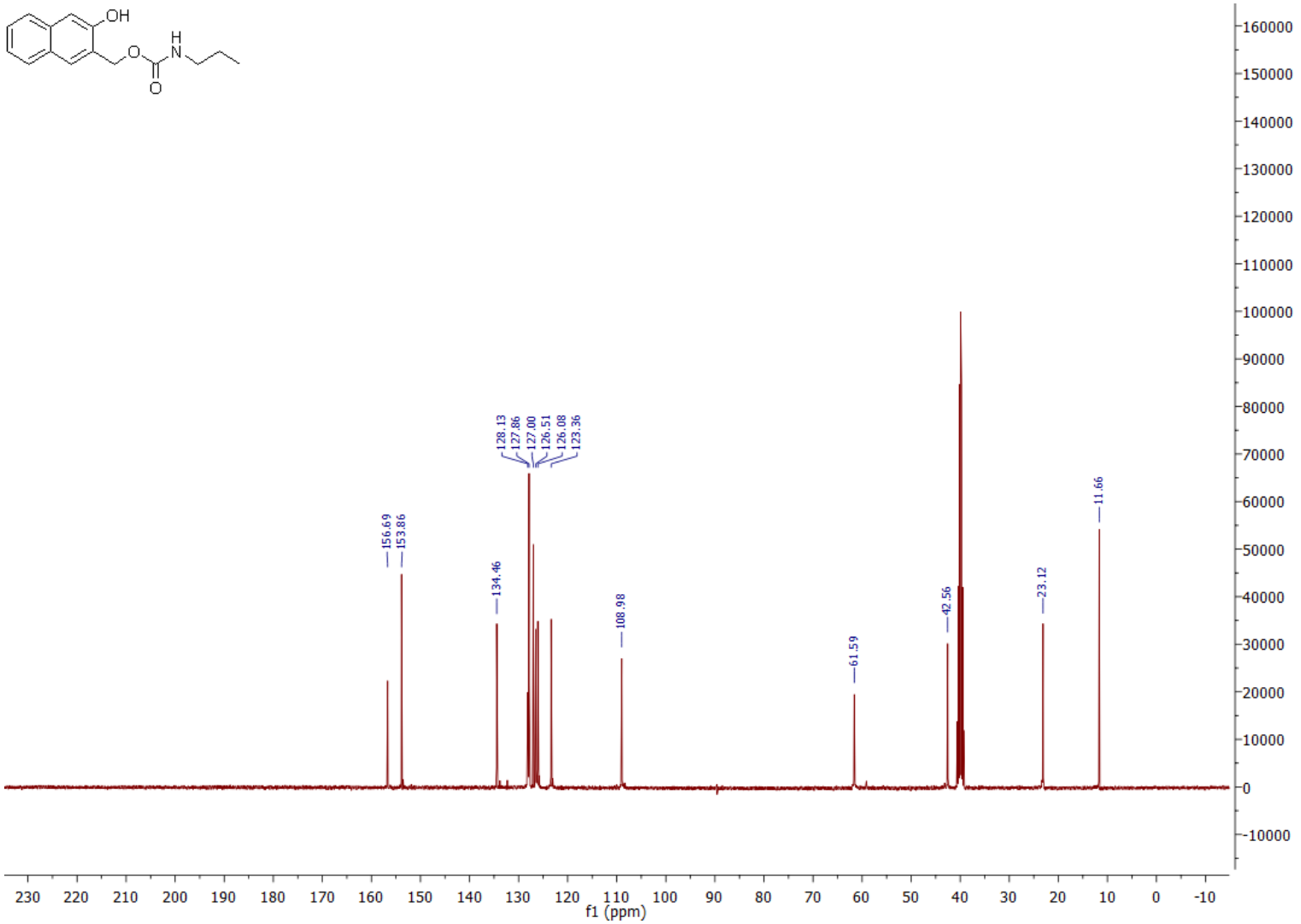

Figure A-4. ^{13}CNMR of (3-hydroxynaphthalen-2-yl)methyl propylcarbamate.