SYNTHESIS AND APPLICATIONS OF DIALDEHYDES

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Synthesis and Applications of Dialdehydes

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ABSTRACT

Due to their reactivity and ease of functional group interconversions, aldehydes have wide-ranging applications in polymer synthesis, such as polyacetals, epoxy resins, and polyurethanes. Recently, room temperature synthesis of polycarbamates using cyclohexanedicarboxaldehydes was reported by Dow Chemical, thus opening up a novel way of making non-isocyanate polyurethanes (NIPUs) with greater applicability. However, preparing NIPUs is limited by the available bio-based dialdehydes.

Therefore, we prepared a series of bio-derived bis-furan and tris-furan dialdehydes through the condensation of furan with four readily available ketones, with subsequent formylation *via* the Vilsmeier-Haack reaction. The incorporation of structurally different spacers in otherwise structurally similar dialdehyde monomers resulted in a variety of melting points dependent on the relative symmetry and rigidity of the structures.

Chapter 1 addresses the synthesis of aldehydes with a review of their current utility in polymer synthesis. Chapter 2 addresses our synthesis of the dialdehydes and their potential applications in polymer synthesis.

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DEDICATION

To my husband, thank you for going through this process with me and always being there. I'm looking forward to the next chapter in our lives.

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LIST OF ABBREVIATIONS

°C .....Degree Celsius

^{1}H NMR .....Proton Nuclear Magnetic Resonance

^{13}C NMR .....Carbon Nuclear Magnetic Resonance

δ.....Chemical Shift in Parts-Per-Million

acac .....Acetylacetonate

Calcd .....Calculated

DCC .....Dicyclohexylcarbodiimide

DCM .....Dichloromethane

DDQ.....2,3-Dichloro-5,6-dicyanobenzoquinone

Di-TMP .....Ditrimethylolpropane

DMF .....N,N-Dimethylformamide

DMSO .....Dimethyl Sulfoxide

DNA.....Deoxyribonucleic Acid

E_g.....Optical Band Gap

EDG .....Electron Donating Group

Et .....Ethyl

EtOH .....Ethanol

EWG .....Electron Withdrawing Group

FT-IR.....Fourier-Transform Infrared Spectroscopy

h.....Hour

HFIP .....Hexafluoroisopropanol

HMF 5-Hydroxymethylfurfural

HRMS .....High Resolution Mass Spectrometry

Hz.....Hertz

J.....Coupling Constant, Hz (NMR)

K_m.....Michaelis Constant

Me .....Methyl

MHz .....Megahertz

Min.....Minute

mL .....Milliliter

Mol.....Moles

Mol. Wt. .....Molecular Weight

mp .....Melting Point

NIPU .....Non-isocyanate polyurethane

NMP N-Methyl-2-pyrrolidone

NMR .....Nuclear Magnetic Resonance

Ph .....Phenyl

POM.....Poly(oxymethylene)

PPA .....Polyphthalaldehyde

R.....Alkyl Group

rt .....Room Temperature

SIPs .....Self-immolative polymers

T_c.....Ceiling Temperature

T_d.....Degradation Temperature

T_g.....Glass Transition Temperature

T_m .....Melting Point

THF .....Tetrahydrofuran

TLC .....Thin Layer Chromatography

TPPTS .....3,3’,3’’-phosphanetriyl-tris(benzenesulfonic acid)

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CHAPTER 1. SYNTHESIS AND UTILITY OF ALDEHYDES

1.1. Introduction

Although aldehydes have been used for centuries, the term aldehyde was first coined by Justus von Liebig[1] in 1835 upon his discovery that ethyl alcohol oxidized by manganese dioxide produced a mixture of an aldehyde, later identified as acetaldehyde, and an acetal. Von Liebig devised the word aldehyde through a contraction of the Latin phrase **al**cohol **dehyd**rogenatum which translates into "alcohol deprived of hydrogen".[2, 3]

While Liebig was the first to identify acetaldehyde as an aldehyde, it should be noted that its first observation was previously recorded in 1774 by Carl Wilhelm Scheele in his essay on *magnesia nigra*.[3] He noted that upon reacting manganese and spirit of wine (*ethanol*) with either spirit of salt (*hydrochloric acid*) or spirit of vitriol (*sulfuric acid*); and followed by subsequent distillation, a strong smell of ether of nitre (*ethyl nitrate*) was observed. The observed odor was later identified as acetaldehyde which was an impurity in the synthesis of ether of nitre.[3] It is interesting to note that at the time ether had a different meaning and was defined by Scheele as "a very volatile, penetrating, colorless, aromatic-smelling oil, soluble in water".[3]

As expected with its long history, the scope of materials that aldehydes are found in is vast incorporating both natural and synthetic materials. In fact, more than 300 unsaturated aldehydes are naturally found in the various foods we eat.[4] Synthetically, aldehydes have found applications as a feedstock for pharmaceuticals and other chemicals. Industrially, one of the most important aldehydes is formaldehyde with an annual global demand of 30 megatons per year.[5] Biologically, aldehydes serve a variety of roles such as binding to G-protein coupled [odor] receptors,[1, 6, 7] lung cancer detection,[8-11] and insect pheromones and attractants.[1, 12]

1.2. Properties of Aldehydes

An aldehyde consists of a carbonyl group attached to a hydrogen and a –R group. The carbonyl bond of aldehydes is polarized with a dipole moment of approximately 2.5 D[13] which facilitates reactions such as ionic polymerization[13] and nucleophilic addition.[14]

1.2.1. Solubility of Aldehydes in Water

Richard M. Stephenson[15] studied the solubility of aldehydes in water. It was reported that the solubility decreases as the molecular weight increases due to the increased length of the nonpolar hydrocarbon backbone. It was similarly noted that straight-chain aldehydes are less soluble than cyclic aldehydes. However, no difference was observed for saturated vs unsaturated aldehydes.[15]

1.2.2. Electrophilicity and Nucleophilicity of Aldehydes

Sanjay Pratihar[16] reported the experimental and theoretical electrophilicity, nucleophilicity, and net electrophilicity values of commonly used aldehydes and also addressed the mechanism of the $KMnO_4$ oxidation of aldehydes. To measure the electrophilicity, sodium borohydride reduction to the alcohol was used; while to determine the nucleophilicity, potassium permanganate oxidation to the acid was utilized. The nucleophilicity (N) and electrophilicity (E) values of the aldehydes were concurrently calculated at the B3LYP/6-311+G** level of theory. The net electrophilicity, which indicates the actual electron accepting character of a molecule, was determined by calculating the difference between the aldehydes N and E values.

Analysis of the mechanism of the oxidation using the Gaussian 03 suite of quantum chemical processes indicated that during the transition state there is a small positive charge at the aldehyde carbon center which is stabilized by electron donating substituents. In the transition state the hydrogen of the aldehyde's carbon was transferred to the oxygen with the breaking of

the O-Mn bond. The free energy of activation for the cleavage of the aldehyde C-H bond, the rate determining step, was determined to be governed by entropy.[16]

1.2.3. Toxicity of Aldehydes

The toxicity of aldehydes was previously reviewed by O'Brien et al.[17] and Feron et al.[18] Building on their works, LoPachin and Gavin[4] reviewed the mechanism of toxicity for different subclasses of aldehydes through the use of the hard-soft acid-base theory to characterize the electronic character (hard vs. soft), electrophilic reactivity, and biological nucleophile targets. The five subclasses consisted of 1)short chain, unhindered aldehydes (hard electrophiles), 2)long chain alkanals (hard electrophiles), 3)aromatic aldehydes, 4)α,β-unsaturated aldehydes (further categorized as either non-hindered, partially hindered, hindered, aromatic alkenal, and oxygenated alkenal), and 5)α-oxoaldehydes. It was reported that within a subclass the mode of action follows the same mechanism; therefore, the toxicity of aldehydes within a subclass can be cumulative.[4] It was also noted in this review that while two aldehydes may exhibit similar electrophilic reactivity and steric bulkiness, the solubility of the aldehyde in the tissue will greatly affect the observed toxicity.[4]

Xi et al.[19] also recently studied the cytotoxic DNA damage induced by aldehydes. From this study, it was reported that aldehyde-induced DNA interstrand cross-links result in critical cytotoxic DNA damage. In regards to toxicity, saturated aldehydes were deemed less toxic than simple aldehydes and short α,β-unsaturated aldehydes, which were in turn less toxic than long, α,β-unsaturated aldehydes. It was reported that weakly toxic aldehydes induce cell death through cytotoxic DNA damage, whereas highly toxic aldehydes induce cell death through protein damage.[19]

1.3. Synthesis of Aldehydes

Aldehydes are traditionally prepared either through oxidation of alcohols or reduction of carbonyl derivatives of higher oxidation states such as esters, acids, amides, or acyl chlorides.[20] Other methods include the formylation of arenes,[21-26] hydroformylation of alkenes,[27] and oxidation of alkyl halides.[28, 29] Figure 1.1 illustrates some of the common precursors used for aldehyde synthesis.

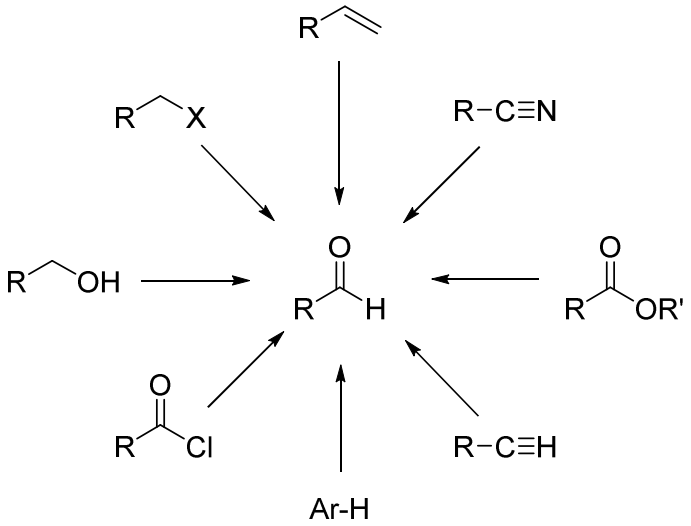


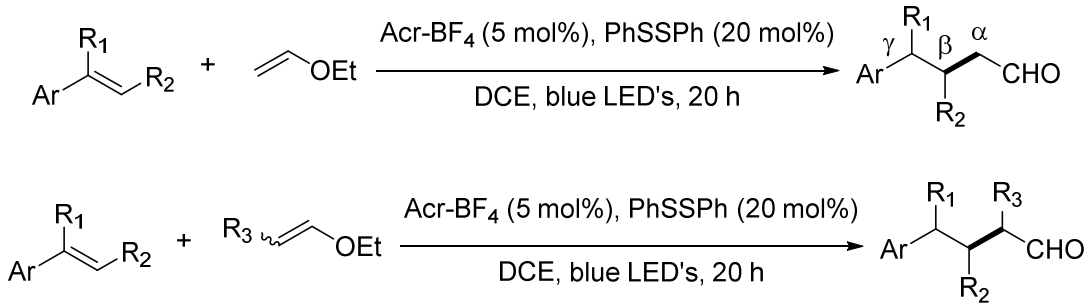
Figure 1.1. Common Precursors for Aldehyde Synthesis

The synthesis of aldehydes has been previously reviewed by Ferguson,[30] Kantlehner,[31] and Olah et al.[32] Therefore, this article will address interesting recent advances in aldehyde synthesis, particularly in the fields of catalysis, enzymatic synthesis, and transition metal-free synthesis.

1.3.1. Synthesis of Aldehydes via Catalytic Methods

In the field of catalysis, there have been several recent advances in aldehyde synthesis. Fengjin Wu et al.[20] recently reported a chemo- and regioselective catalytic synthesis of α,β-

disubstituted aldehydes via photoredox catalysis using an acridinium salt as a photosensitizer and a disulfide as a hydrogen-atom-transfer catalyst as shown in Scheme 1.1.

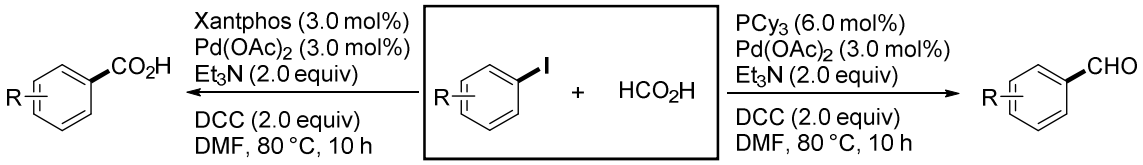


Scheme 1.1. Synthesis of α,β-Disubstituted Aldehydes Using Photoredox Catalysis[20]

This reaction was reported to exhibit a broad substrate scope.[20] Synthesis of aldehydes with β- and/or γ-branches were reported in moderate to good yields and excellent chemo- and regioselectivity. In regards to the β-substituted styrenes, the olefin's geometry has a slight effect on the yield with the *cis* isomers resulting in slightly higher yields than the *trans*. Cyclic alkene substrates were reported to produce products containing a β-ring moiety in yields ranging from 60 to 64%. Tri-substituted styrenes were also shown to be amenable to the reaction conditions. However, arylcyclohexenes were found to produce the desired product in a slightly lower yield of approx. 45% due to the [4 + 2] cycloaddition side reaction. The use of 2-substituted ethyl vinyl ethers allowed for the synthesis of aldehydes possessing an α-branch and were described as more stable towards visible light catalysis and therefore tolerated a wider scope of substrates.[20]

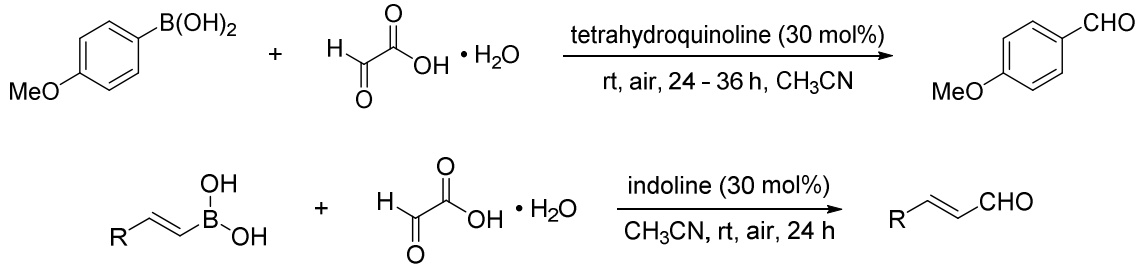
Fu-Peng Wu et al.[33] reported the selective synthesis of aldehydes and carboxylic acids from aryl halides using palladium (II) acetate (catalyst), formic acid (CO source), and DCC (dehydration agent). To obtain the carboxylic acids, xantphos was chosen as the ligand because its wide bite angle and bulkiness facilitated reductive elimination allowing for a more efficient

cross coupling product. To obtain the aryl aldehydes, tricyclohexylphosphine (PCy_3) was chosen as it was a non-bulky monodentate ligand which promoted the aldehyde formation.[33]



Scheme 1.2. Selective Synthesis of Aldehydes and Carboxylic Acids from Aryl Halides[33]

Huang et al.[34] reported the synthesis of aldehydes from boronic acid and glyoxylic acid using either tetrahydroquinoline or indoline as the catalyst for aryl aldehydes or aryl enals, respectively (Scheme 1.3).



Scheme 1.3. Synthesis of Aryl Aldehydes and Enals from Boronic Acids[34]

The synthesis of aryl aldehydes via this procedure was shown to be tolerant to other chloride, bromide, iodide and triflate substituents on the aryl ring.[34] To illustrate the scalability of the reaction conditions, a reaction using 4-methoxyphenylboronic acid was run on the 20 mmol scale with the catalyst loading reduced to 20 mol% which resulted in a 77% yield.[34]

1.3.2. Synthesis of Aldehydes via Enzymatic Catalysis

Enzymatic catalysis is of great interest in organic chemistry as it provides a method to synthesize molecules, which can exhibit regioselectivity and stereoselectivity, in environmentally benign conditions.[35] With over 3000 identified enzymes, enzymatic catalysis

has found use in a wide range of reactions. In fact, enzymatic catalysis has been reported for the synthesis of natural vanillin using yeast and for propane using *Escherichia coli*.[36]

The enzymatic synthesis of aldehydes has been previously reviewed by Kunjapur and Prather[1] (2015) and by Napora-Wijata et al.[37] (2014). More recently, Jarvis et al.[38] illustrated the use of an artificial rhodium hydroformylase to selectively prepare linear aldehydes *via* controlled orientation of the alkene during formylation. To accomplish this, the steroid carrier protein type 2 like domain (SCP-2L) of the human multifunctional enzyme (MFE-2) was mutated so that cysteine residues were present at either end of the apolar tunnel. The exposed cysteine residues were then reacted with aldehyde phosphines. Finally, addition of $Rh(acac)(CO)_2$ resulted in the desired rhodium proteins. To determine the necessity of the Rh, it was exchanged for a phosphine selenide or a phosphine gold complex which supported the role the Rh contributed. When compared to the traditional Rh/TPPTS catalytic system, the artificial metalloenzyme catalyst system exhibited a rate enhancement of at least 10^3 for the biphasic hydroformylation of 1-octene and 1-decene.[38]

Finnigan et al.[36] studied the utility of carboxylic acid reductase (CAR) enzymes for the reduction of carboxylic acids to aldehydes. Five CARs were utilized which were obtained from five diverse host organisms (Table 1.1).[36]

In regards to the substrate scope, it was found that substrates which were more electron rich had a slightly lower Michaelis constant (K_m), and therefore, exhibited a slightly higher catalytic efficiency when compared to that of benzoic acid.[36] However, the addition of a nitro group (EWG) to the benzene ring resulted in a decrease in the turnover number and completely inhibited the reaction when in the *ortho* or *para* position.[36]

Table 1.1. Reported Analysis of the CAR Enzymes[36]

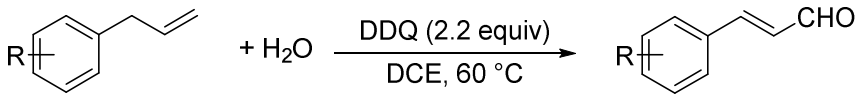
Entry	Abbreviation	Source	Thermostability[a] (°C)	Optimum Activity (pH)	Half-life at 30 °C (h)
1	mpCAR	Mycobacterium phlei	50 (42)	7.0 – 7.6	123.2
2	msCAR	Mycobacterium smegmatis	47 (42)	7.8	53.7
3	niCAR	Nocardia iowensis	44 (42)	7.5	42.9
4	noCAR	Nocardia otitidiscaviarum	44 (38)	7.0 – 7.6	35.3
5	tpCAR	Tsukamurella paurometabola	42 (31)	7.5	25.0

[a)] Temperature residual activity observed, (optimal temperature recorded)

1.3.3. Synthesis of Aldehydes via Metal-free Methods

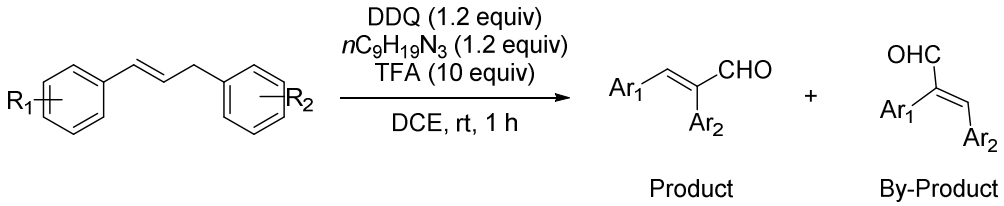
Metal-free synthesis offers economical and environmental advantages and can lead to easier purification. This is of particular importance when the aldehydes are used in pharmaceuticals. To the authors' knowledge, there has not yet been a literature review dedicated strictly to the metal-free synthesis of aldehydes. The scope of this review will include recent advances in the transition metal-free synthesis of aldehydes via formylation or the decarboxylation of an acid. Studies involving oxidation of an alcohol or reduction of carbonyl derivatives of higher oxidation states are outside the scope of this review.

Xu et al.[39] recently reported the metal-free synthesis of cinnamaldehydes from allylarenes using DDQ (Scheme 1.4). The reaction conditions exhibited tolerance for most functional groups; however, free phenolic hydroxyl was not tolerated. The reaction is proposed to proceed *via* a single electron transfer between the allyl double bond of the substrate and the DDQ forming a charge transfer complex; subsequently followed by hydrolysis and oxidation.[39]

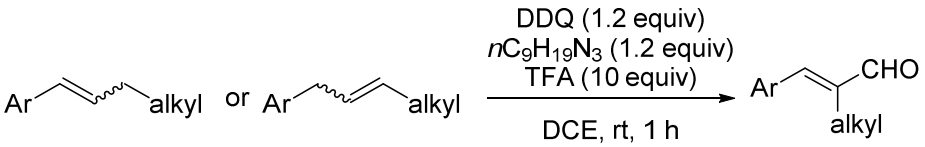


Scheme 1.4. Metal-Free Synthesis of Cinnamaldehydes from Allylarenes Using DDQ[39]

Another method for the synthesis of cinnamyl aldehydes was recently reported by Liu et al.[40] The aldehydes were prepared via cleavage of the allylic carbon-carbon bond using an alkyl azide. The substrate scope included both substituted 1,3-diarylpropenes (Scheme 1.5) as well as aryl olefins possessing an alkyl substituent (Scheme 1.6). The reaction of 1,3-diarylpropenes exhibited high regioselectivity as the electron deficient aryl was reported to migrate preferentially over the electron-rich aryl. The reaction of aryl olefins with an alkyl substituent also exhibited high regioselectivity with the alkyl group preferentially migrating over the aryl group. Overall, the order of preference for the observed migration was alkyl > electron-deficient aryl group > electron-rich aryl groups. The reported yields for the 1,3-diarylpropenes were moderate to good with a range of 48 – 85% yield. Moderate yields (33 – 52%) were obtained for the aryl olefins possessing an alkyl substituent. In all examples, the reaction exhibited high stereoselectivity with strictly the formation of the E product irrespective of the stereochemistry of the starting material.[40]

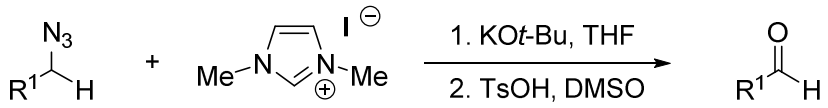


Scheme 1.5. Synthesis of Cinnamyl Aldehydes from 1,3-Diarylpropenes



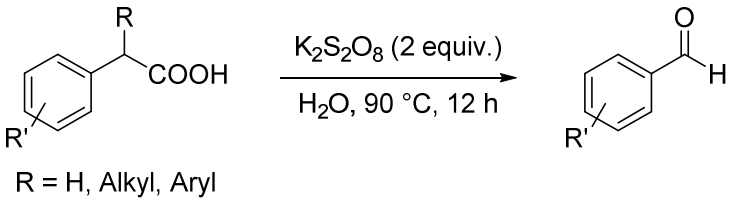
Scheme 1.6. Synthesis of Cinnamyl Aldehydes from Alkyl Substituted Aryl Olefins

Barragan and Bugarin[41] reported the use of π-conjugated triazenes for a two-step, one pot, room temperature synthesis of aldehydes, ketones, ethers, and sulfides without the need for additional metal catalysts (Scheme 1.7). Secondary azides were reported to afford aldehydes in high yields (60 – 72% yield), while an allylic azide afforded a moderate yield of *trans*-cinnamaldehyde (43% yield). Aliphatic primary azides were unreactive under these conditions; whereas benzylic primary azides exhibited sensitivity towards the electronic effects. Therefore, while benzaldehyde was obtained in moderate yield (44%), 4-methoxybenzaldehyde (electron-rich) was obtained in higher yield (60%). Similarly, 4-nitrobenzaldehyde (electron-poor) was obtained in lower yields (23%).[41]



Scheme 1.7. Synthesis of Aldehydes via $\boldsymbol{\pi}$-Conjugated Triazenes[41]

Mete et al.[42] reported a one-pot transition metal free synthesis of aromatic aldehydes and ketones through the oxidative decarboxylation of arylacetic acids in water (Scheme 1.8). To represent the applicability of the reaction conditions, benzaldehyde and benzophenone were prepared on a one gram scale in 83% and 93% yields, respectively. A key advantage of this procedure is that it allows for the direct synthesis of ^{18}O-labeled aldehydes when labeled water ($H_2^{18}O$) is used in the reaction.[42]



Scheme 1.8. Synthesis of Aldehydes via Decarboxylation of Arylacetic Acids in H_2O[42]

1.4. Utility of Aldehydes

As expected with the large quantity of known aldehydes and ease of conversion to other functional groups, aldehydes have found a vast scope of applications. Several examples illustrating the utility of aldehydes for transformation into other functional groups is shown in Figure 1.2.

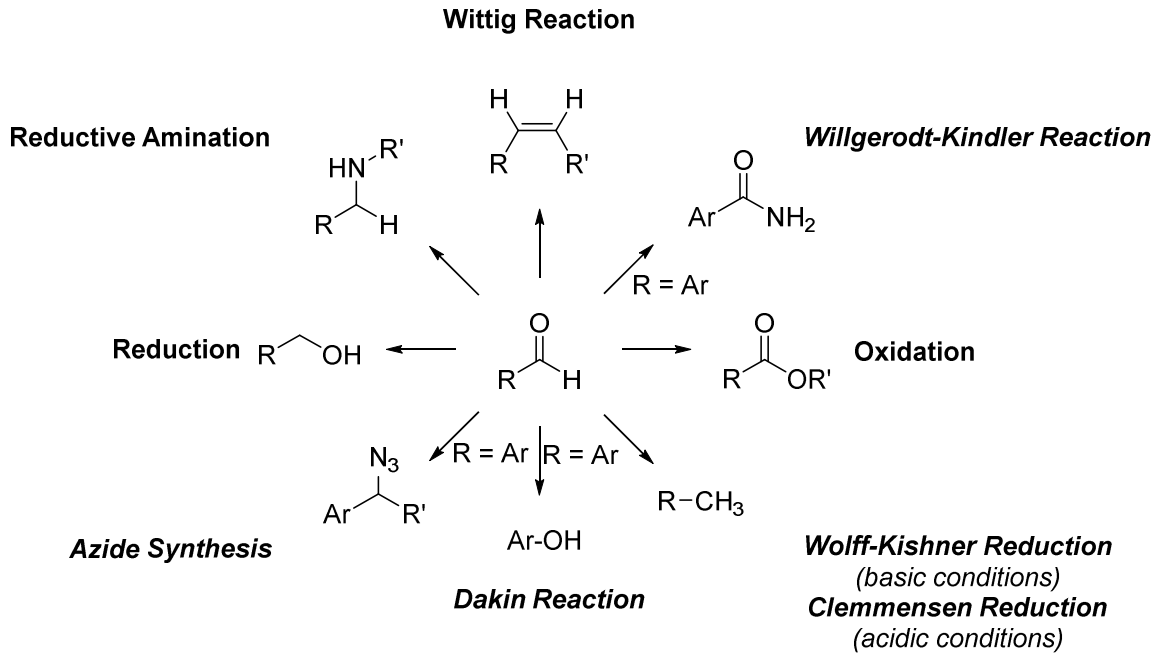


Figure 1.2. Utility of Aldehydes in Chemical Transformations

In addition to the ease of functional group transformations, aldehydes have found utility in a variety of carbon-carbon or carbon-heteroatom bond forming reactions as illustrated in Figure 1.3.

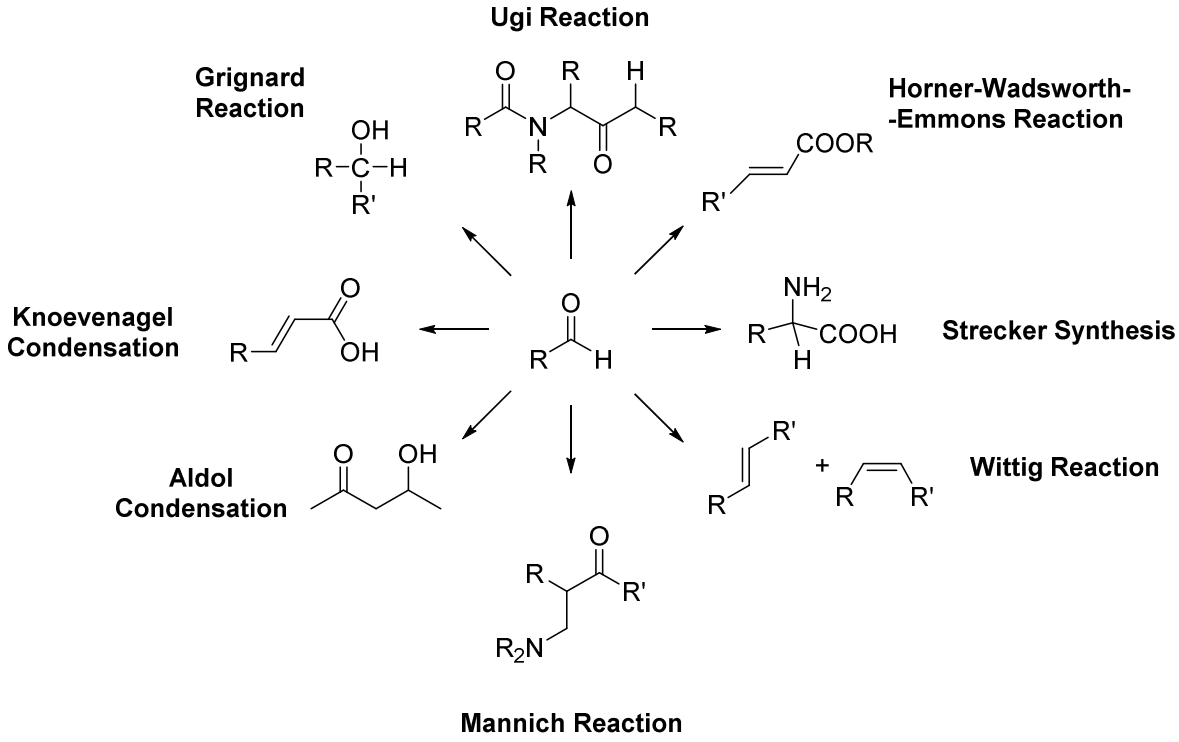


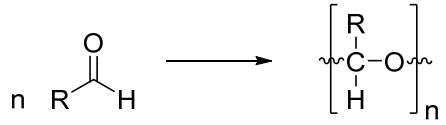
Figure 1.3. Utility of Aldehydes in C-C Bond Forming Reactions

Among the many applications of aldehydes in industry including the synthesis of reactive dyes for the textile industry[43] and pharmaceuticals,[44] one environmentally and biologically important application is the synthesis of polymeric materials which will be the focus of this section of the review.

1.4.1. Utility of Aldehydes in Polyaldehydes

Polyaldehydes have a wide variety of applications including production of extrusion molded parts,[45] and injection and blow molding.[46] The double bond of aldehydes allows them to be susceptible to polymerization. However, unlike alkenes aldehydes do not undergo radical polymerization.[47] Nonetheless, due to the polarity of the aldehydes' carbonyl bond, aliphatic aldehydes are highly susceptible to ionic polymerization, both cationic and anionic.[13] It should be noted, though, that aromatic aldehydes generally do no undergo polymerization due to the resonance stabilization of the carbonyl group.[45] The ionic polymerization of aliphatic aldehydes

results in the formation of a polyacetal as shown in Scheme 1.9.[13] The resultant polymers can also be referred to as polyethers or acetal resins.[48]



R = H, aliphatic, trihalomethyl

Scheme 1.9. Polyacetal Synthesis via Ionic Polymerization[13]

Polyacetals exhibit many excellent properties including high tensile strength, stiffness, resilience, good recovery after deformation, and toughness under repeated impact.[46] In fact, according to Nath,[46] the acetals' stiffness has been ranked highest of all thermoplastic materials allowing it to act as an alternative to metal.[46] For example, toilet anti-siphon valves are now prepared using acetal resin which allows for improved performance, eliminates corrosion, and reduces the cost, while exhibiting a 30-year lifespan.[49] However, while polyacetals exhibit many positive features, there are some key drawbacks which needs to be overcome for industry to be able to utilize them.

One key limitation is that most crystalline polyaldehydes are virtually infusible and insoluble in most solvents.[45] Therefore, crystalline polyaldehydes cannot be utilized *via* common polymer processing technologies. On the other hand, most amorphous polyaldehydes, while elastomeric and soluble, exhibit poor stability and their continual release of monomers through decomposition cannot be avoided.[45]

Traditionally, another key limitation of polyacetals was the low ceiling temperature (T_c), which is the temperature that above which for a given chain polymerization a polymer of high molecular weight is not obtained.[45] More importantly, when the temperature increases past its T_c a prepared bulk polymer will decompose back into its monomeric substituents. Because of this,

polyacetals typically will decompose at rt or slightly elevated temperatures via an unzipping reaction beginning at the hemiacetal chain ends. Therefore, to prevent the decomposition the hemiacetal ends are typically capped. [45] It should be noted that the T_c is inversely related to the length of the aldehyde so as the length increases the T_c decreases. Subsequently, for bulkier aldehydes very low temperatures and high monomer concentrations are required.[47]

While the lower T_c was traditionally seen as a limitation, recently it has resulted in increased interest in polyaldehydes as it is ideal for the application of transient electronics.[50] Transient electronics is defined as an emerging technology in which the controlled, programmable vaporization of a device is required as it is either non-retrievable or it is preferential that a different form of disposal is utilized.[51] A recent article by Schwartz et al.[50] reported a photo-acid generated (PAG) controlled photo-depolymerization of a polyaldehyde consisting of butanal and *ortho*-phthalaldehyde. The incorporation of a copolymer allowed for the crystallization problems of aliphatic aldehydes to be overcome while also enhancing the monomers evaporation rate.[50]

The lower ceiling temperatures and depolymerization tendencies of polyacetals have also resulted in increased interest in their application for self-immolative polymers. Self-immolative polymers (SIPs) are defined as macromolecules that contain a linearly depolymerizing main chain of greater than 10 repeat units and react to multiple types of environmental influences resulting in amplified output responses.[52] The controlled depolymerization of polyacetals can be initiated by removing the end-caps or by cleaving the ether backbone by a chemical or physical or physical trigger.[53] Polyphthalaldehyde (PPA) and its derivatives have received the most attention in this area; however, the utility of aliphatic aldehydes in SIPs has also recently been reported.[53]

Industrially, the most consumed polyacetal is poly(oxymethylene) (POM) prepared from either formaldehyde or trioxane with an annual production of 1 million tons.[45] The major consumers as of 2009 of POM are the automotive industry (27%), electronics (21%), consumer goods (16%), industrial applications (11%), fluid handling (7%), and home appliances (4%).[54]

Numerous review articles have been written about polyacetals;[13, 45, 46, 48] therefore, the scope of this review will be focused on aldehydes which are used in the synthesis of polyacetals. The most common aldehydes used in the synthesis of POM resins are formaldehyde (**1.1**) and trioxane (**1.2**) which is the trimer of formaldehyde. However, other higher aliphatic and aromatic aldehydes have also been reported in the synthesis of POMs.[55] Some representative aldehydes which have been reported in the synthesis of POMs are illustrated in Figure 1.4.[13, 48, 56]

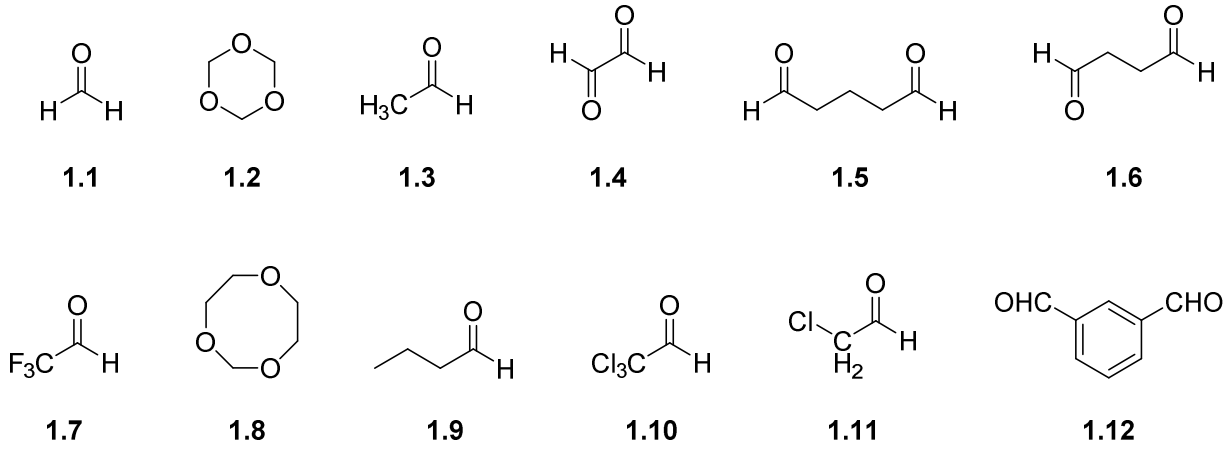


Figure 1.4. Representative Aldehydes Reported for Use in the Synthesis of POMS

The first reported conversion of acetaldehyde (**1.3**) into the atactic (amorphous) form of polyacetaldehyde occurred in 1936.[55] It was discovered that when acetaldehyde was frozen (-123 °C), part of it polymerized forming a white elastic material with a molecular weight reported as upward to 2 million.[57] In 1961, Furukawa et al.[57] reported an improved synthetic method using alumina and cooling to -78 °C. Natta[58] and Furukawa et al.[57] each independently discovered that

the crystalline form of the polyacetal could be prepared using a metal alkyl, hexane, and acetaldehyde.[57] The T_c of the polymerization of **1.3** is -40 °C, as above that temperature, cyclization to the cyclic trimer (paraldehyde) or to the tetramer (metaldehyde), as the minor product, occurs.[55]

In 2011, Li et al.[59] reported the study of the synthesis of poly(acetaldehyde) *via* surface chemistry using ordered $(WO_3)_3$ films on Pt(111) as a model catalytic system. The polymerization process began to occur at 80 K (-193 °C). The initiation is caused by the binding of **1.3** to the tungsten cation (W^{6+}). Therefore, as the electrons of the carbonyl oxygen of **1.3** undergoes partial charge transfer to the tungsten, the formation of a partial positive charge on the carbonyl's carbon of **1.3** increases its reactivity towards a neighboring oxygen of another molecule of **1.3** which results in chain propagation.[59] However, the resultant polymer was found to exhibit a lower T_d than that of polyformaldehyde (-83 °C vs -23 °C, respectively).[59]

Glyoxal (**1.4**) is the simplest of the dialdehydes. Its application in the synthesis of polyglyoxal has previously been reported.[13, 60, 61] The structure of polyglyoxal consists of an acetyl chain with pendent hydroxyl groups and cyclic chelated structures bearing a hydrogen bonded carbonyl and hydroxyl group (Figure 1.5).[60] Polyglyoxal has a T_d of 150 °C and exhibits slight solubility in water and alcohol. After acetylation with acetic anhydride, it exhibits a T_d of 290 °C and is insoluble in all common organic solvents.[61]

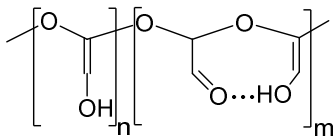


Figure 1.5. Structure of Polyglyoxal

Glutaraldehyde (**1.5**) and succinaldehyde (**1.6**) have also been converted into low molecular weight amorphous polymers.[62] However, these result in copolymers as

cyclopolymerization resulting in 6 or 5 membered rings, respectively, occurs along with the normal carbonyl polymerization. The resulting cyclopolymerization is caused by the aldehyde carbonyls of the monomers being spaced two to three carbons apart.[62]

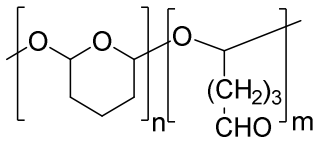


Figure 1.6. Structure of Polyglutaraldehyde[63]

Fluoral (**1.7**) is reported to be only aldehyde which polymerizes via the opening of the carbonyl double bond by a free radical mechanism.[55] Polyfluoral can be prepared by either anionic or cationic conditions. However, the rate of polymerization for anionic conditions is higher than that for cationic. Catalysts for anionic conditions include alkali metal cyanides and halides, carboxylates, ammonium and sulfonium salts, phosphines and phosphates. Catalysts for cationic polymerization include strong Lewis acids such as PF_5, $SbCl_5$, BF_3, $AlCl_3$, and $SnCl_4$.[55] Polyfluoral is an amorphous polymer, and when prepared from solution or are melt-pressed at approximately 125 °C results in the formation of clear films and coatings.[48] The films and coating were reported to exhibit oil and water repellence while also exhibiting high vapor permeability towards oxygen and moisture. [48]

1,3,6-Trioxocane (**1.8**) can be homopolymerized via cationic polymerization using triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$) in DCM at -10 °C resulting in a high molecular weight (M_n = 81000) polymer.[64] The reaction exhibited a fast polymerization rate with equilibrium reached within 15 minutes. The polymerization resulted in the formation of both high weight linear and lower weight macrocyclic polymers.[64] Poly(diethylene oxide-*alt*-oxymethylene), prepared via the ring opening cationic polymerization of **1.8**, has recently been studied as a potential polymer matrix for electrolytes in battery cells.[65]

n-Butyraldehyde (**1.9**) can be homopolymerized via anionic polymerization to form an isotactic polymer or can serve as a component monomer for the synthesis of a copolymer.[13] Polybutanal has been described as a waxy solid[66] with a melting point of 245 °C.[62] Weideman et al.[53] recently reported a metal-free synthesis of polybutanal from **1.9** using a phosphazene base resulting in 80% conversion in approximately 10 minutes in the hopes of increasing the attractiveness for its utility in SIPs.[53]

The anionic and cationic polymerization of chloral (**1.10**) has been previously reviewed by Kubisa et al.[55] Although not FDA approved, the hydrated form of **1.10** is an oral sedative hypnotic prodrug which converts into the active form trichloroethanol upon absorption into the body.[67] Therefore, Bartus et al.[68] studied the polymerization of **1.10** as a method of allowing a controlled release of it since upon contact with an aqueous environment it undergoes almost instantaneous conversion of chloral hydrate. Uncapped polychloral alkoxide was found instable and acetate end-capped polychloral was insoluble and too stable. However, tertiary amine initiated polychlorals were found to exhibit the right stability/instability to make them potential drug release candidates.[68]

Monochloroacetaldehyde (**1.11**) is an unstable monomer which rapidly polymerizes even in the absence of a catalyst. Iwata et al.[69] reported the conditions for the polymerization of **1.11**. The prepared polymers' morphology can be controlled by the choice of catalyst used. The use of boron trifluoride as catalyst yielded an amorphous polymer, whereas diethylzinc or diethylmagnesium produced a crystalline polymer. The use of aluminum alkyl catalysts resulted in the formation of a polymer exhibiting both amorphous and crystalline portions. Poly(monochloroacetaldehyde) which was prepared using triethylaluminum was found to exhibit higher thermal stability than polyacetaldehyde. This was attributed to the electron withdrawing

chlorine group as it reduced the electron density on the oxygen and helped stabilize the skeletal chain.[69]

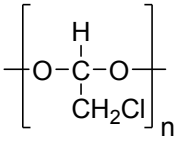


Figure 1.7. Structure of Poly(monochloroacetaldehyde) [69]

ortho-Phthalaldehyde (**1.12**) can be homopolymerized through chain growth polymerization, a feature which sets it apart from all other aromatic aldehydes.[47] Polyphthalaldehyde (PPA) has a T_c of -40 °C.[45] PPA has previously been reviewed by Köstler (2012)[45] as well as by Wang and Diesendruck (2017).[47] Aso and Tagami first reported its cationic polymerization using $BF_3 \cdot OEt_2$ and low temperature (-78 °C) in 1967.[47] Due to its low ceiling temperature and ease of depolymerization, during the 1980s Ito and Wilson[45] studied its potential application for photoresist materials.[45]

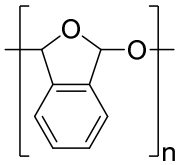
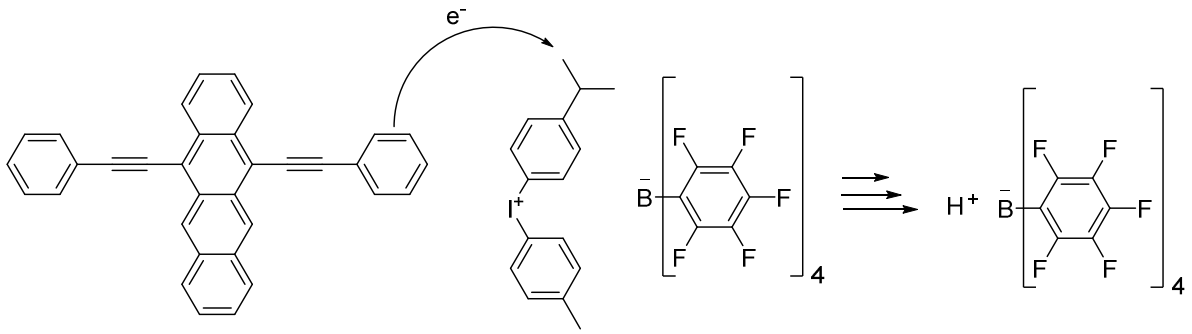


Figure 1.8. Structure of Polyphthalaldehyde (PPA)

Recently, PPA has been studied for its application in transient electronics. Lee et al.[70] studied its catalytic photo-triggered depolymerization using green-emitting OLEDs which were directly attached to the homopolymer *via* silver nanowire electrodes. A photoacid generator (PAG) Rhodorsil-Faba and a photosensitizer, 5,12-bis(phenylethynyl)tetracene (PBET) was utilized. PBET was incorporated as it can absorb wavelengths in the range of 450 and 600 nm. Upon absorption, the PBET was excited to its excited singlet state allowing for an exothermic electron transfer reaction to occur with the PAG. Upon electron transfer, the products then

underwent a rapid, radical decomposition releasing a strong Brønsted acid capable of catalytically cleaving PPA's backbone bonds.[70]



Scheme 1.10. Generation of Brønsted Acid via e^- Transfer from BPET to Rhodorsil Faba[70]

FTIR analysis indicated that the resultant substrates predominantly contained depolymerized monomeric species. However, PPA's low vapor pressure inhibited the complete vaporization of the material. Therefore, future studies should include the copolymerization of PPA with monomers of higher vapor pressure to promote complete vaporization[70]

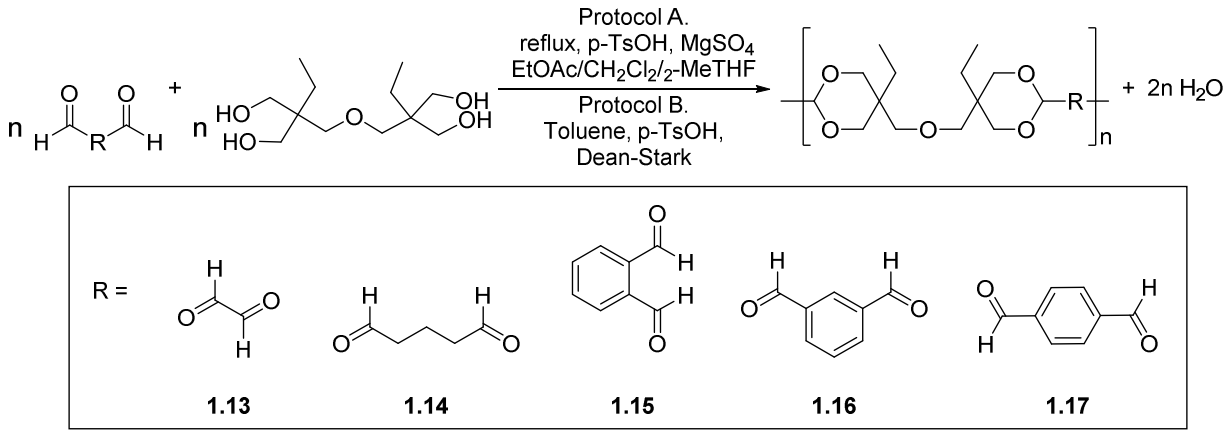
In conclusion, polyacetals have recently gained increased attention as their low ceiling temperatures and ease of depolymerization have lent themselves to applications such as self-immolative polymers and transient electronics. Polyacetals can be prepared as homopolymers or copolymers typically through cationic or anionic polymerization. The resulting polyacetals can be amorphous or crystalline depending on the monomers' structures and reaction conditions.

1.4.2. Utility of Aldehydes in the Synthesis of Poly(cycloacetals)

Aldehydes have found utility in the synthesis of poly(cycloacetals) which are a class of polymers that have been prepared through an acetalization reaction between a tetravalent alcohol and a dialdehyde.[71] The resulting polymer contains cyclic acetal moieties in its rigid backbone which should result in an enhanced T_g.[72] For a recent review on the synthesis and utility of polyacetals see Hufendiek et al.[73]

One key advantage of the acetal linkage is that it allows for the degradation of the resultant polymer. In fact, since the landfill's leachate is slightly acidic, poly(cycloacetals) could be degradable regardless of landfill depth or level of microbial activity.[72] In addition, the degradability of acetal functional groups has caused interest in their utility for medical applications.

Lingier et al.[71] reported the synthesis of high molecular weight poly(cycloacetals) using commercially available dialdehydes and di-trimethylolpropane (Di-TMP). Di-TMP was used instead of the traditional pentaerythritol in order to prevent the formation of spiropolymers; thereby enhancing the solubility of the resultant polymers. The five dialdehydes which were analyzed included glyoxal (**1.13**), glutaraldehyde (**1.14**), and *ortho*- (**1.15**), *meta*- (**1.16**), and *para*-phthalaldehyde (**1.17**).[71]



Scheme 1.11. Synthesis of Poly(cycloacetals) from Di-TMP and Dialdehydes[71]

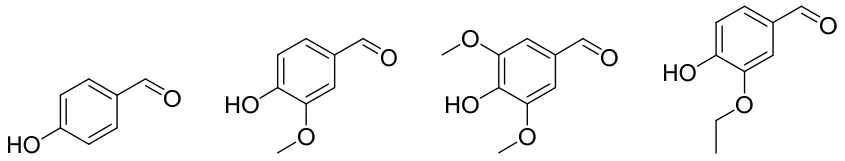
In the model studies, glyoxal was found to contain dimers and oligomers in the starting mixture and so was not included in the study as their presence would induce cross-linking.[71] It was also found that glutaraldehyde underwent acetalization much more rapidly than the phthalaldehydes did which was attributed phthalaldehydes containing a conjugated electron system which resulted in the inactivation of the second aldehyde upon acetalization of the first.[71]

Upon testing the two protocols for the polymer synthesis, protocol B occurred at a rate approximately 10 times faster than protocol A, indicating the use of toluene and *p*-TsOH in a Dean-Stark apparatus would be the more viable option.[71] The polymerization of glutaraldehyde resulted in a transparent and colorless polymer which exhibited molecular weights of up to 38 kDa, high elastic modulus, T_d of up to 370 °C, and ductile behavior at room temperature. The phthalaldehydes exhibited lower molecular weights as they contained the aromatic system. In addition, they also were highly rigid, brittle, non-transparent, and appeared yellowish in color. However, they exhibited a higher T_g than those prepared from glutaraldehyde, which was attributed to the rigidity of the phthalaldehydes versus the more flexible aliphatic glutaraldehyde.[71]

The *p*-phthalaldehyde-based polymer precipitated out of the solution and was insoluble in the common organic solvents; therefore, the molecular weight could not be obtained.[71] Of the polymers prepared from the *o*-, *m*-, and *p*-phthalaldehydes, the *p*-phthalaldehydes exhibited the highest T_g (115 °C), followed by the *o*-phthalaldehydes (102 °C), and then finally the *m*-pthalaldehydes (84 °C). The difference in resulting temperature is due to the position of the aldehydes (regioisomerism) which affects how the aromatic ring can stack in the polymer backbone. Thus, as the amount of free volume increases, the resulting T_g decreases.[71]

The hydrolytic stability of the poly(cycloacetals) from glutaraldehyde were studied by immersing 0.1 g of the polymer in either 10 mL water (pH=7), sodium hydroxide solution (pH=10) or a hydrochloric acid solution (pH=3) for one month.[71] As there was not a significant loss in weight, and negligible swelling was observed in water, it was concluded that the polymers exhibited high hydrophobicity preventing the interaction of the aqueous solution and the labile acetal functional groups.[71]

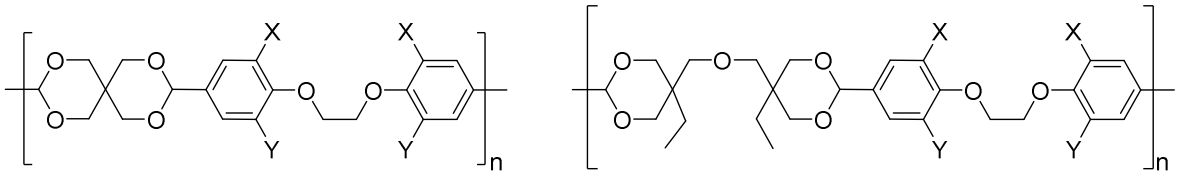
Pemba et al.[72] also utilized Di-TMP along with pentaerythritol for the synthesis of lignin derived cyclic and spirocyclic polyacetal ethers. As mentioned *vida supra* pentaerythritol results in the formation of spirocyclic polyacetals, whereas Di-TMP results in the formation of cyclic polyacetals. The four aldehydes which were used are shown in Figure 1.9. Compounds **1.18** – **1.20** are formed from the pyrolytic breakdown of lignin whereas **1.21** (ethylvanillin) is not natural in nature; however, it was included to study effects that the size of the substituents cause. The monomers were prepared by reacting each with an alkyl halide (1,2-dibromoethane) resulting in the formation of a dimer bound by ether linkages.[72]



1.18 **1.19** **1.20** **1.21**

Figure 1.9. Lignin Derived and Synthetic Lignin Mimetic Aldehydes[72]

The resulting starting materials were then condensed with either Di-TMP or pentaerythritol resulting in a series of 8 polymers.[72] Polymers **1.22** – **1.25** were prepared via pentaerythritol; conversely, polymers **1.26** – **1.29** were prepared via Di-TMP. The resulting polymers **1.22** and **1.26** were difficult to synthesize or characterize using GPC characterization as they were insoluble in the common solvents. However, analysis via NMR indicated that the resultant polymers were obtained.[72]



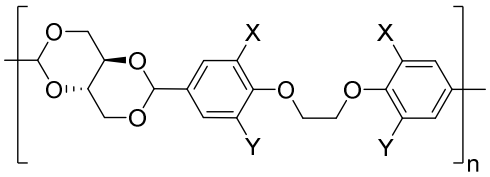
1.22 X = Y = H
1.23 X = OMe, Y = H
1.24 X = Y = OMe
1.25 X = OEt, Y = H

1.26 X = Y = H
1.27 X = OMe, Y = H
1.28 X = Y = OMe
1.29 X = OEt, Y = H

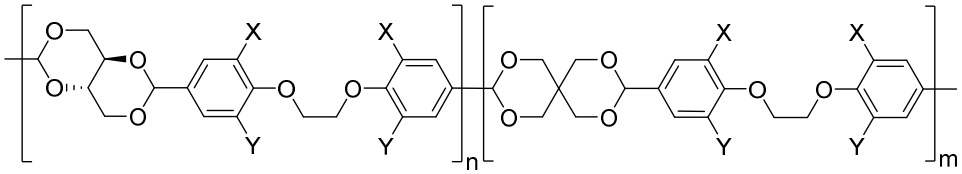
Figure 1.10. Polymers Prepared from Pentaerythritol (**1.22**-**1.25**) and Di-TMP (**1.26**-**1.29**)[72]

Due to increased rigidity, the spirocyclic polyacetals (**1.22** – **1.25**) exhibited a higher T_g and lower solubility than the cyclic polyacetals (**1.26** – **1.29**).[72] In fact, the spirocyclic polyacetals exhibited T_g which were between 40 and 58 °C higher than the cyclic counterpart. The lower T_g of **1.29** when compared to **1.27** has been attributed to an increase in free volume due to the presence of the ethyl group instead of the methyl group. Polyacetals **1.24** and **1.28** exhibited the highest T_g in their respective series which is attributed to the conformational rigidity imparted by the presence of the two methoxy substituents. In regards to the degradation in acidic conditions, it was found that the cyclic polymers (**1.26** – **1.29**) degraded more rapidly than the spirocyclic compounds (**1.22** – **1.25**); however, degradation was observed in both sets.[72]

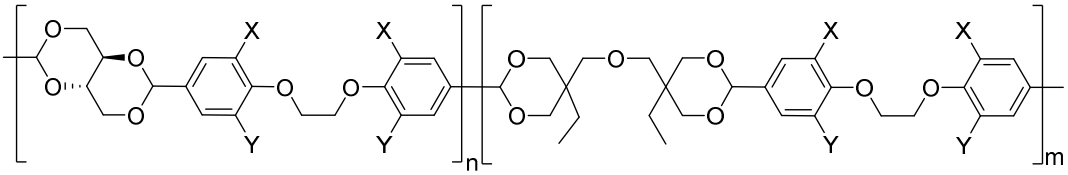
Rostagno et al.[74] later furthered this work by studying the use of erythritol as a bio-based tetraol for the polymerization of the prepared biaryl dialdehydes from vanillin and syringaldehyde. Erythritol is a biogenic tetraol which can be found in fruits and fermented foods and has been approved by the U.S. FDA as a low-calorie sweetener which is safe for human consumption.[74] Polymers **1.23**, **1.24**, **1.27**, and **1.28** were again prepared as illustrated previously and the resultant properties compared with those of polymers **1.30** and **1.31**.[74] In addition, copolymers were prepared with pentaerythritol (**1.32**-**1.33**) and Di-TMP (**1.34**-**1.35**).



1.30 X = OMe, Y = H
1.31 X = Y = OMe



1.32 X = OMe, Y = H
1.33 X = Y = OMe



1.34 X = OMe, Y = H
1.35 X = Y = OMe

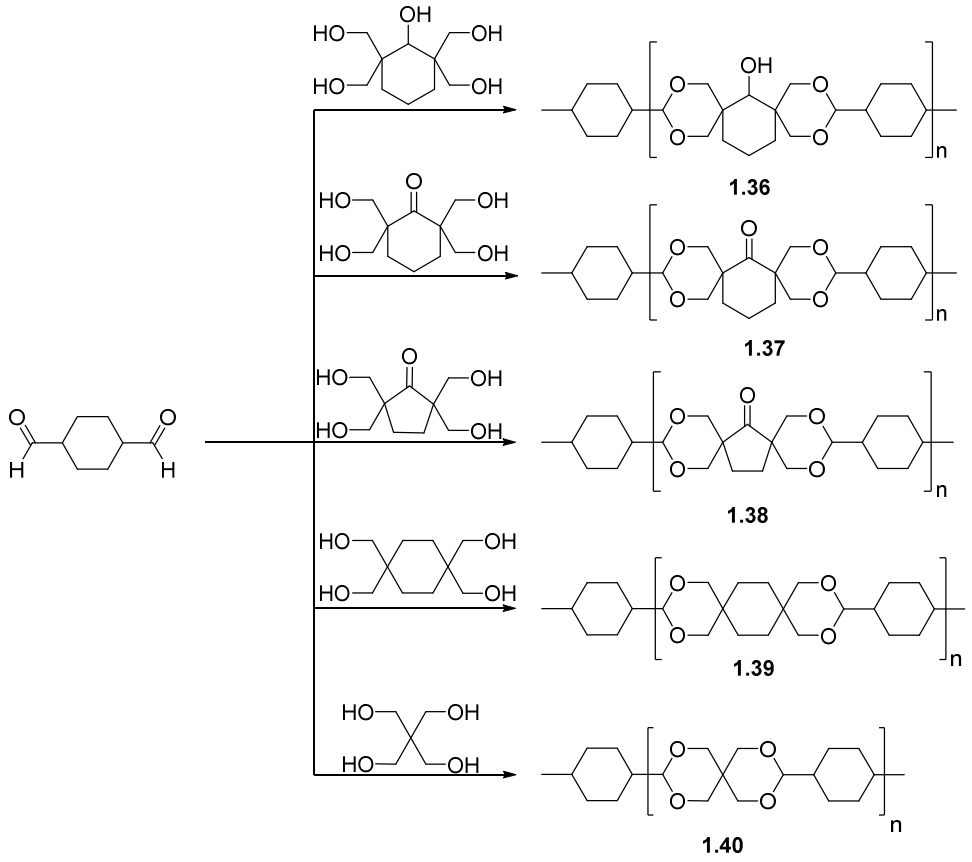
Figure 1.11. Polymers and Co-polymers Prepared Using Erythritol as the Tetraol[74]

Polymers **1.30** and **1.31** were obtained in relatively low yields of 46.1% and 28.4%, respectively.[74] The lower yields were attributed to erythritol possessing two primary and two secondary alcohols which lowered its reactivity. Therefore, copolymers were prepared using erythritol with either pentaerythritol or Di-TMP to help promote the reaction. The resulting polyacetals were generally amorphous due to the lack of stereoselectivity of the enchained erythritol. The polymers prepared from syringaldehyde exhibited a higher T_g than those prepared from vanillin with a similar trend observed for the copolymers (71-159 °C vs 57-110 °C). This increase in T_g is due to the conformational rigidity induced by the extra methoxy group of the syringaldehyde polymers.[74]

As expected with the lower reactivity of erythritol, the yield and molecular weight of the copolymer was lower when the percent of erythritol feed material exceeded 70% versus when it

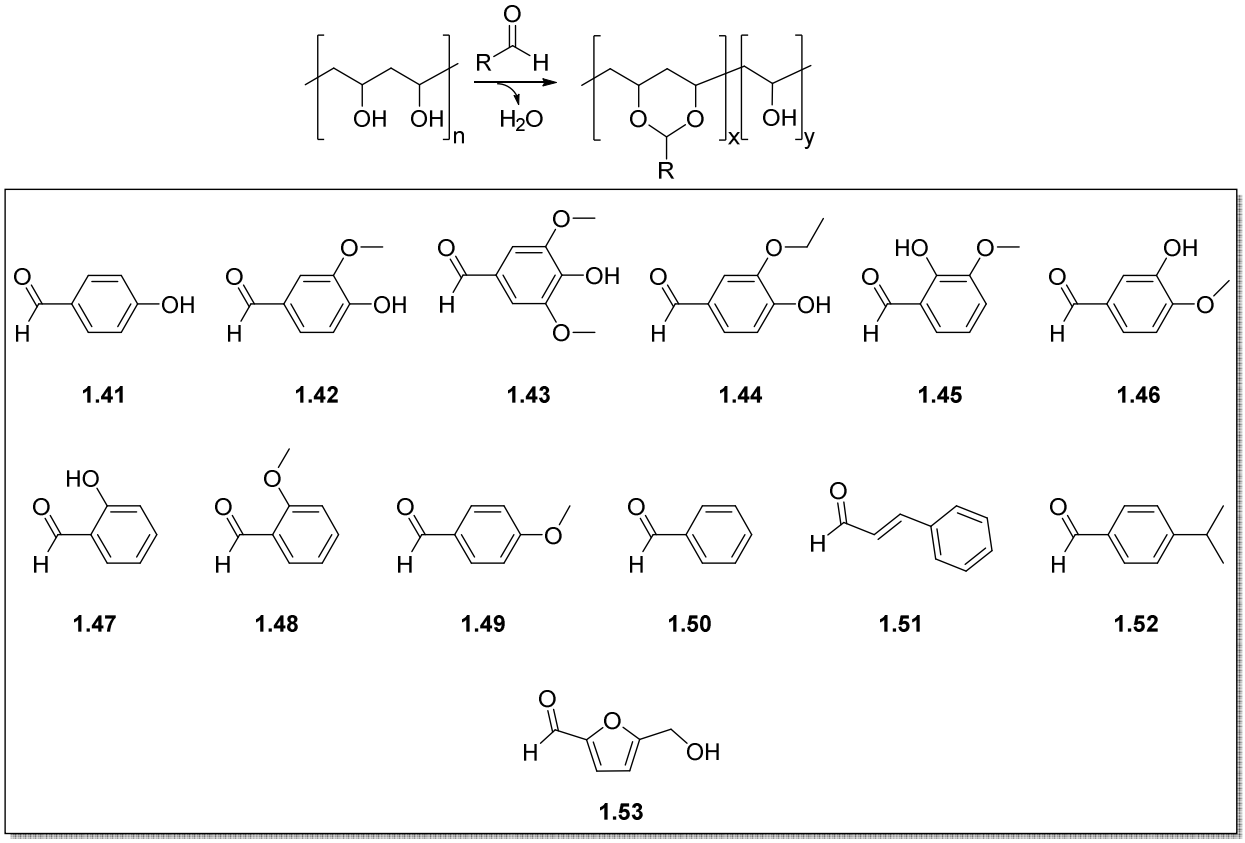
was less than 30%.[74] However, the thermal properties were shown to be tunable based on the chosen dialdehyde and amount of each tetraol used. Preliminary degradation studies showed that the monomer can be completely recovered in concentrated HCl within 24 hours. In addition, a long term study over one year showed that the polyacetals exposed to deionized, sea, or tap water and also pH=5 or pH=1 buffer can possess a long shelf life, as decomposition occurred only in the pH=1 solution.[74]

Akbulut et al.[75] reported the synthesis of a series of polyspiroacetals prepared from 1,4-cyclohexanedicarboxaldehyde with five different tetraols (Scheme 1.12). In addition, five model compounds were prepared using the same five tetraols with cyclohexanecarboxaldehyde. While the resultant model compounds were completely soluble in several common organic solvents, the corollary polymers were generally not soluble which is typical for polyspiroacetals. Polymers **1.37** – **1.39** are completely insoluble in common solvents and only slightly soluble upon heating in hexafluoroisopropanol (HFIP). However, **1.36** was slightly soluble upon heating in THF, DMSO, NMP, and DMF. This slight solubility was attributed to the presence of the hydroxyl group which promoted hydrogen bonding with those solvents. Polymer **1.40** was also slightly soluble upon heating in DMSO, NMP, and DMF. TGA analysis of the polymers thermal stability indicated that **1.39** exhibited the highest thermal stability which was attributed to its linear structure. The order of stability for the remaining polymers was **1.40** > **1.38** > **1.37** ≈ **1.36**.[75] All of the prepared polymers exhibited thermal stability with $T_{d,\,5\%}$ between 200 and 300 °C.[73, 75]



Scheme 1.12. Synthesis of Spirocyclic Acetals from 1,4-Cyclohexanedicarbaldehyde[75]

Polyvinyl alcohol (PVA) is a linear polymer which is prepared *via* the polymerization of vinyl acetate in methanol with subsequent hydrolysis using sodium hydroxide.[76] Each year, over 1.2 billion kg is produced annually.[76] However, PVA's T_g is 80 °C[77] and its derivatives polyvinyl formyl (PVF) and polyvinyl butyl (PVB) are 325 – 381 °C[78] and 62 – 78 °C,[76] respectively. As these structural modifications resulted in changes to both T_g as well as the polymer's properties, Rostagno et al.[76] studied the effect of the acetalization of polyvinyl alcohol using thirteen different bioaromatic aldehydes as shown in Scheme 1.13.



Scheme 1.13. Acetalation of PVA with Bioaromatic Aldehydes[76]

Aromatic aldehydes were chosen as aromatic components have been shown to increase the T_g due to quadrupolar interactions, pi stacking, and increased conformational barriers.[76] Two kinetic studies using vanillin (**1.42**) were performed which indicated that the optimal polymerization time is two hours, which was true for all the aldehydes except HMF and benzaldehyde which required six hours to complete. Polymers were obtained in low to good yields with a range of 31.1 – 84.6%.[76]

In all cases, the T_g of the resulting polymers was higher than that of PVA with an observed range of 114 – 157 °C.[76] Aldehydes which contained a hydroxyl exhibited higher T_g than those containing a methyl in the same location. For example, the polyacetal from **1.41** had a T_g of 157 °C, but **1.49** had a T_g of only 116 °C. Similarly, **1.47** had a T_g of 150 °C, whereas **1.48**

exhibited a T_g of 121 °C. The polyacetal obtained using **1.53** exhibited a T_g of 144 °C which was lower than **1.41** and **1.47**. This is attributed to the increase in free space lowering the T_g due to the hydroxyl pendent arm.[76]

The five polymers prepared from **1.48**, **1.49**, **1.50**, **1.51**, and **1.52** are incapable of forming hydrogen bonds, and thus their T_g are lower with a range of 116 – 137 °C.[76] Amongst these five, **1.52** exhibited the highest T_g due to its steric bulk limiting the percent of PVA acetalated which resulted in a larger degree of hydrogen bonding among the hydroxyls in the unreacted portions of PVA. Analysis of the degradation of the polymer prepared from **1.42** was performed using deionized and salt water and also aqueous buffer solutions with pH=1, 2, 3, or 5. At pH = 4, degradation back to PVA and **1.42** occurred in 48 hours. At pH = 2, degradation occurred 24 hours, and at pH = 1, degradation occurred in 2 hours. Therefore, in stomach acid of animals it should be able to decompose safely back into PVA and **1.42**.[76]

In conclusion, poly(cycloacetal)s and spirocyclic acetals have shown promising utility in commercial plastics as the increased rigidity of the polymer's backbone causes an enhanced T_g. In addition, the incorporation of the hydrolytic acetal groups allows for acid catalyzed degradation which has implications in industrial[74], environmental[72], and medical fields.[79, 80]

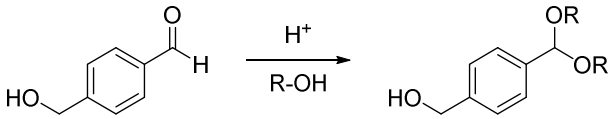
1.4.3. Utility of Aldehydes in the Synthesis of Dendrimers and Hyperbranched Polymers

The reactivity of aldehydes have also made it an attractive starting material for the synthesis of dendrimers and hyperbranched polymers. Dendrimers are defined as radially symmetric molecules that are nano-sized and exhibit a well-defined structure with homogenous branches that are similar in length.[81] Dendrimers are used in the synthesis of organic nanoparticles and nanotubes and also in molecular printboards and drug delivery systems.[82] In fact, dendrimers have been deemed as one of the most promising synthetic macromolecules for

biomedical applications, especially in the pharmaceutical field where it can be used as drug or gene carriers. [82] However, current utility in the clinic is less common than that of linear polymers. This is because most dendrimers are not biodegradable in vivo leading to accumulation which can cause side effects [82] Dendrimers containing acetal linkages on the other hand, exhibit controlled degradation which may enable them to remain stable in the blood but then release their payload when they enter an acidic environment of the targeted location.[82]

Hyperbranched polymers are a subclass of dendritic macromolecules.[83] They differ from dendrimers in that they contain dendritic and linear units that are randomly dispersed throughout the interior of the macromolecular unit and therefore exhibit irregular structures.[84] In hyperbranched polymers the large quantity of peripheral end-groups serve a dominant role in controlling the resulting solution and bulk properties.[85] Hyperbranched polymers have applications in polymeric, material, and biomedical sciences.[83] One area of research that is of interest is the synthesis of dendrimers and hyperbranched polymers capable of undergoing controlled degradation through hydrolyzable linkages.[82, 85]

Polymers containing acetal linkages have been shown to generate relatively benign products upon hydrolytic degradation. In 2011, Chatterjee and Ramakrishnan[85] reported the synthesis of hyperbranched polyacetals that exhibited tunable degradation rates. 4-hydroxymethylbenzaldehyde was acetalated using either methanol, butanol, or hexanol (Scheme 1.14) in an attempt to control the rate of degradation. The acetalated monomers were then polymerized to form a hyperbranched polyacetal via melt condensation at 100 °C using a mildly acidic catalyst.



R = Methyl (**1.54**), n-butyl (**1.55**), or n-hexyl (**1.56**)

Scheme 1.14. Synthesis of Monomers from 4-Hydroxymethylbenzaldehyde[85]

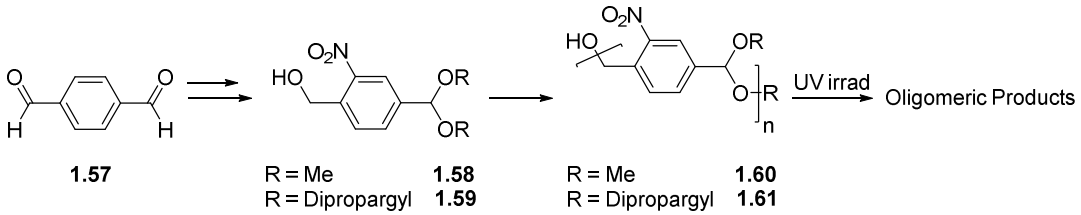
The hyperbranched polyacetal prepared from **1.54** appeared as an amorphous soft white solid with a molecular weight of approximately 21,000 and a PDI of 3.0. The hyperbranched polyacetal prepared from **1.54** exhibited rapid degradation that began slowly in the very early stages, indicating a short induction period.[85] The hyperbranched polyacetal prepared from **1.55** was a semi-solid with a molecular weight of 22,300. The hyperbranched polyacetal prepared from **1.56** was a highly viscous liquid with a molecular weight of 50,100.

Of the prepared polymers, the polyacetal containing **1.56** exhibited the longest induction time with no degradation after three days due to the hydrophobic hexyl groups providing a barrier to the aqueous acid. However, once the barrier was broken the polymer degraded at a similar rate as the butyl and methyl-substituted polymers. Because of this, hyperbranched polyacetals with tunable degradation may have utility as drug delivery agents.[85]

In addition to solubility, the peripheral group was shown to affect the T_g of the polymer with the T_g inversely related to the length of the alkyl peripheral group. Therefore, the polyacetal containing **1.54** had a T_g of 23.4 °C, the polyacetal containing **1.55** was 8.2 °C, and the polyacetal containing **1.56** was -3.6 °C. Consequently, the physical state of a material can be tailored by choosing appropriate functional groups for the peripheral groups.[85]

In 2013, Chatterjee and Ramakrishnan[86] furthered this work and reported the first synthesis of a photodegradable hyperbranched polyacetal that can be used as a positive photoresisist.[86] Compound **1.57** was converted into **1.58** in a six step process with an overall

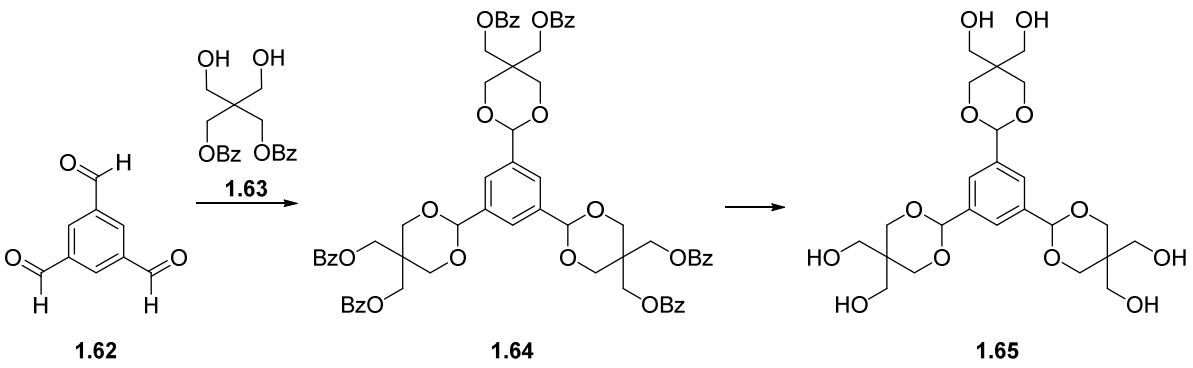
yield of 12% (Scheme 1.15). Compound **1.58** then underwent melt condensation resulting in polymer **1.60** which exhibited a molecular weight of approximately 11,800 as determined by GPC, a PDI of 2.9, and a T_g of approximately 22 °C. The degree of branching was determined by ^{1}H NMR to be approximately 51%.[86] Irradiation of the resultant polymer (**1.60**) with a 365 nm light source indicated that it could undergo pattern reproduction with micron level resolution.[86]



Scheme 1.15. Synthesis of a Photodegradable Hyperbranched Polyacetal[86]

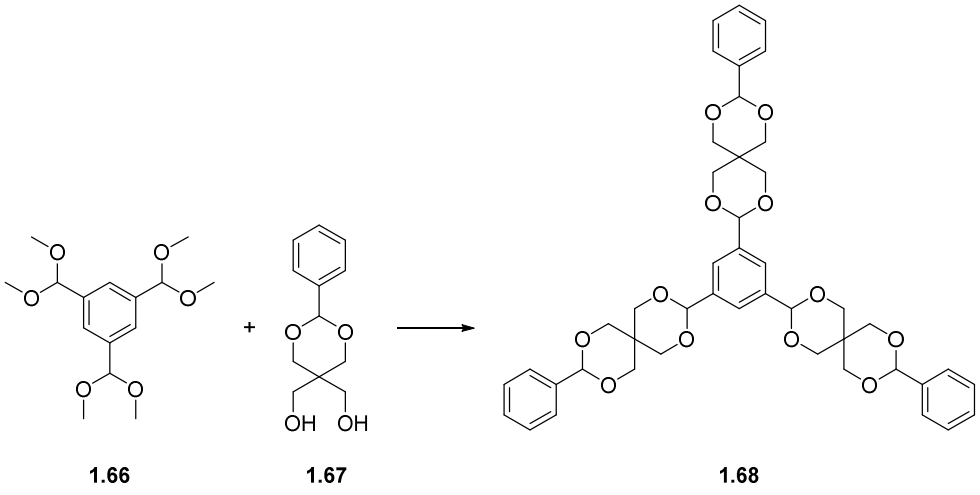
Compound **1.59** was similarly prepared from **1.57** with an overall 6% yield. Compound **1.59** then underwent melt polymerization to form **1.61** with a 66% yield. The resulting polymer **1.61** contained peripherally clickable propargyl units. Irradiation of **1.61** with a 365 nm light source indicated that the propargyl groups underwent interfacial click reactions, which indicates that the peripheral propargyl groups would be capable of undergoing other potentially useful surface modifications.[86]

In 2002, Lemcoff and Fuchs[87] reported the first synthesis of polyacetal dendrimers. Dibenzoylpentaerythritol (**1.63**) was chosen because it was found that the second acetalation of the monoaldehyde-monoacetal was not effective when using the non-protected pentaerythritol. This is due to the first acetal formed acting as a weak EDG, thus inhibiting the reaction. Reaction of **1.62** with **1.63** followed by subsequent deprotection by ammonolysis in methanol allowed for the formation of **1.65**, a first-generation dendrimer core (Scheme 1.16).[87]



Scheme 1.16. Synthesis of a First Generation Dendrimer Core[87]

It was discovered that benzaldehydes with EDG substituents will not induce transacetalation of benzylidenepentaerythritols; however benzaldehydes possessing EWG will induce transacetalation.[87] In addition, through a transacetalation model reaction (Scheme 1.17) it was found that transacetalation reactions occur readily as hydrolytically less stable acyclic acetals form the favored cyclic acetals. The resultant dendrimer **1.68** possesses three spiroundecane units and was expected to possess two diastereomeric forms. However, it was reported that both NMR and HPLC indicated only one diastereomeric product.[87]

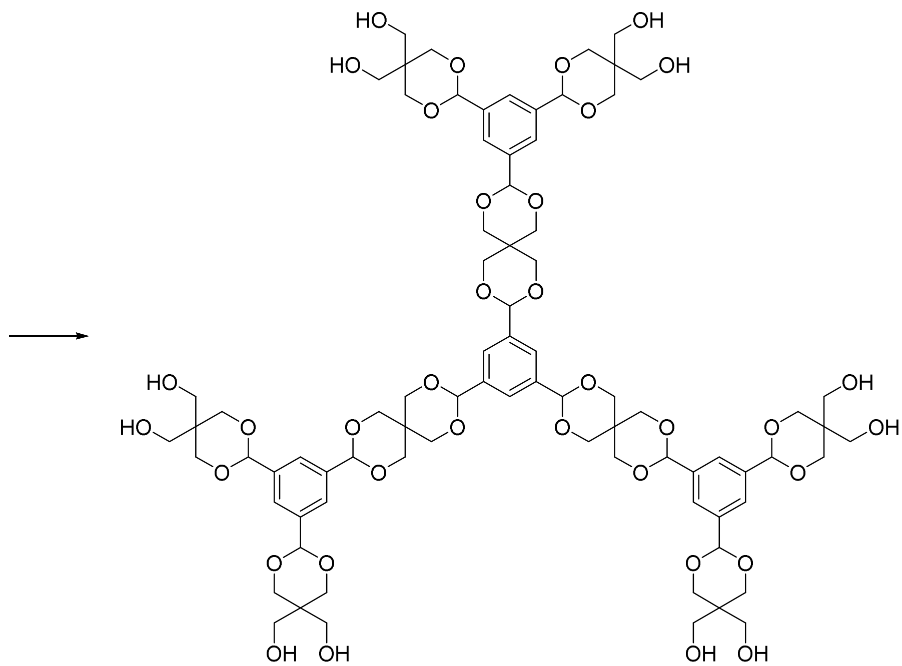


Scheme 1.17. Synthesis of a 2,4,8,10-Tetraoxaspiro[5,5]undecane Dendrimer[87]

To test the feasibility of creating higher generation dendrimers, **1.65** was reacted with **1.66** to yield **1.69** in a 57% yield.[87] An interesting note about **1.69** is all three of its dendronic

sidearms extend in the same direction above the central benzene core. This is attributed to efficient Π-stacking of the three aromatic rings and to the hydrogen bonding between the hydroxyl groups.[87]

1.65 + 1.66

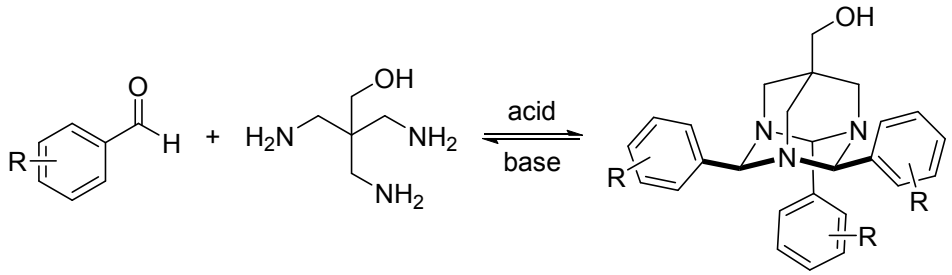


1.69

Scheme 1.18. Transacetalation of 1,3,5-Benzenetricarbaldehyde Hexamethylacetal[87]

Finally, **1.69** was further reacted with dimethylacetal which allowed for the formation of a quasi-2nd generation dendrimer which also exhibited all three of its dendronic sidearms extending in the same direction away from the benzene core.[87]

In 2009, Kohman and Zimmerman[82] reported the synthesis of dendrimers containing a degradable 1,3,5-triazaadamantane (TAA) at each branch point. The TAA unit was capable of undergoing pH dependent hydrolysis yielding the starting materials.[82] The rate of hydrolysis of TAA was previously shown to be dependent on the substitution of the aromatic rings; however an extensive study was not performed.[88]

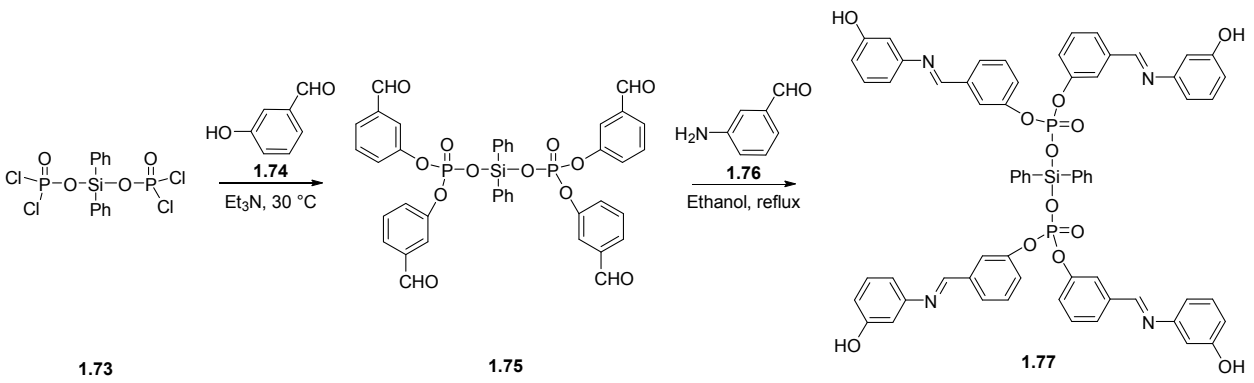


1.70 **1.71** **1.72**

Scheme 1.19. Synthesis and Degradation of 1,3,5-Triazaadamantane (TAA)[82]

The dendrimers were prepared using a divergent strategy[82] in which the synthesis started at the core and the arms were attached in a step-wise manner.[81] The prepared dendrimers were shown to be fully degradable *via* addition of HCl to a solution of dendrimer in THF-MeOH. The largest of the prepared dendrimers contained 39 TAA molecules with 81 functional groups[82] on its periphery and exhibited a molecular weight greater than 35 kDa. One key advantage of this procedure is that it allows for the incorporation of various TAA molecules that exhibit different rates of degradation allowing for control of both spatial and temporal degradation.[82]

In 2010, Dadapeer et al.[89] reported the synthesis and characterization of a dendrimer which contained a phosphorous and a diphenylsilanediol as the core unit. To achieve this goal, they chose to utilize the chemistry between amines and aldehydes. Therefore, each step was an alternating pattern of reacting either $POCl_3$ with a hydroxyl, **1.74** with a phosphorous chloride, or **1.76** with an aldehyde (Scheme 1.20). Although not illustrate, this sequential process of building the dendrimer (**1.78**), indicative of a divergent synthesis, was repeated twice. Through this method **1.78** was prepared with a molecular weight of 3039.8 in 5 steps (Figure 1.12) from **1.73**, which itself was prepared by condensing diphenyl silanol with $POCl_3$.



Scheme 1.20. Synthesis of the First Two Intermediates in the Synthesis of the Dendrimer[89]

Dendrimer **1.78** is stable up to 85 °C, with slight decomposition occurring when the temperature reaches 90 °C with a weight loss of ~ 4% which is attributed to loss of water. At 270 °C, the dendrimer further decomposes losing the 3-((4-hydroxyphenylimino)methylene)phenoxy groups which results in a weight loss of ~ 50%. The decomposition steps were determined to be endothermic with endotherms occurring at 90 °C (loss of water), 135 °C, 150 °C, 165 °C, (loss of dendrimeric branches) and 270 °C (loss of 3-((4-hydroxyphenylimino)methylene)phenoxy group).

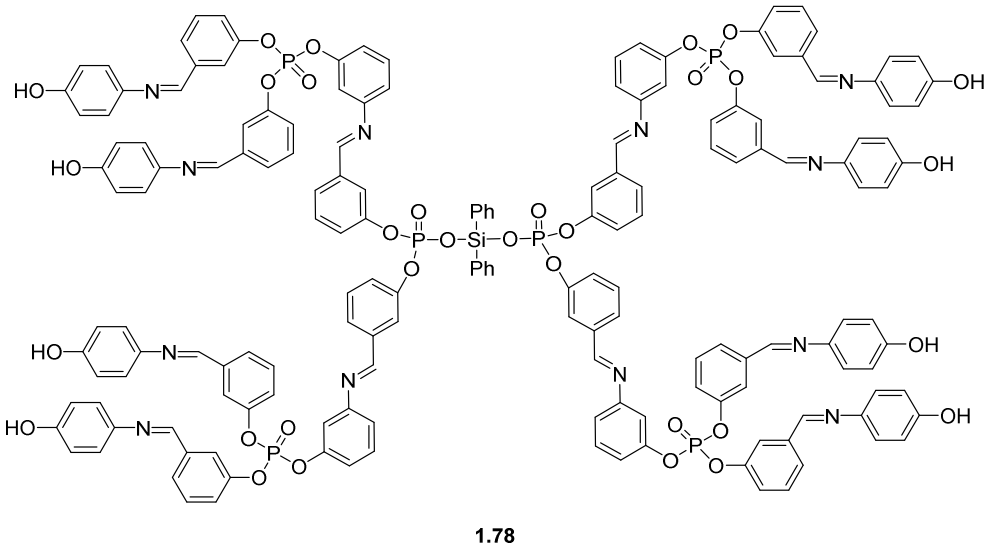
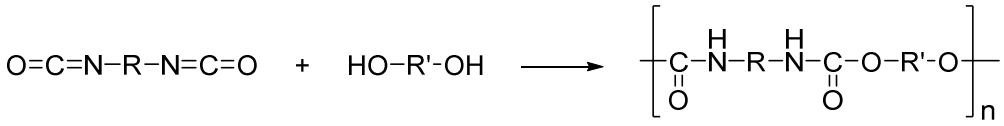


Figure 1.12. Final Phosphorous Containing Dendrimer[89]

In conclusion, due to their reactivity aldehydes have found utility in dendrimers and hyperbranched polymers. The incorporation of an acetal linkage allows for controlled degradation of the products which is of particular importance in the biomedical and pharmaceutical fields.[82]

1.4.4. Utility of Aldehydes in Polyurethane (PU) Coatings

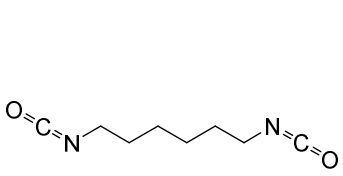
Polyurethanes were first reported in 1937 by Dr. Otto Bayer and coworkers. Since then they have found a wide variety of applications including fibers, foams, insulating materials, plastics, composites, films, sealants, adhesives, inks, and coatings.[90] While representing the smallest percentage of PU applications, the market for PU resins for coatings, adhesives, and sealants is vast with 2200 kilotons produced in 2016, a market totaling approximately $7.9 billion.[90] Traditionally, polyurethanes are prepared by reacting a polyisocyanate with a polyol. The reaction between a diisocyanate and a diol results in the formation of a linear polyurethane. (Scheme 1.21).



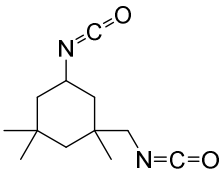
Scheme 1.21. Synthesis of Polyurethane via Reaction Between a Diisocyanate and a Diol

The most commonly used diisocyanates are illustrated in Figure 1.12.[91] The aliphatic diisocyanates are hexamethylene diisocyanate (HDI, **1.79**), isophorone diisocyanate (IPDI, **1.80**) and 4,4′-methylenebis(cyclohexyl isocyanate) (H_{12}MDI, **1.81**). The aromatic diisocyanates include 2,6-toluene diisocyanate (2,6-TDI, **1.82**) 4,4′-diphenylmethane diisocyanate (4,4′-MDI, **1.83**), 2,4-toluene diisocyanate (2,4-TDI, **1.84**), 2,4-diphenylmethane diisocyanate (2,4-MDI, **1.85**), and polymeric MDI(PMDI, **1.86**).[91]

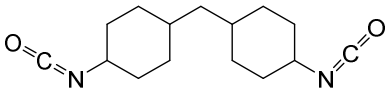
a) Aliphatic Diisocyanates



1.79

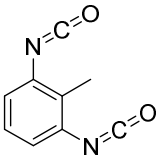


1.80

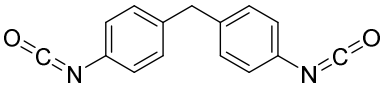


1.81

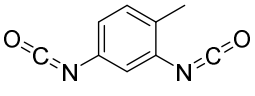
b) Aromatic Diisocyanates and Polymeric Isocyanate



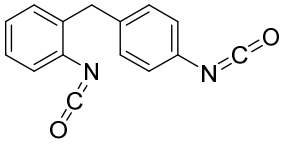
1.82



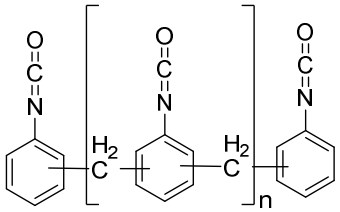
1.83



1.84



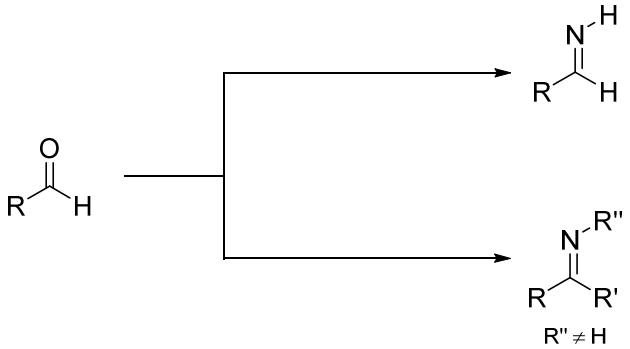
1.85



1.86

Figure 1.13. Commonly Used Diisocyanates and Polyisocyanate[91]

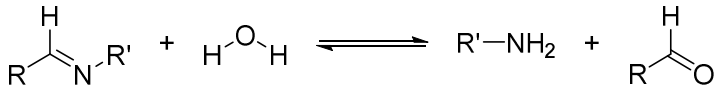
While aldehydes are not typically used directly in polyurethane coatings, adhesives, and sealants they are used in the synthesis of some of their components such as primary aldimines and Schiff bases (secondary aldimines).



Scheme 1.22. Conversion of Aldehydes into Aldimines and Schiff Bases

The synthesis and chemistry of aldimines has previously been reviewed by Layer.[92] Aldimines are classified as compounds in which R is either an alkyl or aryl and R' is a hydrogen (Scheme 1.11). Aldimines are prepared by nucleophilic addition of an aldehyde to an amine, followed by elimination of water. The dipole moment of the C=N bond for aliphatic aldimines is 1.4 D, which is less than that for the carbonyl bond of aldehydes (2.5 D).[92] In addition, aldimines exhibit greater steric hindrance than aldehydes.[93] Due to the decreased electronegativity and increased steric hindrance, they are less likely to undergo nucleophilic addition.[93] Their synthesis from aldehydes and amines was first reported in 1864 by Dr. Hugo Schiff; subsequently, secondary aldimines are typically referred to as Schiff bases.[92]

Upon contact with atmospheric moisture, hydrolysis of the aldimine results in the formation of the constituent aldehyde and amine (Scheme 1.23).[94] The resulting amine is then capable of reacting spontaneously with aliphatic polyisocyanates while preventing the hydrolysis of the isocyanates, thus reducing the risk of forming CO_2 and urea.[95] However, this technique does not generally apply to aromatic isocyanates since they are more reactive.[95]



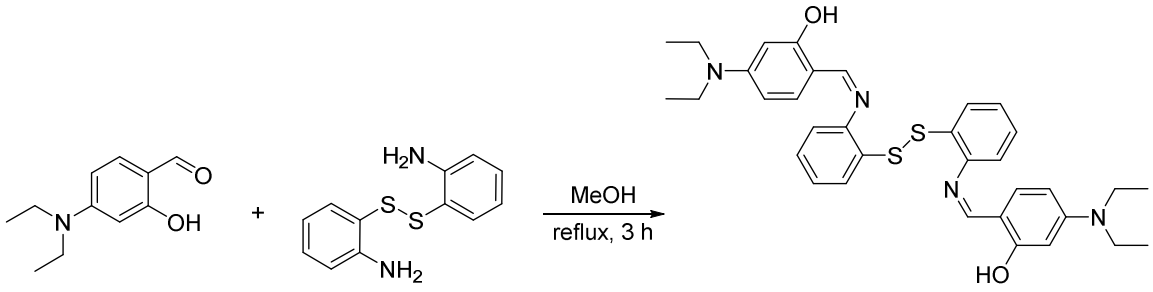
Scheme 1.23. Conversion of Aldimines into Constituent Aldehyde and Amine[94]

Elchueva et al.[96] reported the utility of aldimines and Schiff bases as cross-linking agents in the synthesis of single-component urethane sealants. The four diamines used (ethylenediamine, hexamethylenediamine, phenylenediamine, and diaminodiphenylmethane) were each reacted with the three dialdehydes (benzaldehyde, nitrobenzaldehyde, and furfural). Curing time was found to be dependent on the structure of the aldimine with decreased time required when EWG were incorporated at the *para* position of benzaldehyde. In addition, the

strength of the sealants was dictated by whether aromatic or aliphatic imines were utilized, with aromatic imines yielding a stronger product due to the incorporation of the aromatic ring into the polymer structure.[96]

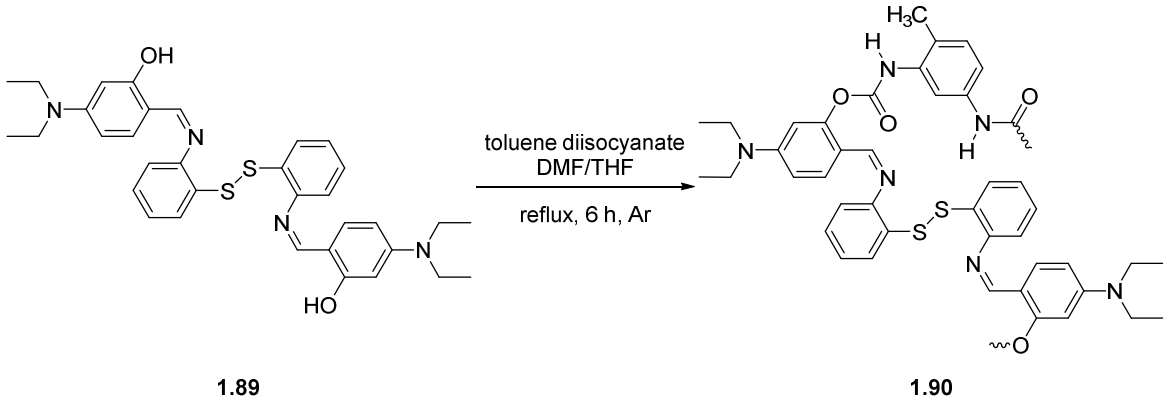
In 2015, Kamaci and Kaya[97] reported the synthesis of a poly(azomethine-urethane) (PAMU) which could be used as a fluorescence probe to identify the presence of transition metal ions such as Cd^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+}, Zn^{2+}, and Cr^{3+}. This ability to detect the transition metals is due to the presence of the azomethine ligand which exhibits a strong affinity for transition metal ions due to the nitrogen atom and its special coordination ability with the transition metal ions.[97]

In particular, the utility of the prepared polymer as a fluorescent probe for the selective identification of Zn^{2+} was studied.[97] Zn^{2+} is found naturally in biological and environmental systems, however, excessive amounts can result in acute or chronic toxicity in animals and/or lower soil microbial activity in the environment. As Cd^{2+} has similar coordination properties and is also a Group IIB element with a d^{10} electronic structure, it is often difficult to distinguish between the two metal ions with a fluorescent probe. However, the prepared polymer was able to distinguish between the two ions.[97]



1.87 **1.88** **1.89**

Scheme 1.24. Condensation of 4-(Diethylamino)salicylaldehyde with 2,2′-Dithiodianiline[97]

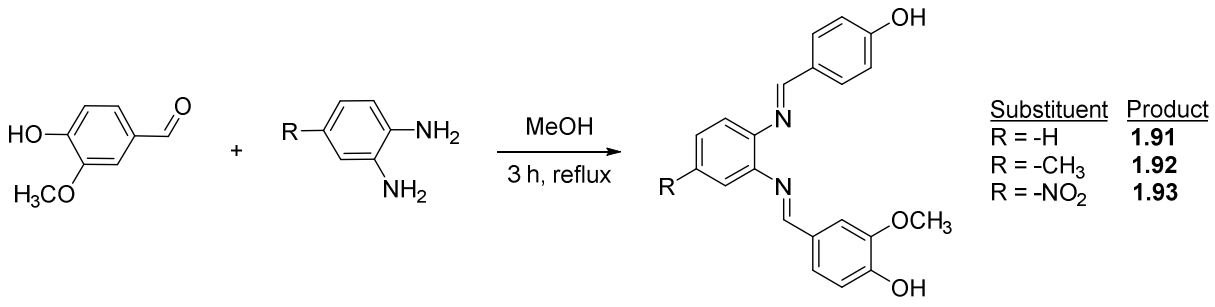


1.89 **1.90**

Scheme 1.25. Step Polymerization of Prepared Schiff Base[97]

Polymer **1.90** was obtained in 79% yield, had a number-average molecular weight (M_n) of 21,600 g/mol, a molecular weight of 39,800 g/mol, and a polydispersion index of 1.843. Studying the solvent effect, the polymer exhibited the highest emission intensity and Stoke shift value in THF indicating that it would be the best solvent for the fluorescence sensor as the Stoke shift value is inversely related to the background signal noise. The prepared polymer was shown to be capable of distinguishing between Zn^{2+} and Cd^{2+}. The detection limit for the proposed fluorescent sensor was determined to be 3.06×10^{-4} mol/L.[97]

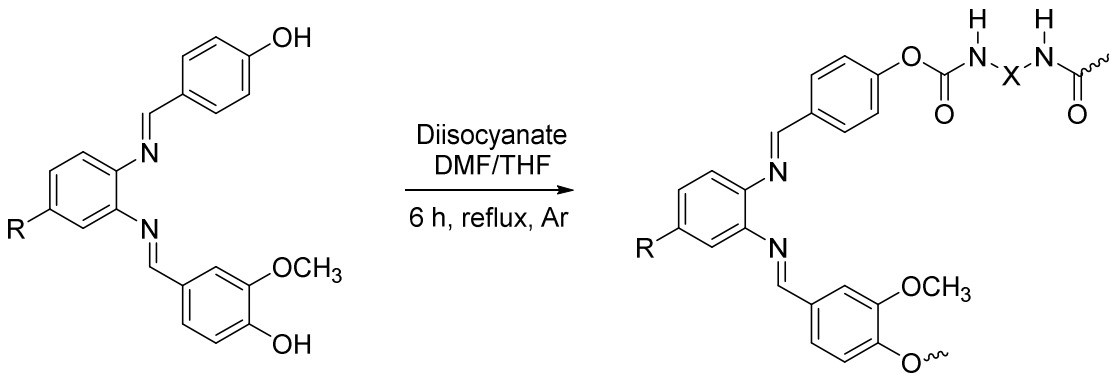
Later, in 2016 Kamaci and Kaya[98] reported the synthesis of a series of low-band gap polyurethanes along with their photophysical, electrochemical, thermal and morphological properties. The series of Schiff bases were prepared via a condensation reaction between vanillin and three different diamines with substituents representing EWG and EDG.[98]



Substituent	Product
R = -H	**1.91**
R = $-CH_3$	**1.92**
R = $-NO_2$	**1.93**

Scheme 1.26. Condensation of Vanillin with Diamines[98]

Each Schiff base was then polymerized with both an aliphatic (HDI, **1.79**) and then an aromatic diisocyanate (TDI, **1.82**) to form a set of six PAMU derivatives using step-polymerization. The prepared PAMUs were washed with MeOH and MeCN to remove any unreacted material and dried under vacuum at 75 °C for 24 h.[98]



Substituent	SM	X	Product
R = -H	**1.91**	TDI	**1.94 a**
R = -CH_3	**1.92**	TDI	**1.95 a**
R = -NO_2	**1.93**	TDI	**1.96 a**
R = -H	**1.91**	HDI	**1.94 b**
R = -CH_3	**1.92**	HDI	**1.95 b**
R = -NO_2	**1.93**	HDI	**1.96 b**

Scheme 1.27. Step-Polymerization of Prepared Schiff Bases[98]

The reported yields and physical properties such as color, number-average molecular weight (M_n), optical band gap (E_g), electrochemical energy band gap (E'_g), char yield, glass transition temperature (T_g), and melting point (T_m) of the prepared polyurethanes are listed in Table 1.2.

As shown, the polymers prepared from HDI (**1.94b** – **1.96b**) had higher average molecular weights than those obtained from TDI (**1.94a** – **1.96a**). In addition, **1.96a** and **1.96b** exhibited the lowest optical activity in each series. This is due to the electron withdrawing nitro group at the meta- and ortho- positions of the imine linkage which decreases the electron density. The prepared polyurethanes possessed electrochemical energy band gaps that were lower than

2.0 eV. This indicates they can potentially be used in heterojunction solar cells. The reported char yield for the TDI series was higher than that for the HDI series as the TDI polyurethanes are completely aromatic in nature, whereas the HDI series consist of aliphatic and aromatic groups.[98]

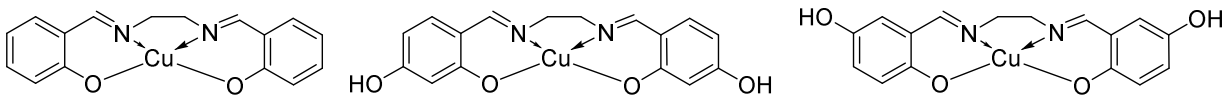
Table 1.2. Properties of Polymers Prepared from Schiff Bases and Diisocyanate[98]

SM	X	Product	Yield[a] (%)	Color	M_n (g/mol)	E_g (eV)	E'_g (eV)	Char Yield (%)	T_g[b] (°C)	T_m (°C)
1.91	TDI	**1.94 a**	65	Dark Red	6400	3.45	1.71	17.30	88	342
1.92	TDI	**1.95 a**	64	Dark Red	7900	3.54	1.67	41.20	125	373
1.93	TDI	**1.96 a**	68	Dark Red	7350	2.98	1.86	41.50	117	390
1.91	HDI	**1.94 b**	78	Dark Brown	9060	3.42	1.64	10.90	141	357
1.92	HDI	**1.95 b**	71	Yellow	9580	2.95	1.77	14.00	173	382
1.93	HDI	**1.96 b**	68	Yellow	10640	2.90	1.98	10.00	120	355

a) Isolated Yields b) Obtained using DSC

Overall, the T_g for the polymers prepared from HDI were higher than those prepared from TDI. It should be noted that the T_g was also obtained using DMA analysis with reported temperatures exhibiting slight variations. This was attributed to DMA analysis measuring the change in mechanical response of the polymer chains; whereas, DSC measures the change in heat capacity from frozen to unfrozen chains. The T_m for the two series was relatively similar with a range of 342 – 390 °C for the TDI series and 355 – 382 °C for the HDI series.[98]

Recently, Naik et al.[99] reported the utility of three copper complexed *salen*-based Schiff bases as fire protective agents for thermoplastic polyurethanes. The three *salen*-based Schiff bases were *N,N′*-bis(salicylidene)ethylenediamine (**1.97**), *N,N′*-bis(4-hydroxysalicylidene)-ethylenediamine (**1.98**), and *N,N′*-bis(5-hydroxysalicylidene)ethylenediamine (**1.99**).[99]



1.97 **1.98** **1.99**

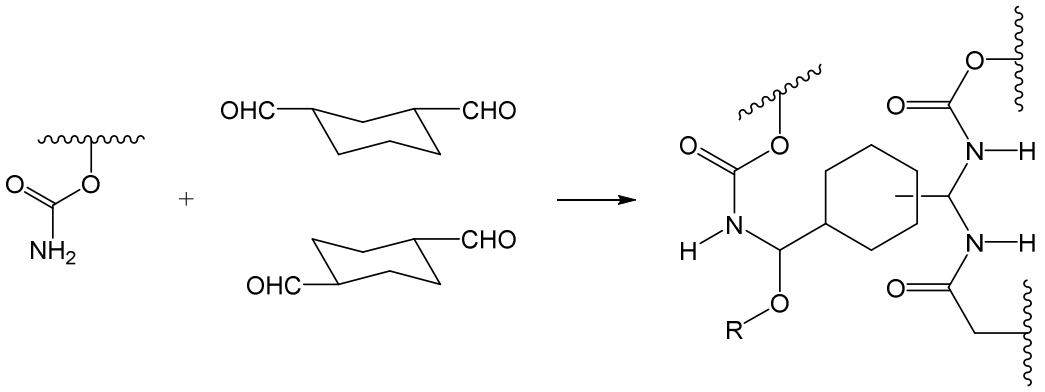
Figure 1.14. Prepared Cu-*Salen* Complexes[99]

The prepared Schiff base-*Salen* complexes were added to the thermoplastic polyurethane (TPU) elastomer Elastollan with 10% loading and the resultant properties were compared to the original TPU. In each instance, the polymer matrix was found to be unaltered by the addition of the *salen* complex; however, the *salen* complex's geometry around the copper was modified and the hydrogen bonding with the matrix was realigned as it underwent loss of coordinated water molecules due to high processing temperatures.[99]

TPU exhibited a time to ignition of 65 seconds. However, the addition of **1.97** resulted in a decrease in the time of ignition at 50 seconds; while **1.98** resulted in an increase to 75 seconds. The increase in ignition time for **1.98** has been attributed to char formation. The addition of **1.99** to the TPU resulted in the greatest increase of time to ignition, with a gain of 65 seconds to 110 seconds respectively. This increase in time is due to **1.99** exhibiting flame retardancy through intumescence. In addition, the addition of **1.99** resulted in a 50% reduction in the peak heat release rate, which taken with the delay in time of ignition makes it a suitable flame retardant for the TPU.[99]

Another utility of aldehydes in polyurethanes is in the synthesis of non-isocyanate polyurethanes (NIPUs). As previously mentioned, polyurethanes are typically produced by the reaction of a diisocyanate and a diol. However, as diisocyanates exhibit problems with toxicity and moisture sensitivity during synthesis and application, research has shifted its focus to the synthesis of NIPUs.

In 2015, the DOW company reported the synthesis of a NIPU which utilized a polycarbamate and either 1,3- or 1,4-cyclohexanedicarboxaldehyde (Scheme 1.28).[100, 101] The incorporation of a primary alcohol (either methanol or ethanol) as a cosolvent allows for an increased pot-life without affecting the cure rate or hardness. This is due to the formation of acetal protecting groups which inhibit the reaction. Upon application, the alcohol evaporates leaving the aldehydes free to undergo rapid cross-linking with the polycarbamate.[101] When the prepared coatings were compared to an isocyanate control, the gloss and color retention were found to be comparable or enhanced for the polycarbamate coating.[101] In addition, it exhibited a shorter sand time (40 min) when compared to the control (180 min). Solvent resistance was measured using the standard procedure of methyl ethyl ketone (MEK) double rubs (rubbing forward and backward). The MEK double rubs reached over 100 after 24 h and over 200 after 7 days. This technology exhibits important applications as it will allow for ambient temperature application and a faster turn-around in industrial coatings.[101]



Scheme 1.28. Synthesis of NIPUs using Polycarbamate and Cyclohexanedicarboxaldehyde[100, 101]

As illustrated *vide supra*, aldehydes have found utility in polyurethanes through the synthesis of aldimines and Schiff bases as well as for cross-linkers with polycarbamates. The scope for polycarbamate chemistry is vast as there is a wide range of polyols and the urea

feedstock is economical; however, one of the key limitations is the finite number of polyaldehydes.[102] Therefore, future studies about the synthesis of novel polyaldehydes which can be utilized for polyurethanes are needed.

1.5. Conclusions

In conclusion, aldehydes can be prepared in a vast number of ways. This review looked at recent advances in the synthetic methodology of aldehydes *via* catalytic, enzymatic, and metal free methods, and also at the utility of aldehydes in polymer science. As aldehydes exhibit higher reactivity and undergo functional group transformations with relative ease, they have found utility in a wide range of polymers including polyaldehydes, polycycloacetals, dendrimers and hyperbranched polymers, and polyurethanes. In addition, due to the pH instability of the acetal bond, the incorporation of acetal groups increases the degradability of the polymers. While polyaldehydes exhibit low T_c, this makes them suitable for materials such as transient electronics and self-immolative polymers. The synthesis and properties of poly(cycloacetals) are currently being studied for their utility in industrial applications due to their potential for degradability. Dendrimers and hyperbranched polymers have found utility in medicine and industry. Finally, polyurethanes are used in many applications. The synthesis of NIPUs at room temperature using cyclohexanedicarboxaldehydes and polycarbamates as reported by Dow Chemical opens up a novel way to prepare NIPU's with greater applicability as high temperatures are not required to drive the reaction forward.

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CHAPTER 2. SYNTHESIS OF NOVEL BIO-DERIVED DIALDEHYDES

2.1. Introduction

As illustrated in chapter 1, aldehydes and polyaldehydes have a vast range of applications, however, the scope of available bio-derived polyaldehydes is limited. Those reported in literature are illustrated in Figure 2.1.

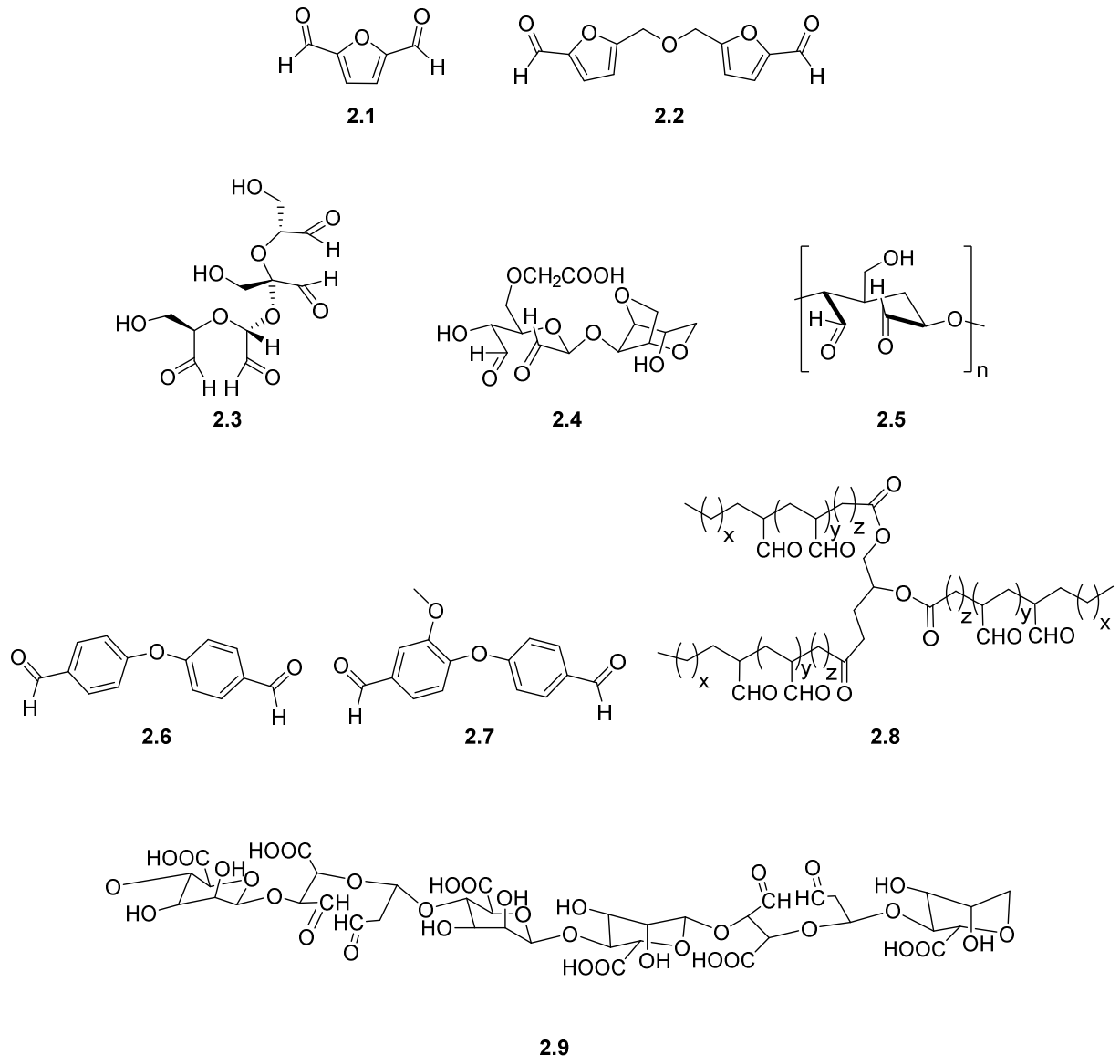


Figure 2.1. Polyaldehydes Currently Reported in the Literature[1-5]

Compounds **2.1-2.2** have been prepared from 5-hydroxymethylfurfural and have found applications in polymer synthesis[1-5]. Compound **2.3** was prepared via oxidation of sucrose and has been utilized as a cross-linker in starch films.[6] Compound **2.4** was prepared from carboxymethylagarose obtained from seaweed and was reported to be a viable alternative for formaldehyde for protein binding applications.[7] Compound **2.5** was prepared via sodium periodate oxidation of microcrystalline cellulose and has been used in the preparation of fine films.[8] Compounds **2.6** and **2.7** were prepared from 4-hydroxybenzaldehyde or vanillin, respectively, and was used in the preparation of formaldehyde-free phenolic resins.[9] Several vegetable oils have been hydroformylated to yield polyaldehydes (**2.8**) which has been previously reviewed.[10] Compound **2.9** was prepared through the sodium periodate oxidation of sodium alginate and has been used as a dialdehyde cross-linker with casein in hydrogel synthesis.[11]

The variability in structures of the reported bio-derived polyaldehydes limits the ability to selectively tune the properties of the resultant polymers. Therefore, the goal of this project was to expand the scope of available bio-based dialdehydes by creating a series of bio-based bis- and tris-furan dialdehydes with tunable properties based on the linkage unit.

To the authors' knowledge no study has been reported which addresses the effect of the linkage unit in bis- or tris-furan dialdehydes in polymer synthesis; however, previous literature studies have reported the ability to tune the properties of polymers prepared from bis-furan diamines through varying the structure of the spacer. Hu et al.[12] reported that the addition of the methyl group of 5,5-ethylidenedifurfurylamine resulted in a higher T_g when compared to 5,5'-methylenedifurfurylamine.[12] However, the effect of other spacer units has not been systematically studied. In addition, it has been reported that the length and molecular weight of

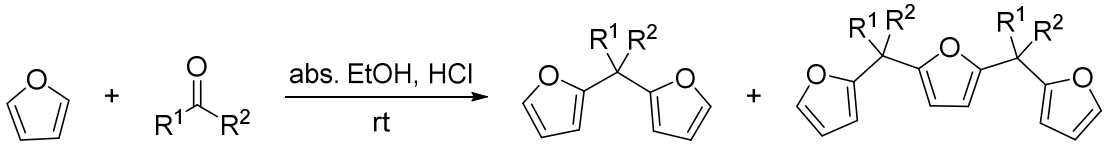
the cross-linker affects the properties of the polymer. For example, Allen and Ishida[13] have reported that the length of aliphatic diamines affects properties such as room temperature modulus, T_g, cross-link density, thermal degradation, and char yield in polybenzoxazine resins.[13]

Herein, we report a series of bio-based dialdehydes prepared from bis-furans and tris-furans with different spacers. The dialdehydes will be tested by our collaborators for their use in polyurethane synthesis.

2.2. Results and Discussion

Through an acid catalyzed condensation of carbonyl compounds with furan, a series of bis- and tris-furan compounds were prepared following literature precedence (Table 2.1).[14-19] Other synthetic methods have been reported in the preparation of bis-furan dialdehydes from furanic compounds[20, 21]; however, these methods do not allow the tris-furan dialdehydes to be prepared *via* the same conditions.

Table 2.1. Condensation of Furan with Ketones



2.10-2.13 a **2.10-2.13 b**

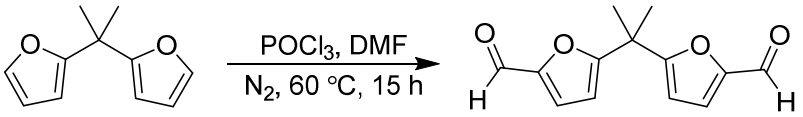
Entry	R_1, R_2	Product	Yield, %[a]	Product	Yield, %[a]
1	$R^1 = R^2 = Me$	**2.10a**	20	**2.10b**	15
2	$R^1, R^2 = -(CH_2)_5-$	**2.11a**	14	**2.11b**	4
3	$R^1 = Me, R^2 = Et$	**2.12a**	6	**2.12b**	11
4	$R^1 = R^2 = Et$	**2.13a**	8	**2.13b**	--

[a] Isolated Yields

The prepared bis- and tris-furan compounds were analyzed via ^1H NMR, ^{13}C NMR, and IR. However, with the exception of compound **2.11b**, we were unable to obtain the molecular

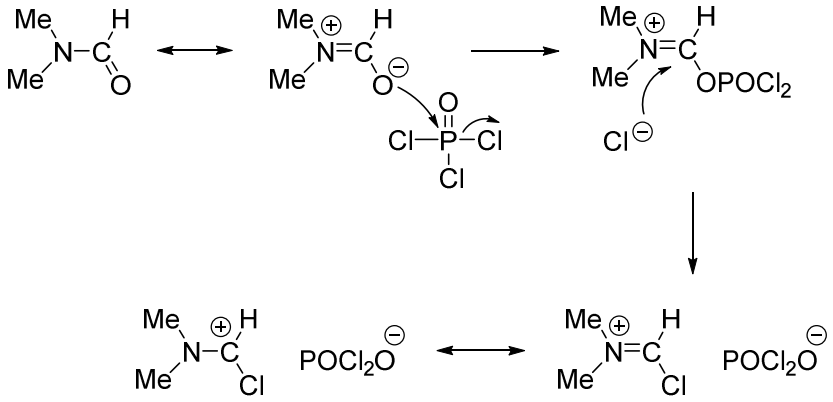
mass using HRMS. We suggest that the furan polymerizes during the mass determination as the same high molecular weights were observed irrespective of the compound.

The prepared bis- and tris-furan compounds were formylated *via* the Vilsmeier-Haack reaction following literature precedence (Scheme 2.1).[17, 22]



Scheme 2.1. Formylation of Bis-furan via Vilsmeier-Haack Reaction

The Vilsmeier-Haack reaction was first reported in 1927 by Dr. Anton Vilsmeier and Dr. Albrecht Haack and has been extensively reviewed.[23-28] In the Vilsmeier-Haack reaction an inorganic acid halide (in this case phosphoryl chloride) reacts with a disubstituted amide (N,N-dimethylformamide, DMF) resulting in the formation of the active complex (a halomethyleniminium salt) which is commonly known as the Vilsmeier reagent.[23] The reported mechanism for the formation of the Vilsmeier reagent is shown in Scheme 2.2.[23]

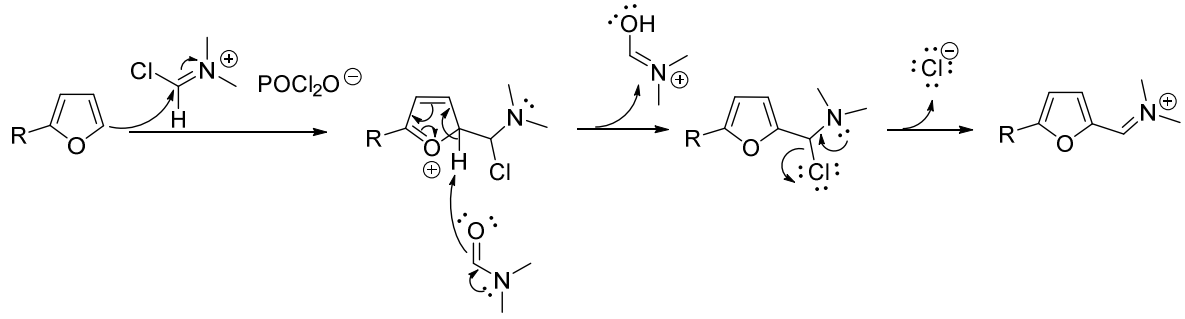


Scheme 2.2. Formation of the Vilsmeier Reagent from DMF and Phosphoryl Chloride[23]

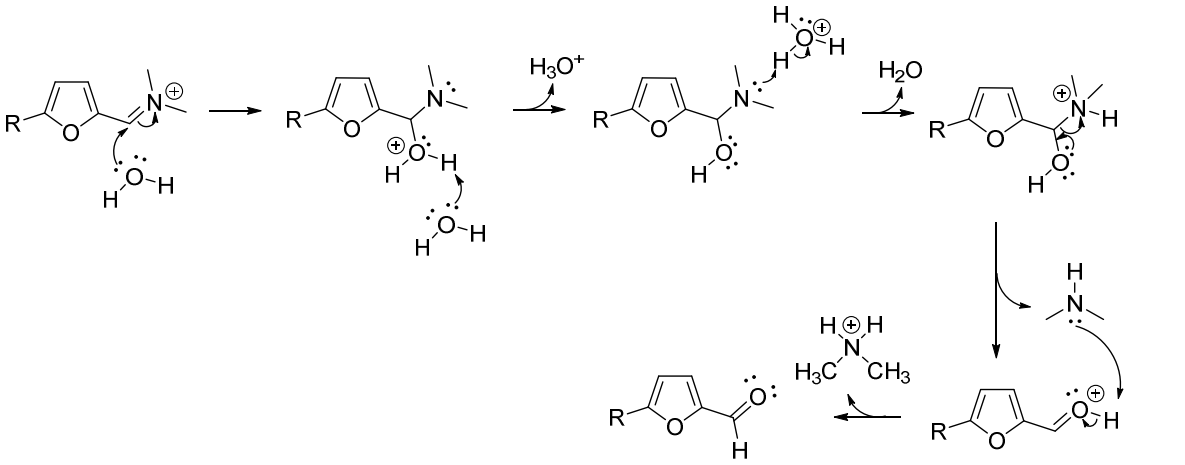
The Vilsmeier reagent prepared in situ is then capable of formylating the electron rich aromatic furan rings *via* the following mechanism (Scheme 2.3).[29] In the first part of the mechanism, the electron rich aromatic furan ring attacks the iminium ion of the Vilsmeier

reagent leading to the formation of an iminium intermediate. The desired aldehydes are then obtained upon aqueous workup.[29]

a) Formation of iminium ion



b) Hydrolysis of iminium ion upon aqueous workup



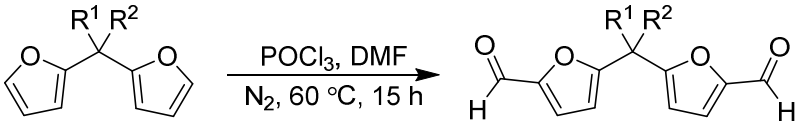
Scheme 2.3. Mechanism for the Formylation of Furanic Compounds Using Vilsmeier Reagent[29]

The prepared dialdehydes were obtained in good to fair yields (Table 2.2). The lower yields of **2.16** and **2.17** may be attributed to the hydrolysis of the $POCl_3$ into phosphoric acid. Therefore, future work should include the synthesis of **2.16** and **2.17** with freshly distilled $POCl_3$.

The regioselectivity of the formylation is controlled as furans preferentially undergo electrophilic aromatic substitutions (such as formylation) at the 2 and 5 (α) positions. This is because the resulting sigma complex is more stable as there are three possible resonance

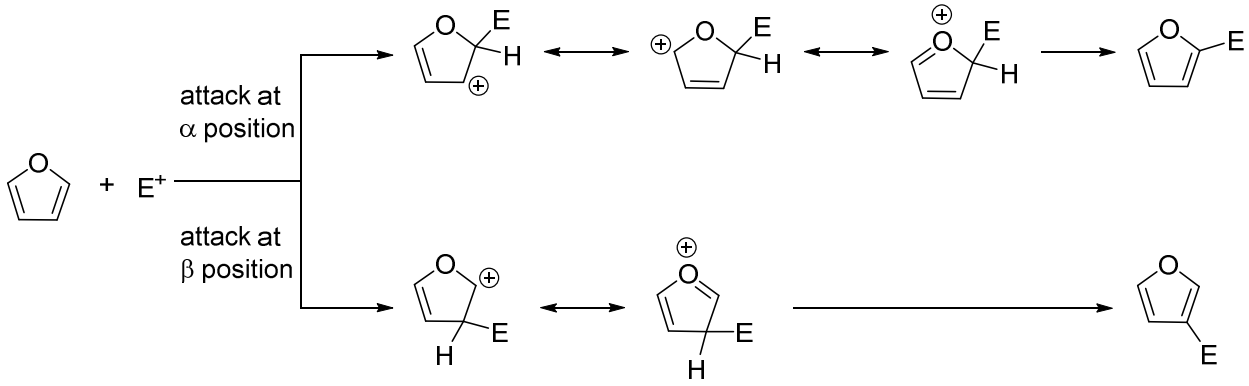
structures, whereas there are only two potential resonance structures when bonded at the 3-position (β) (Scheme 2.4).[30]

Table 2.2. Formylation of Prepared Bis-furans via Vilsmeier-Haack Reaction



Entry	R_1, R_2	SM	Product	Yield, %[a]	mp, °C[b]
1	$R^1 = R^2 = Me$	**2.10a**	**2.14**	96	90.2 – 91.5
2	R^1, $R^2 = -(CH_2)_5-$	**2.11a**	**2.15**	91	152.0 – 153.8
3	$R^1 = Me$, $R^2 = Et$	**2.12a**	**2.16**	71	69.5 – 71.4
4	$R^1 = R^2 = Et$	**2.13a**	**2.17**	53	87.5 – 89.5

[a)]Isolated Yields; [b]mp's obtained using REACH Devices RD-MP digital melting point apparatus and have not been corrected



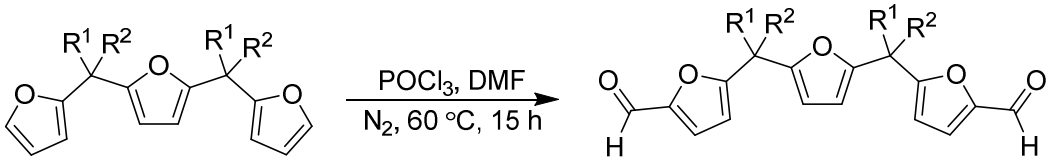
Scheme 2.4. Stability of Sigma Complex from Electrophilic Aromatic Substitution[30]

As illustrated in Table 2.2, the melting points of the prepared dialdehydes varied based on the spacer unit with symmetrical molecules exhibiting higher melting points than unsymmetrical molecules. The monomer possessing the rigid cyclohexyl spacer unit exhibited the highest

melting point of 152.0 -153.8 °C. This is in accordance with literature which indicates rigid molecules containing cyclic structures exhibit higher melting points than those that do not.[31]

The yields and melting points of the tris-furan dialdehydes are illustrated in Table 2.3. As indicated the tris-furan dialdehydes were also obtained in good yields. The melting point of the tris-furan **2.18** (Table 2.3) was slightly lower than that of the bis-furan **2.14** (Table 2.2). However, the melting point of the tris-furan **2.19** was approximately the same as that for the bis-furan **2.15**. Therefore, the lower melting point for **2.18** could be attributed to the increased structural flexibility due to the presence of the two spacer units.

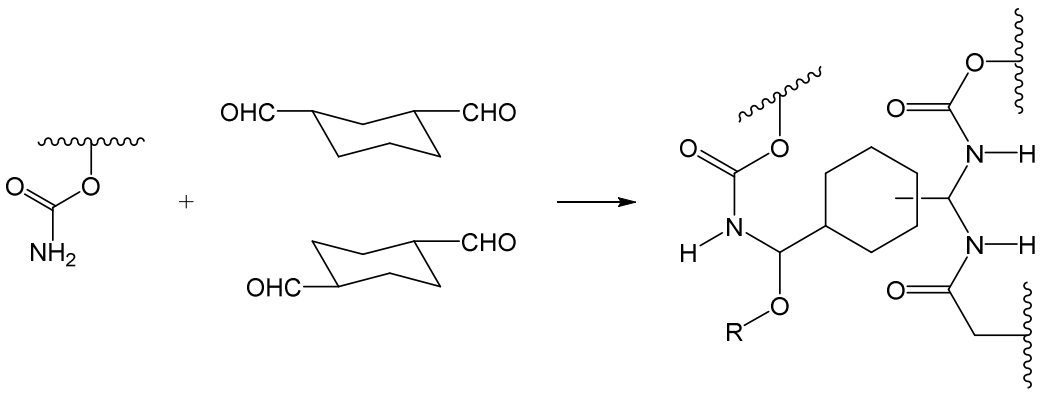
Table 2.3. Formylation of Prepared Tris-furans via Vilsmeier-Haack Reaction



Entry	R_1, R_2	SM	Product	Yield, %[a]	mp, °C[b]
1	$R^1 = R^2 = Me$	**2.10b**	**2.18**	74	82.5 – 85.8
2	R^1, $R^2 = -(CH_2)_5-$	**2.11b**	**2.19**	90	152.0 – 154.6

[a)]Isolated Yields; [b]mp's obtained using REACH Devices RD-MP digital melting point apparatus and have not been corrected

As mentioned *vide supra*, one potential application for the prepared dialdehydes is to serve as cross-linkers in polyurethane synthesis. In 2015, the DOW Company reported the synthesis of a NIPU which could react at room temperature. The reported NIPU utilized a polycarbamate and a mixture of 1,3- and 1,4-cyclohexanedicarboxaldehyde as the cross-linker (Scheme 2.5).[32, 33]



Scheme 2.5. Reported NIPU Synthesis via a Polycarbamate and Cyclohexanedialdehydes[32, 33]

As Sonnenschein[34] previously reported, one of the key limitations for the expansion of polycarbamate chemistry is the limited availability of polyaldehydes.[34] Therefore, this series of dialdehydes expands the scope of available biobased dialdehydes which can be used as cross-linkers for polyurethane synthesis. In addition, the prepared bis- and tris-furan dialdehydes can easily undergo functional group transformations and be utilized in a variety of other applications as shown in Figure 2.2.

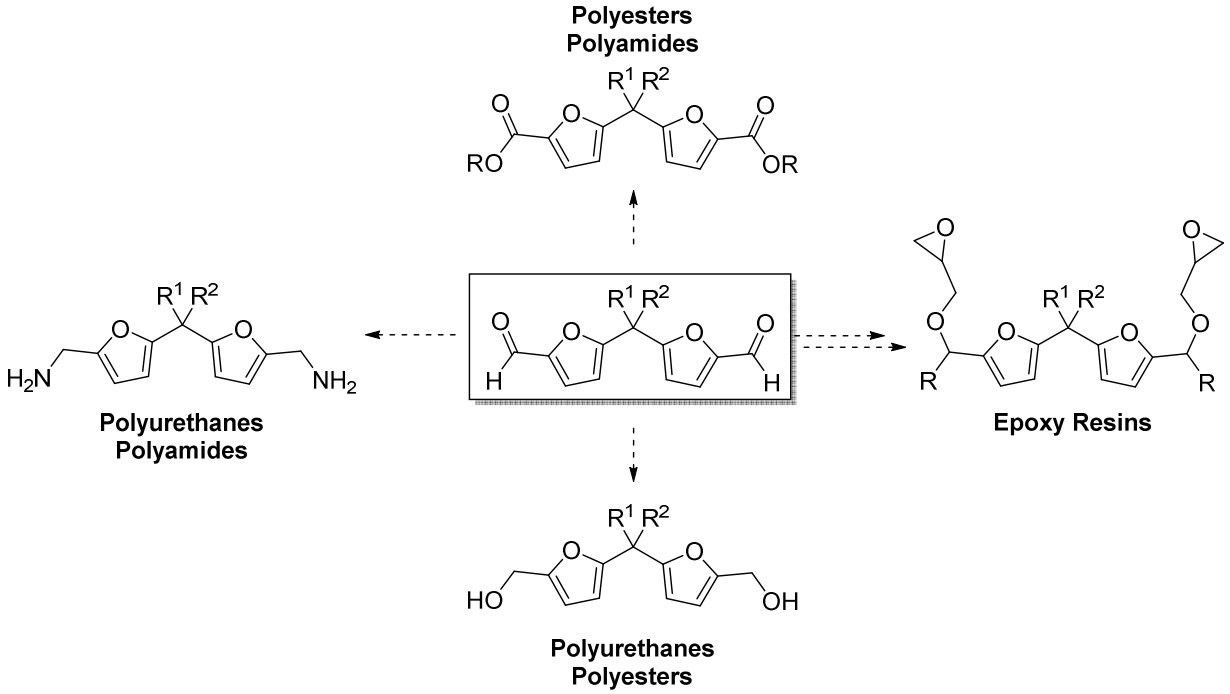
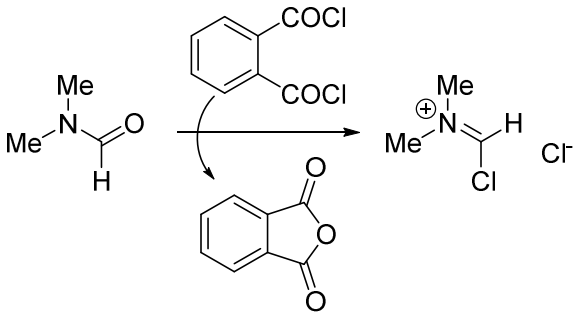


Figure 2.2. Potential Utility of Prepared Dialdehydes

2.3. Conclusions and Future Work

In conclusion, a series of bis- and tris-furan dialdehydes with different spacer units were prepared by condensation of furan with different ketones followed by formylation via the Vilsmeier Haack reaction. The prepared bis- and tris-furan dialdehydes exhibited differences in their melting points due to the incorporation of different spacer units. The dialdehyde containing the rigid cyclohexyl spacer exhibited the highest melting point. The dialdehydes which exhibited symmetry but still had some freedom of rotation about the carbon bond in the spacer unit exhibited the next highest melting points. The lowest melting point was observed in the unsymmetrical dialdehyde (**2.16**) which contained the 2-butyl spacer.

To increase the scalability of the formylation reaction, the use of an isolatable solid Vilsmeier reagent which was recently reported by Warashina et al.[35] for the formylation of the bis- and tris-furans could be studied. The key advantage of the solid Vilsmeier reagent is that it eliminates the need for large quantities of hazardous reagents, and it also avoids the formation of phosphorous containing wastewater. The Vilsmeier reagent was prepared using DMF and phthaloyl dichloride (Scheme 2.6).[35]



Scheme 2.6. Synthesis of a Solid Vilsmeier Reagent[35]

However, they found it only to be soluble in chloroform, with slow but selective heterogeneous reactions occurring in acetonitrile, DMF, and dichloromethane; therefore, other solvent conditions should be identified.[35]

Future work should involve testing the utility of the prepared dialdehyde monomers for use in polycarbamate chemistry. The prepared monomers can also be converted into esters, acyl chlorides, diamines, and diglycidal ethers through simple chemical transformations which can be incorporated into a wide variety of polymer synthesis.

2.4. Experimental

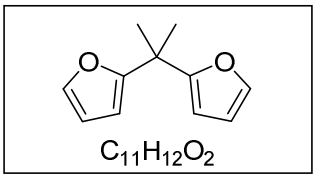
General Experimental Information: ^{1}H NMR was recorded on a Bruker Ascend 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet), coupling constant(s) and integration. ^{13}C NMR was recorded on Bruker Ascend (100 MHz) spectrometer using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.23) as an internal standard. Melting points were recorded using a REACH Devices RD-MP digital melting point apparatus and are uncorrected. FT-IR spectra were recorded using a Thermo Scientific Nicolet iS10 and processed using Omnic Software. High-resolution mass spectra (HRMS) [ESI+] were recorded using a Waters Synapt G2-Si high definition mass spectrometer and processed using MassLynx.

Materials and Methods: Cyclohexanone, *N,N*-dimethylformamide, 3-pentanone (98% Reagent grade) and phosphorus (V) oxychloride ReagentPlus were purchased from Sigma-Aldrich. The obtained phosphorous (V) oxychloride was purified via distillation. Furan stabilized

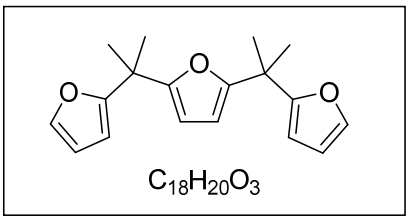
with BHT was purchased from TCI Chemicals and from Sigma-Aldrich. 2,2'-(Propane-2,2-diyl)difuran was purchased from TCI Chemicals. 2-Butanone was purchased from Alfa-Aeser. Acetone Optima was purchased from Fischer Chemicals. Absolute ethanol was purchased from Decon Laboratories. Unless otherwise noted (*vide supra*), all chemicals were used without further purification.

2.4.1. Condensation of Furan with Acetone[19]

Furan (20.00 g, 0.29 mol) was added to a 100 mL 2-neck rb flask, which was subsequently charged with a stir bar and condenser. The rb flask was placed in an ice bath. Absolute EtOH (8.8 mL, 0.15 mol) was subsequently added, followed by conc. HCl (5.9 mL, 0.19 mol). To this solution, acetone (4.8 mL, 0.15 mol) was added dropwise while stirring. The reaction was allowed to come to rt naturally and was allowed to stir overnight (18 h). The stirring was discontinued and the reaction mixture was allowed to separate into two phases. The upper aqueous phase appeared pink in color; whereas the lower organic phase appeared orange in color. The two phases were separated and the organic layer was washed with 5% sodium bicarbonate solution until neutral as indicated by pH paper. The organic layer was then dried over anhydrous sodium sulfate, and the solvent was evaporated using a rotary evaporator. The obtained products were then purified via fractional distillation under high vacuum. Compound **2.10a** was obtained as a colorless oil which distilled at 73 - 76 °C. Subsequently, **2.10b** was obtained in a second faction which distilled at 120 - 125 °C. Upon freezing overnight, compound **2.10b** crystallized yielding a white solid.



2,2-Di(2-furyl)propane (2.10a): Pale yellow oil; yield: 20%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 6H), 6.06 (dd, *J*= 3.2 Hz, *J*= 0.8Hz, 2H), 6.31 (dd, *J*= 3.2 Hz, *J*= 1.8 Hz, 2H), 7.35 (dd, *J*= 1.8 Hz, *J*= 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 37.3, 104.0, 110.0, 141.2. The obtained spectroscopic data for the product corresponded to those recorded in the literature.[36]

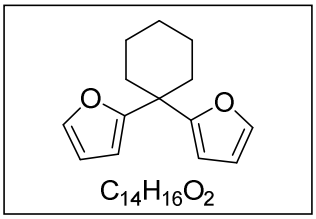


2,5-Bis(2-furyl-2-propyl)furan (2.10b): White solid; yield: mp = 46 - 48.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63 (s, 12H), 5.91 (s, 2H), 5.96 (dd, *J*= 3.2 Hz, *J*=0.8 Hz, 2H), 6.28 (dd, *J*= 3.2 Hz, *J*= 1.8 Hz, 2H), 7.30 (dd, *J*= 1.8 Hz, *J*= 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 26.3, 37.5, 104.0, 104.3, 109.9, 141.0, 158.5, 160.3. IR (neat): 3148, 3106, 3001, 2981, 2937, 2872, 739 cm^{-1}. Exact molecular mass could not be obtained.

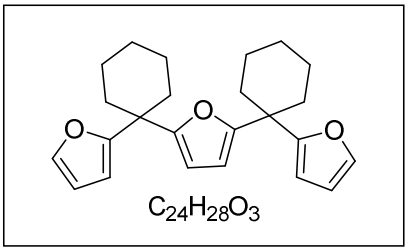
2.4.2. Condensation of Furan with Cyclohexanone[14]

Furan (13.6 g, 200 mmol) was added to a 100 mL 2-neck rb flask, which was subsequently charged with a stir bar and condenser. The rb flask was placed in an ice bath. Absolute EtOH (8.0 mL, 137 mmol) was subsequently added, followed by conc. HCl (6.0 mL, 197 mmol). To this solution, cyclohexanone (10.4 mL, 99.9 mmol) was added dropwise while stirring. The reaction was allowed to come to rt naturally and was allowed to stir overnight (18 h). The stirring was discontinued and the reaction mixture separated into two layers. The lower

organic layer was extracted from the upper aqueous layer. The organic layer was then neutralized with 5% aqueous sodium bicarbonate solution until neutral as indicated by pH paper. It was subsequently dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained products were then isolated using fractional distillation under high vacuum. The first faction identified as 2.11a was distilled between 94 - 98 °C. The second faction identified as 2.11b was distilled between 200 - 205 °C.



1,1-Di(2-furyl)cyclohexane (2.11a): Colorless oil; yield: 11.9%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (m, 6H), 2.20 (m, 4H), 6.04 (dd, *J*= 3.2 Hz, *J*= 0.8 Hz, 2H), 6.31 (dd, *J*= 3.2 Hz, *J*= 1.8 Hz, 2H), 7.34 (dd, *J*= 1.8 Hz, *J*= 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 22.5, 25.8, 33.9, 41.7, 105.0, 110.0, 141.0, 159.2. IR (neat): 2934, 2859, 726 cm^{-1}. Exact molecular mass could not be obtained.

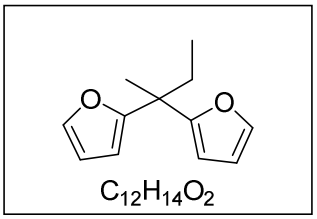


2,5-Bis[1-(2-furanyl)cyclohexyl]furan (2.11b): White solid; yield: mp = 88 – 89.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (m, 12H), 2.15 (m, 8H), 5.89 (s, 2H), 5.93 (dd, *J*= 3.2 Hz, *J*= 0.8 Hz, 2H), 6.28 (dd, *J*= 3.2 Hz, *J*= 1.8 Hz, 2H), 7.31 (dd, *J*= 1.8 Hz, *J*= 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 22.4, 25.8, 33.9, 41.9, 104.8, 105.5, 109.9, 140.7, 157.0, 159.7. IR (neat):

3148, 3106, 3001, 2981, 2937, 2872, 740 cm^{-1}. HRMS calcd for $C_{24}H_{28}O_3$: 365.2117; Found: 365.2104.

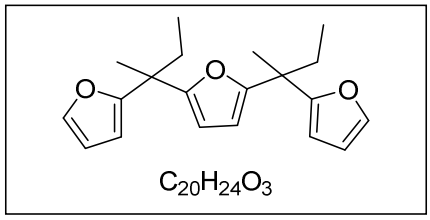
2.4.3. Condensation of Furan with 2-Butanone[15]

Furan (6.00 g, 88.0 mmol) was added to a 2 neck 25 mL rb flask which was subsequently charged with a stir bar and condenser. The rb flask was placed in an ice bath. Absolute ethanol (2.65 mL, 45.3 mmol) was then added, followed by dropwise addition of conc. HCl (1.7 mL, 57.6 mmol). The reaction mixture was allowed to stir in the ice bath for 15 min. 2-Butanone (3.9 mL, 44 mmol) was then added in dropwise via a syringe. The reaction mixture was allowed to stir in the ice bath and come to rt naturally. The reaction was then allowed to stir for 48 h. The stirring was stopped and the two layers were allowed to separate. The lower organic layer was then separated from the upper pink aqueous phase. The upper aqueous layer was extracted using DCM and the organic layers were combined. The organic layer was then washed with 5% sodium bicarbonate ($NaHCO_3$) solution until neutral. The aq. $NaHCO_3$ layer was then back extracted with DCM to ensure the desired compound was not lost in the aqueous layer. It was then dried over anhydrous sodium sulfate, filtered, and then concentrated using the rotary evaporator. The crude products were isolated *via* distillation using a Kugelrohr under high vacuum. The first faction identified as **2.12a** was distilled between 64 - 66 °C. The second faction identified as compound **2.12b** was distilled between 143 - 146 °C.



2,2-Di(2-furyl)butane (2.12a): Colorless oil; yield: 6%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (t, *J* = 7.4 Hz, 3H), 1.62 (s, 3H), 2.10 (q, *J*= 7.4 Hz, 2H), 6.09 (dd, *J*=3.2 Hz, *J*=0.8 Hz, 2H),

6.31 (dd, *J*= 3.2 Hz, *J*= 1.8 Hz, 2H), 7.35 (dd, *J*= 1.8 Hz, *J*= 0.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 8.8, 22.3, 31.7, 41.4, 104.9, 109.8, 141.2, 159.3. IR (neat): 3118, 2971, 2938, 2880, 726 cm^{-1}. Exact molecular mass could not be obtained.

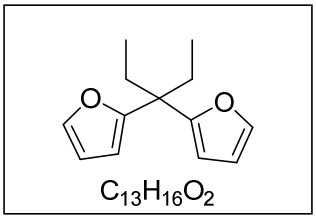


2,5-bis[1-(2-furanyl)-1-methylpropyl]furan (2.12b): Yellow oil; yield: 11%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, *J*=7.4 Hz, 6H), 1.57 (s, 6H), 2.00-2.08 (m, 4 H), 5.95 (d, *J*=0.9 Hz, 2H), 6.00 (dd, *J*= 3.2 Hz, *J*= 0.9 Hz, 2H), 6.29 (dd, *J*= 3.2 Hz, *J*= 1.8 Hz, 2H), 7.33 (dd, *J*= 1.8 Hz, *J*= 0.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 8.9, 22.3, 22.37, 22.40, 32.0, 41.5, 104.8, 105.2, 109.8, 140.9, 157.6, 159.6. IR (neat): 2971, 2937, 2879, 728 cm^{-1} Exact molecular mass could not be obtained.

2.4.4. Condensation of Furan with 3-Pentanone[18]

Furan (10.00 g, 146.9 mmol) was added to a 2 neck 25 mL rb flask which subsequently was charged with a stir bar and a condenser. The rb flask was then placed in an ice bath and absolute EtOH (5.6 mL, 95.48 mmol) was added. Conc. HCl (6.2 mL, 204.2 mmol) was subsequently added at a rapid dropwise pace. Finally, 3-pentanone (4.8 mL, 73.44 mmol) was added dropwise via syringe. After addition of the 3-pentanone, the reaction went from clear and colorlessto taking on a clear light brown tinge. The reaction was left in the ice bath and allowed to come to room temperature slowly. The reaction was allowed to stir for 24 h. The lower organic layer was then separated from the upper aqueous layer. The organic layer was washed with 5% sodium bicarbonate solution until neutral as indicated by pH paper. Upon neutralization

the reaction turned from a greenish color to orange in color. The organic layer was then dried over anhydrous sodium sulfate and the solvent was evaporated using a rotary evaporator. The crude compound was purified via Kugelrohr distillation under high vacuum. The distillate of compound 2.13a was distilled between 75 - 80 °C.

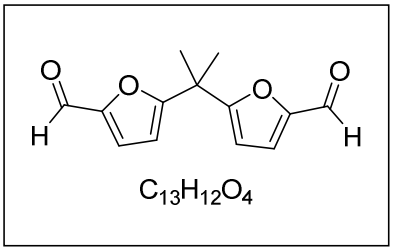


3,3-Difurylpentane (2.13a): Pale yellow oil; yield: 15%; ^{1}H NMR (CDCl3, 400 MHz) δ 0.74 (t, J=7.4 Hz, 6H), 2.08 (q, J=7.4 Hz, 4H), 6.16 (dd, J= 3.2 Hz, J= 0.8 Hz, 2H), 6.33 (dd, J= 3.2 Hz, J= 1.8 Hz, 2H), 7.35 (dd, J= 1.8 Hz, J= 0.8 Hz, 2H); ^{13}C NMR (CDCl3, 100 MHz); δ 8.3, 27.7, 45.7, 106.2, 109.7, 141.1, 158.2. IR (neat): 2969, 2939, 2879, 725 cm^{-1}. Exact molecular mass could not be obtained.

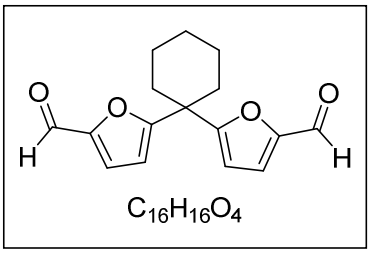
2.4.5. Representative Procedure for the Formylation of Bis- and Tris-furans[17]

2,2-Di(2-furyl)propane (10.000 g, 56.75 mmol) was added to a 100 mL 2 neck rb flask which was subsequently charged with a stir bar and a condenser. The flask was subsequently placed under argon and cooled in an ice bath. DMF (13 mL, 170.2 mmol) was then added via syringe. $POCl_3$ (6.4 mL, 68.1 mmol) was added via syringe dropwise. During the addition, the reaction mixture took on a deep reddish black color. The reaction mixture was allowed to stir at 0 °C for 10 minutes and was subsequently transferred to an oil bath and heated to 60 °C. The reaction mixture was then allowed to stir for 5 hours. Subsequently, the reaction mixture was allowed to cool to rt. By this point the reaction mixture was a thick black viscous mixture with a liquid layer at the top. The reaction mixture was again cooled in an ice bath. DMF (13 mL, 170.2 mmol) was added via syringe followed by a dropwise addition of $POCl_3$ (5.3 mL, 56.8

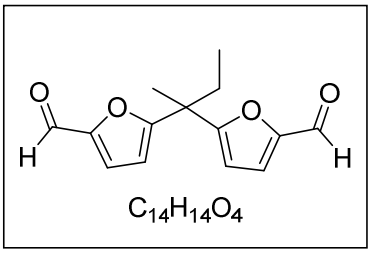
mmol). During the addition of $POCl_3$, the flask was gently agitated by hand to induce mixing since stir bar would not stir. The reaction mixture was then transferred back into an oil bath and heated at 60 °C for 10 h. The reaction mixture was allowed to cool and was poured onto crushed ice using distilled water to aid in the process. The reaction mixture was then neutralized using 10% sodium hydroxide solution as indicated by pH paper resulting in the product crystallizing out of the solution. The reaction mixture was allowed to crystallize for one hour. The pH was again checked and a small quantity of 10% sodium hydroxide solution was utilized to again neutralize the solution. The obtained product was then filtered, washed with a small quantity of distilled water, and allowed to dry. The obtained product was then recrystallized from 95% EtOH.



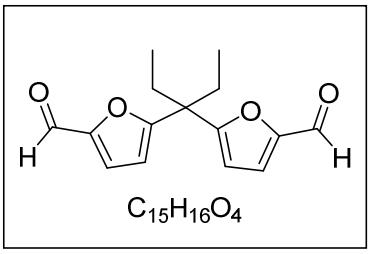
2,2-bis(5-formyl-2-furyl)propane (2.14): Pale yellow solid; yield: 96%; mp = 90.2-91.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (s, 6H), 6.36 (d, *J*=3.6 Hz, 2H), 7.20 (d, *J* = 3.6 Hz, 2H), 9.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 25.8, 38.5, 108.4, 122.5, 152.2, 164.8, 177.5; IR (neat): 3120, 2980, 2936, 2851, 1660, 1514, 1370, 1357, 766 cm^{-1}. HRMS calcd for $C_{13}H_{12}O_4Na^+$: 255.0633; Found: 255.0634. The obtained spectroscopic and analytical data for the product corresponded to those recorded in the literature.[17]



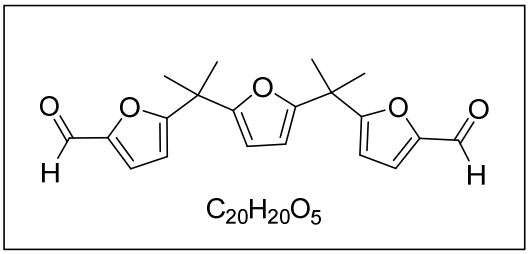
5,5'-cyclohexylidenebis-2-furancarboxaldehyde (2.15): Pale yellow solid; yield: 91%; mp= 152–153.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.569 (m, 6H), 2.33 (m, 4H), 6.36 (d, *J*=3.6 Hz, 2 H), 7.21 (d, *J*=3.6 Hz, 2H), 9.58 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 22.3, 25.2, 33.4, 43.0, 109.4, 122.5, 152.0, 164.1, 177.4; IR (neat): 3119, 2920, 2856, 1663, 759 cm^{-1}; HRMS calcd for $C_{16}H_{16}O_4Na^+$: 295.0946; Found: 295.0955.



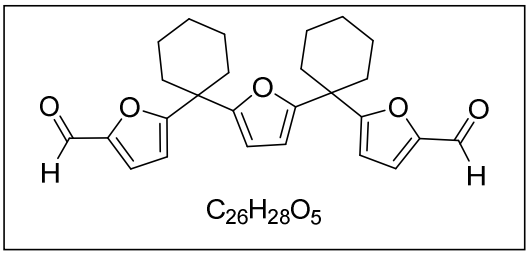
5,5'-(1-methylpropylidene)bis-2-furancarboxaldehyde (2.16): Pale yellow solid; yield: 71%; mp= 69.5–71.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, *J*= 7.2 Hz, 3H), 1.76 (s, 3H), 2.23 (q, *J* = 7.2 Hz, 2H), 6.39 (d, *J*=3.6 Hz, 2H), 7.21 (d, *J*=3.6 Hz, 2H), 9.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 8.7, 21.7, 31.6, 42.7, 109.3, 122.4, 152.2, 164.2, 177.4; IR (neat): 3116, 2984, 2938, 2879, 1661, 739 cm^{-1}. HRMS calcd for $C_{14}H_{14}O_4Na^+$ 269.0790; Found: 269.0799.



5,5'-(1-bispropylidene)bis-2-furancarboxaldehyde (2.17): Pale yellow solid; yield: 53%; mp= 87.5 – 89.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, *J*=7.4 Hz, 6H), 2.23 (q, *J*=7.4 Hz, 4H), 6.46 (d, *J*=3.6 Hz, 2H), 7.23 (d, *J*=3.6 Hz, 2H), 9.58 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 8.3, 27.7, 47.1, 110.4, 122.3, 152.2, 163.4, 177.3; IR (neat): 3150, 2983, 2954, 2836, 1663, 1500, 734 cm^{-1}; HRMS calcd for $C_{15}H_{16}O_4Na^+$: 261.1127; Found: 261.1124.



5,5'-[2,5-Furandiylbis(1-methylethylidene)]bis[2-furancarboxaldehyde] (2.18): Light yellow solid; yield: 74%; mp= 82.5–85.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 12H), 6.07 (s, 2H), 6.16 (d, *J*=3.2 Hz, 2H), 7.15 (d, *J*=3.2 Hz, 2H), 9.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 25.9, 38.1, 105.4, 107.8, 122.7, 151.8, 157.3, 167.0, 177.3; IR (neat): 3127, 3102, 2976, 2935, 2871, 2810, 1667, 732 cm^{-1}. HRMS calcd for $C_{20}H_{20}O_5Na^+$: 363.1208; Found: 363.1202.



5-(1-{5-[1-(5-formylfuran-2-yl)cyclohexyl]furan-2-yl}cyclohexyl)furan-2-carbaldehyde (2.19): Pale yellow solid; yield: 90%; mp= 152.0–154.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (m, 12H), 2.22 (m, 8H), 6.08 (s, 2H), 6.12 (d, *J*=3.6 Hz, 2H), 7.15 (d, *J*=3.6 Hz, 2H), 9.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 22.3, 25.5, 33.5, 42.6, 106.9, 108.4, 122.8, 151.7, 155.4, 166.9, 177.2; IR (neat): 2935, 2857, 1669, 796, 764 cm^{-1}; HRMS calcd for $C_{26}H_{28}O_5Na^{+}$: 443.1834; Found: 443.1832.

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APPENDIX

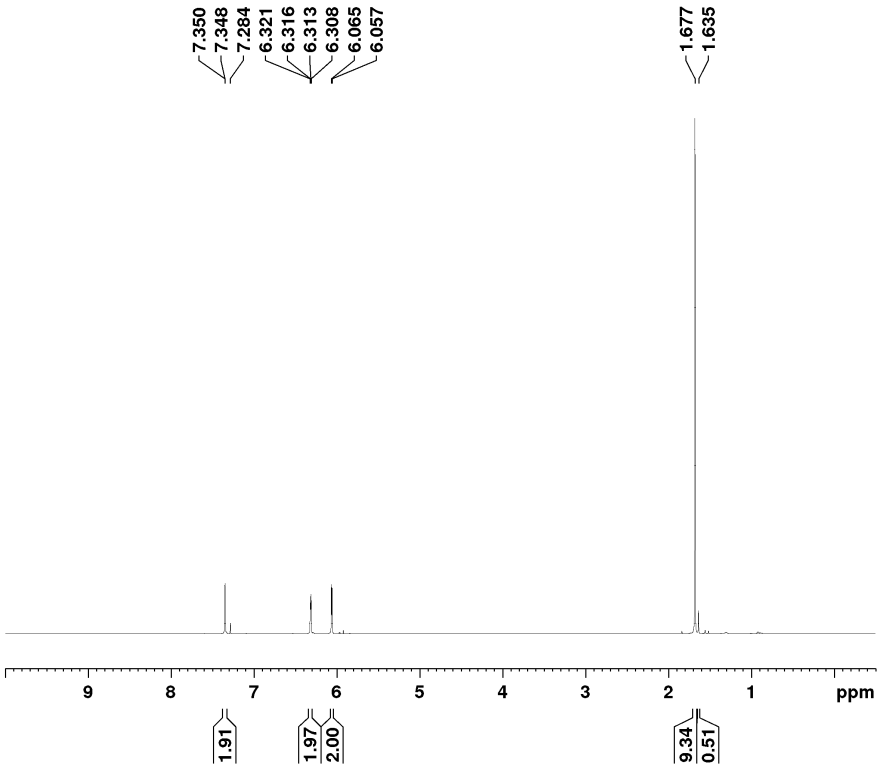

Figure A1. [1]H NMR Spectrum of 2,2-Di(2-furyl)propane (**2.10a**)

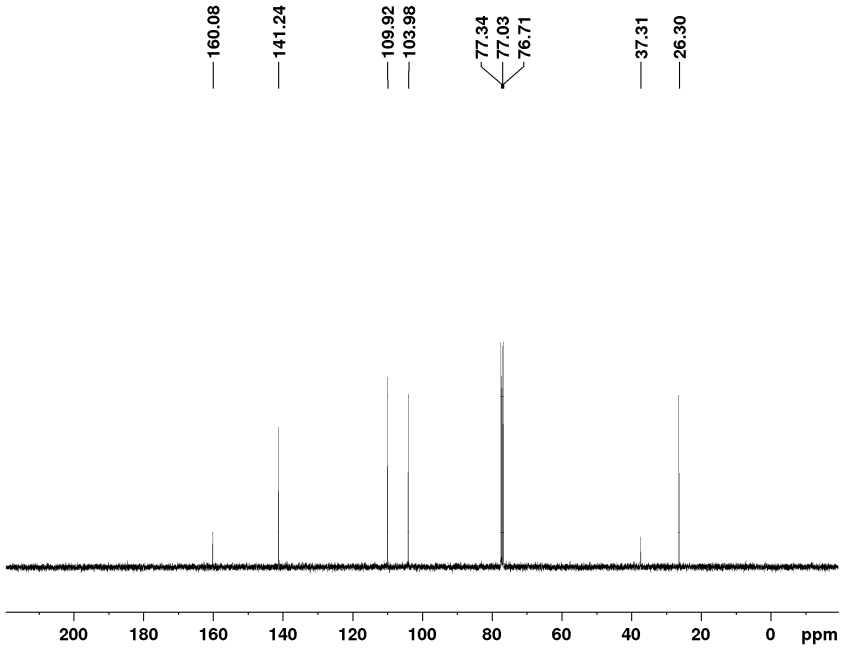

Figure A2. [13]C NMR Spectrum of 2,2-Di(2-furyl)propane (**2.10a**)

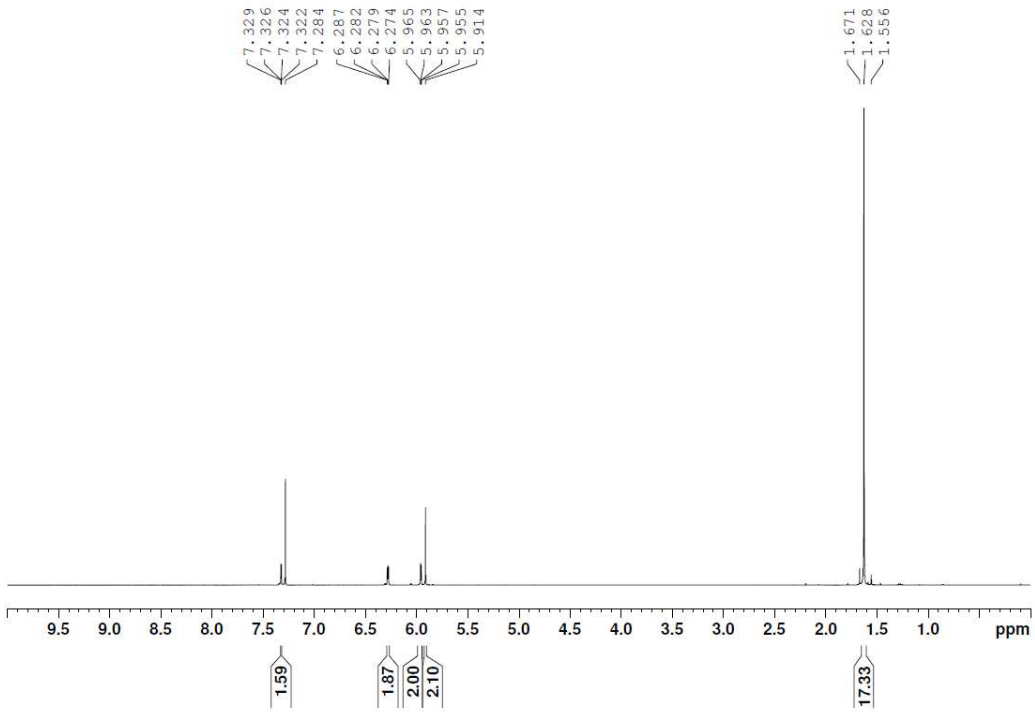

Figure A3. ^{1}H NMR Spectrum of 2,5-Bis(2-furyl-2-propyl)furan (**2.10b**)

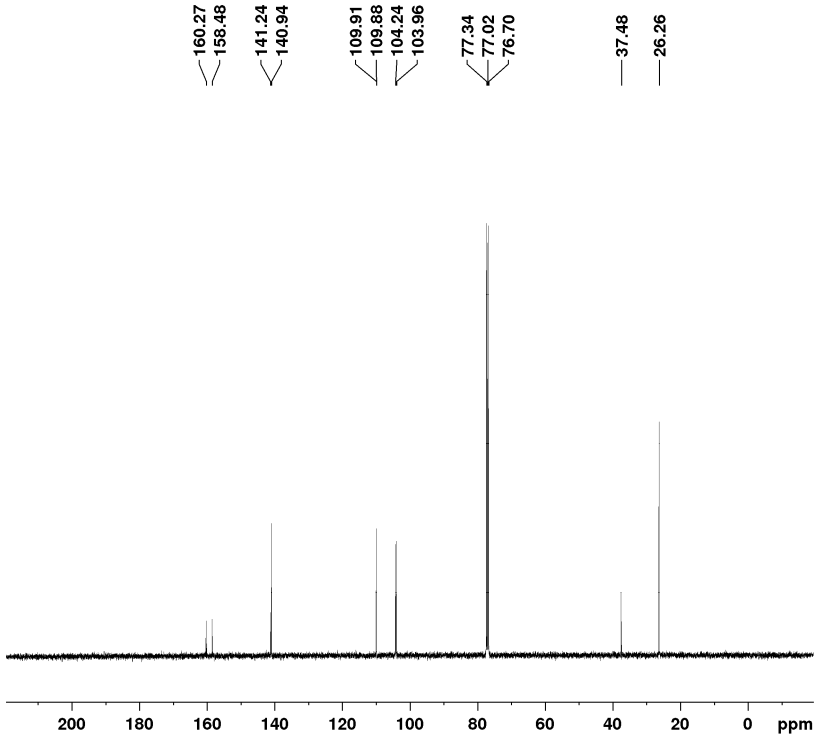

Figure A4. ^{13}C NMR Spectrum of 2,5-Bis(2-furyl-2-propyl)furan (**2.10b**)

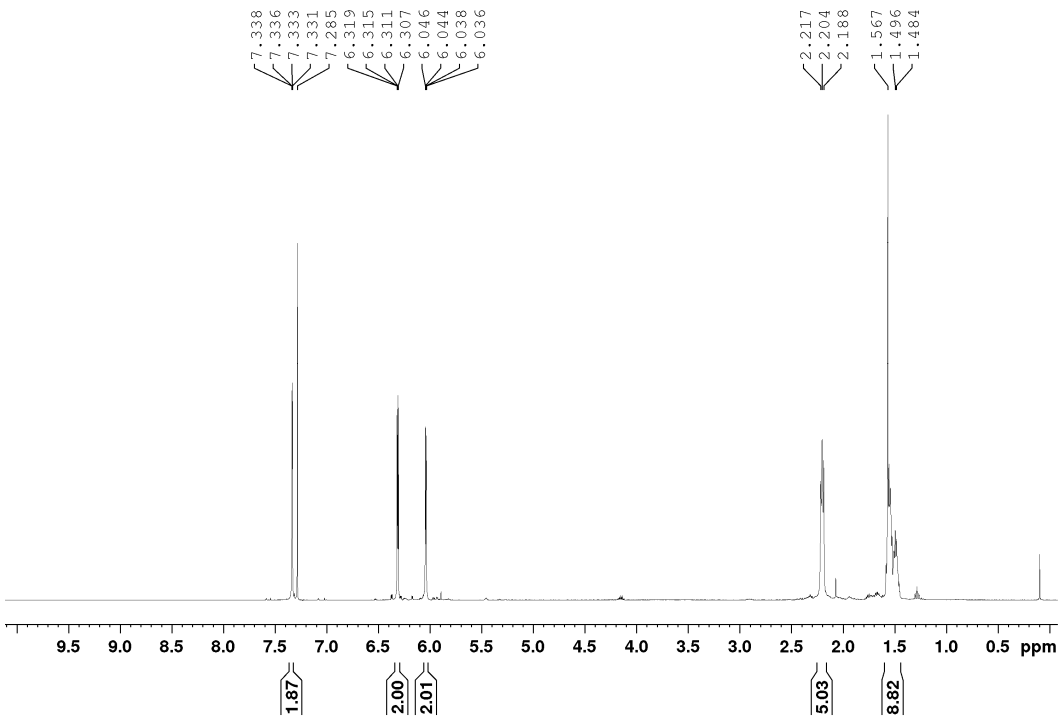

Figure A5. ^{1}H NMR Spectrum of 1,1-Di(2-furyl)cyclohexane (**2.11a**)

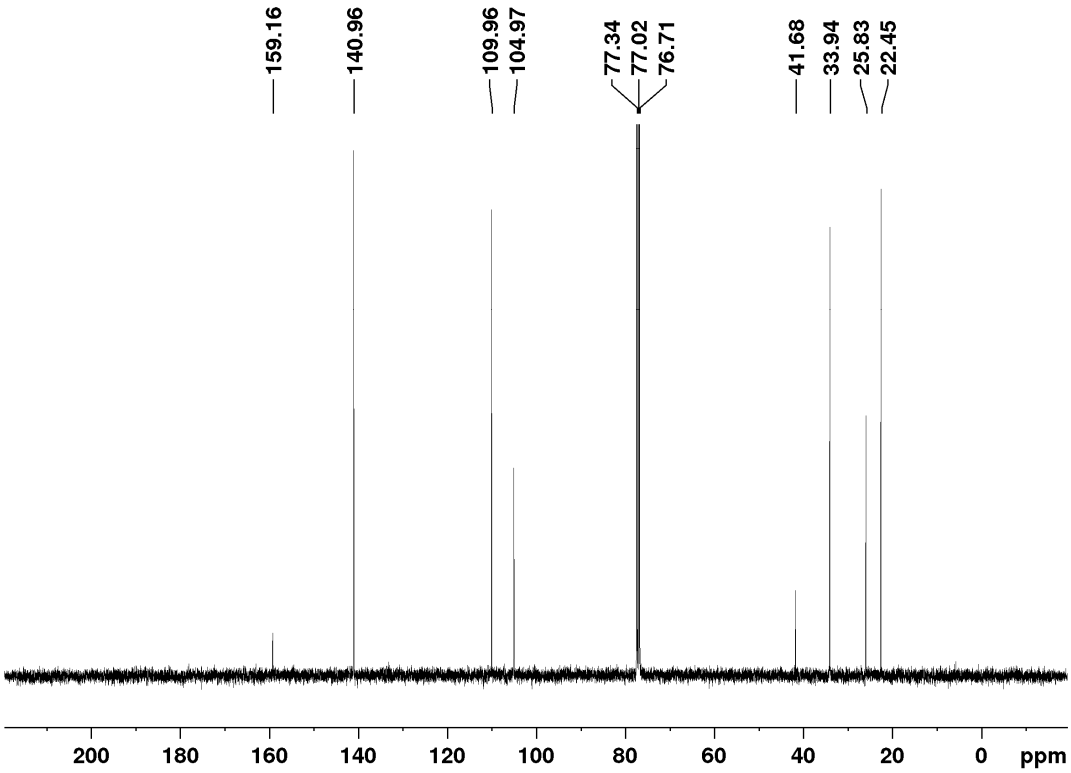

Figure A6. ^{13}C NMR Spectrum of 1,1-Di(2-furyl)cyclohexane (**2.11a**)

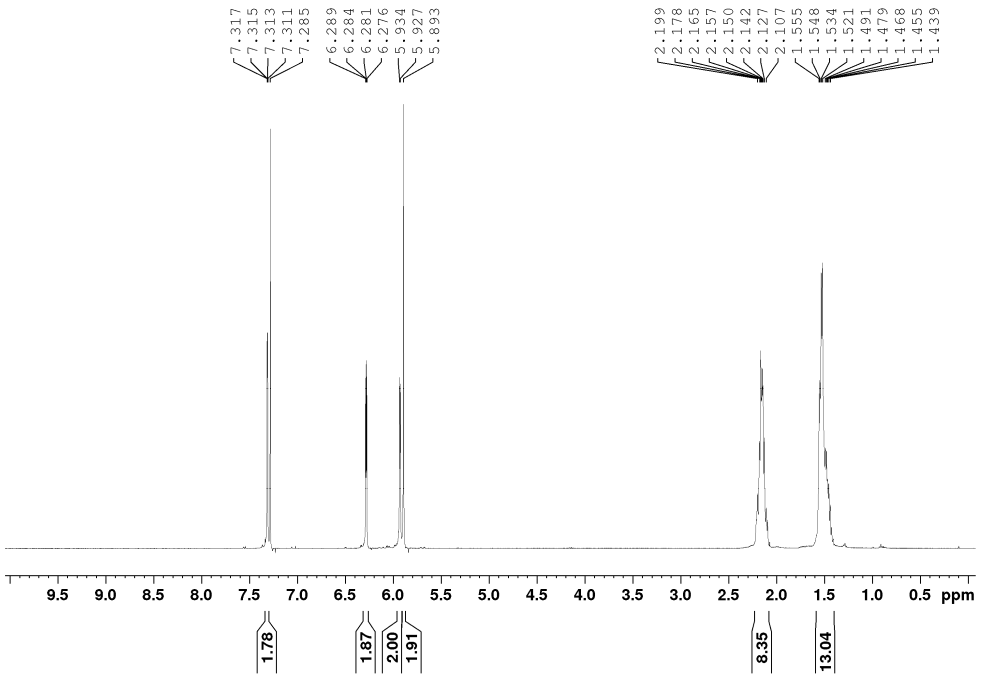

Figure A7. ^{1}H NMR Spectrum of 2,5-Bis[1-(2-furanyl)cyclohexyl]furan (**2.11b**)

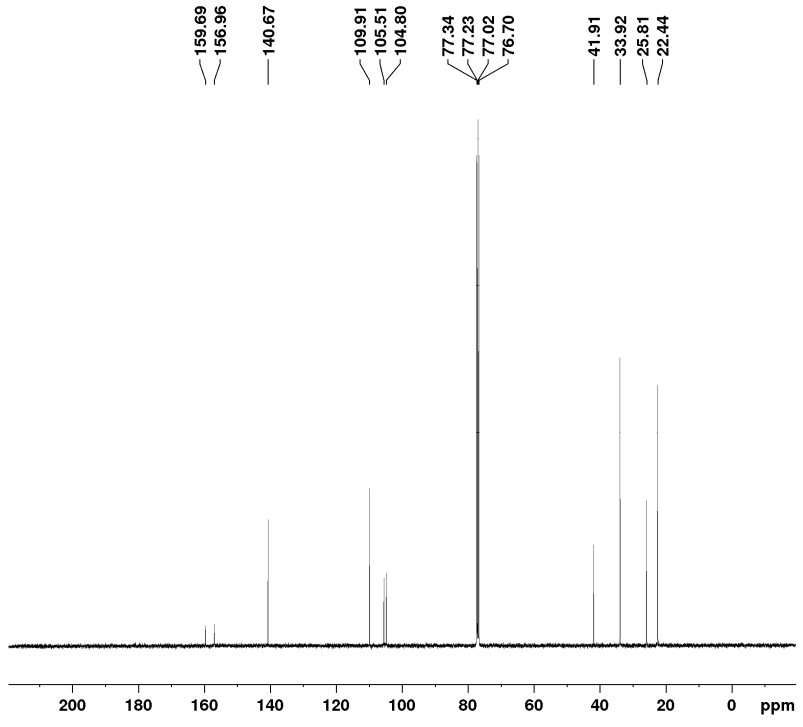

Figure A8. ^{13}C NMR Spectrum of 2,5-Bis[1-(2-furanyl)cyclohexyl]furan (**2.11b**)

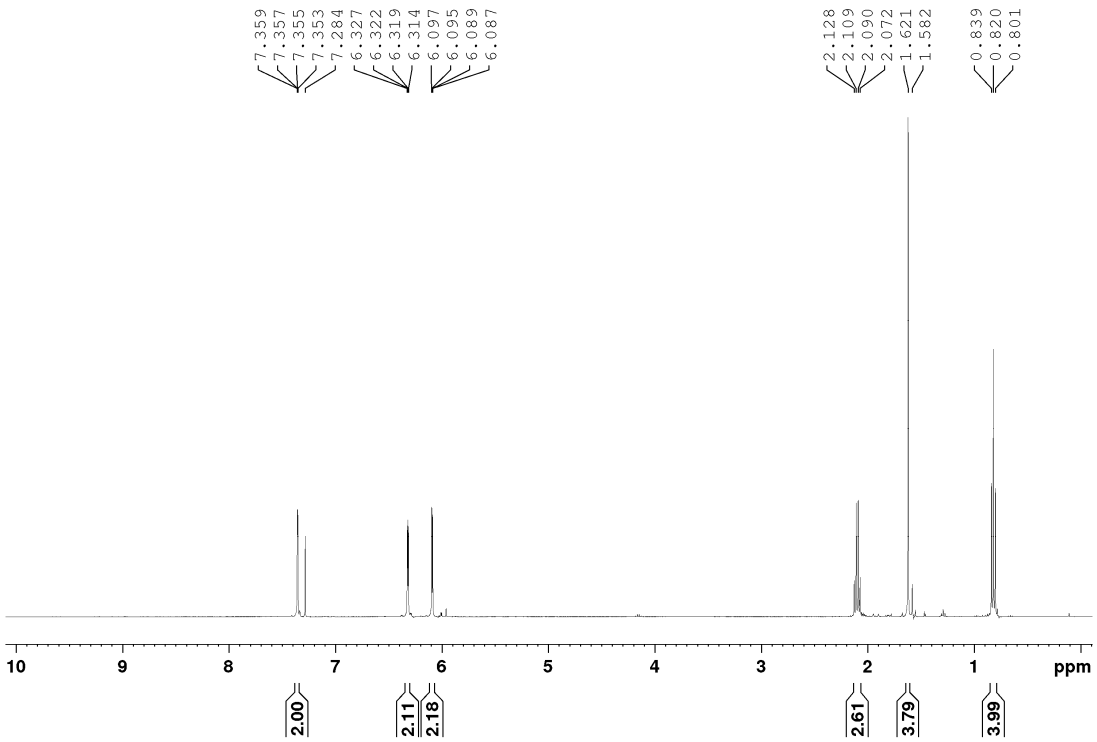

Figure A9. ^{1}H NMR Spectrum of 2,2-Di(2-furyl)butane (**2.12a**)

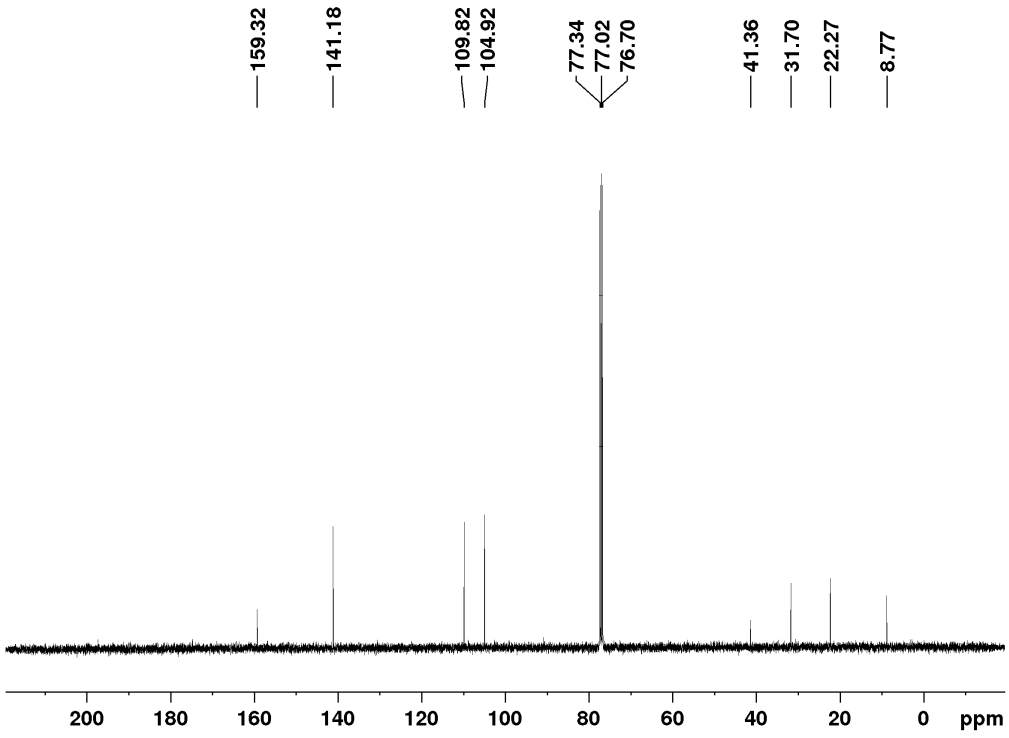

Figure A10. ^{13}C NMR Spectrum of 2,2-Di(2-furyl)butane (**2.12a**)

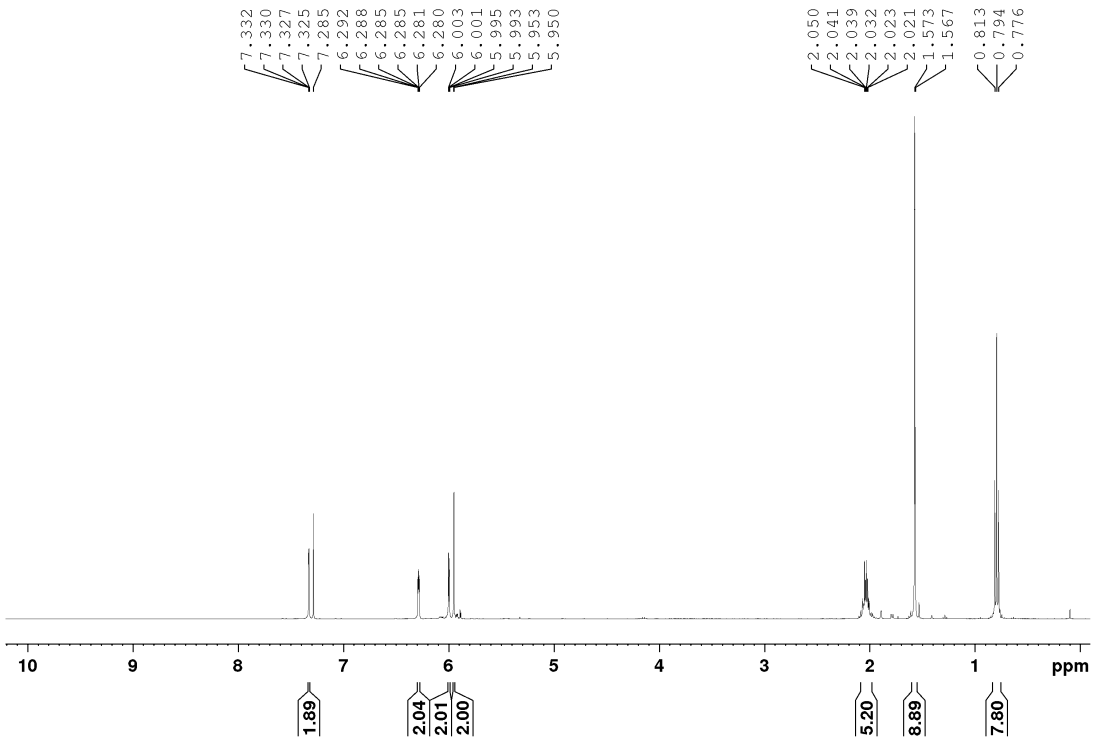

Figure A11. [1]H NMR Spectrum of 2,5-Bis[1-(2-furanyl)-1-methylpropyl]furan (**2.12b**)

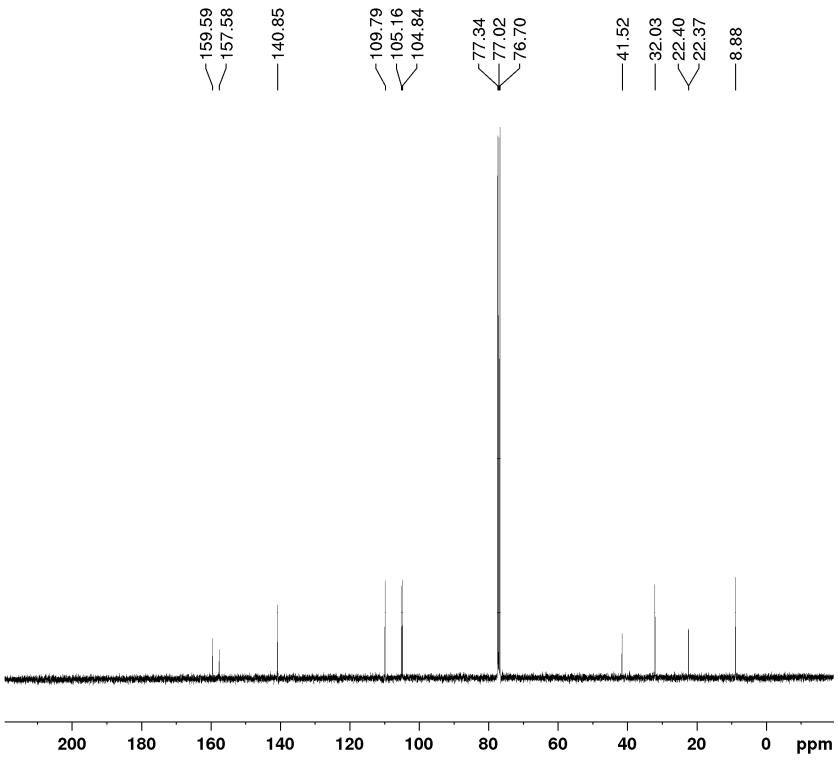

Figure A12. [13]C NMR Spectrum of 2,5-Bis[1-(2-furanyl)-1-methylpropyl]furan (**2.12b**)

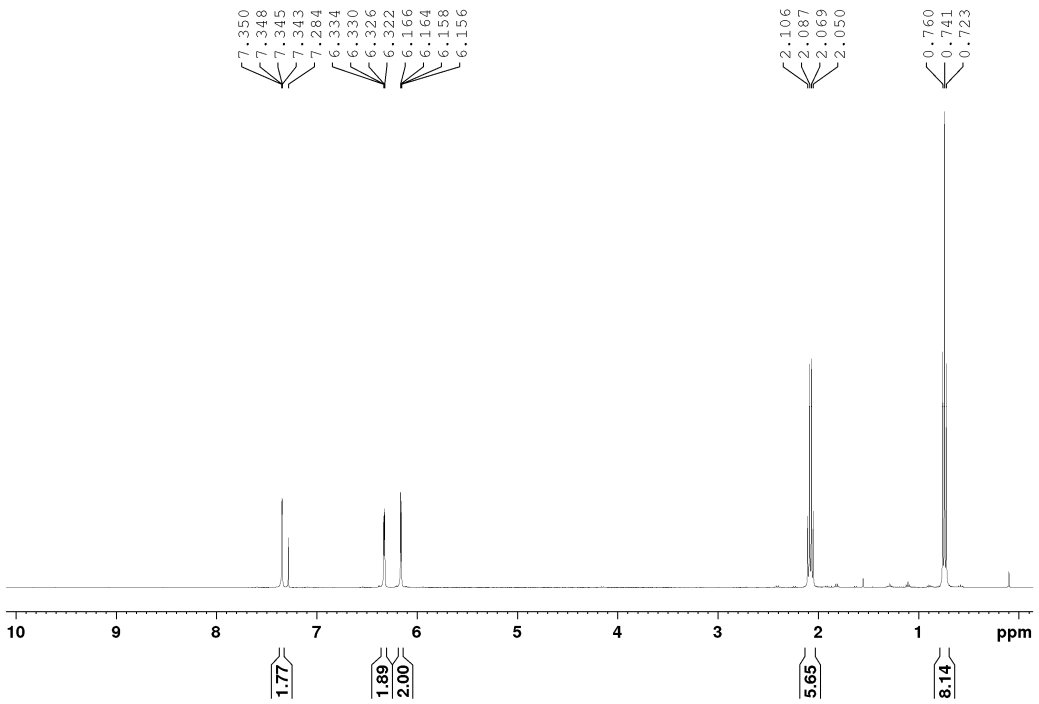

Figure A13. ^{1}H NMR Spectrum of 3,3-Difurylpentane (**2.13a**)

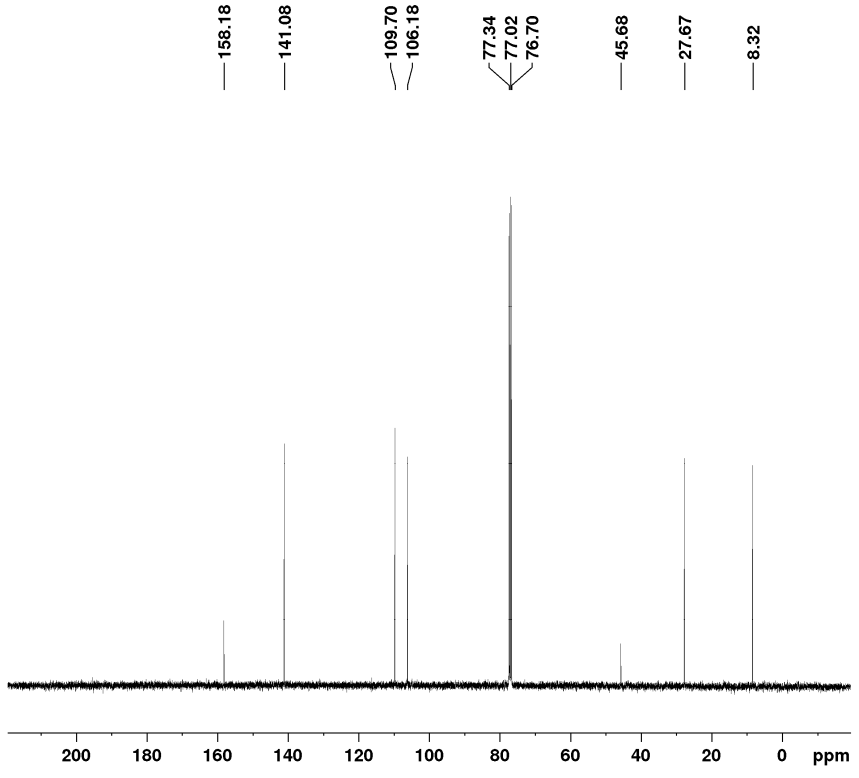

Figure A14. ^{13}C NMR Spectrum of 3,3-Difurylpentane (**2.13a**)

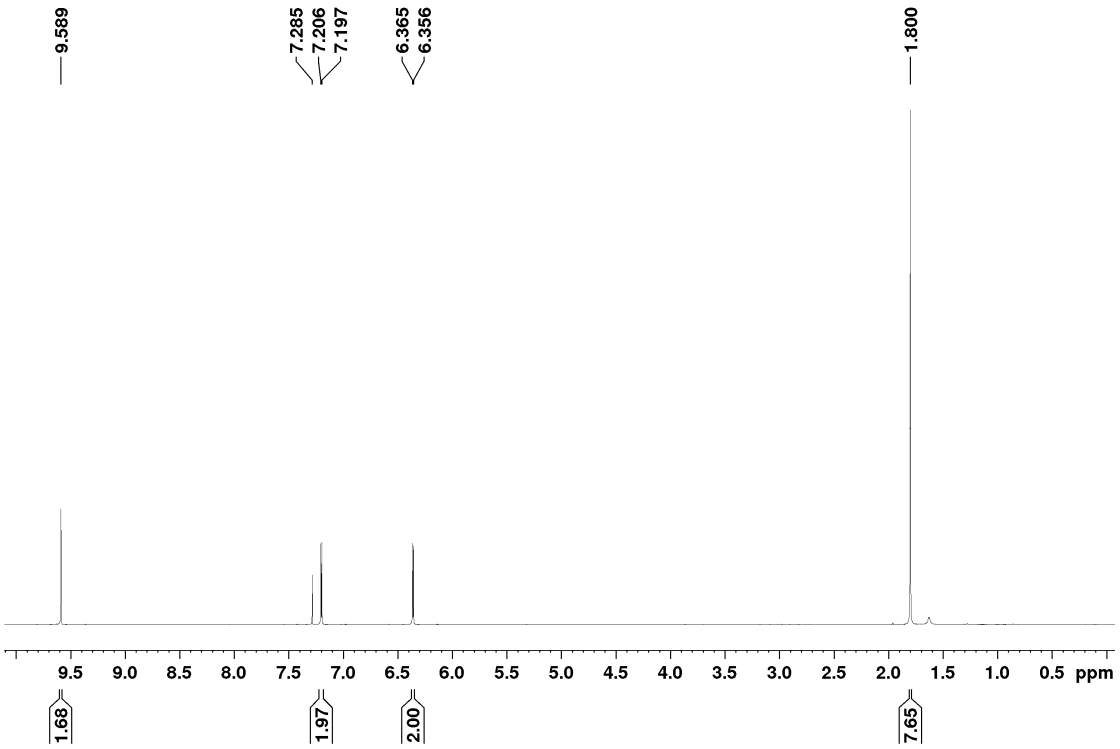

Figure A15. ^{1}H NMR Spectrum of 2,2-Bis(5-formyl-2-furyl)propane (**2.14**)

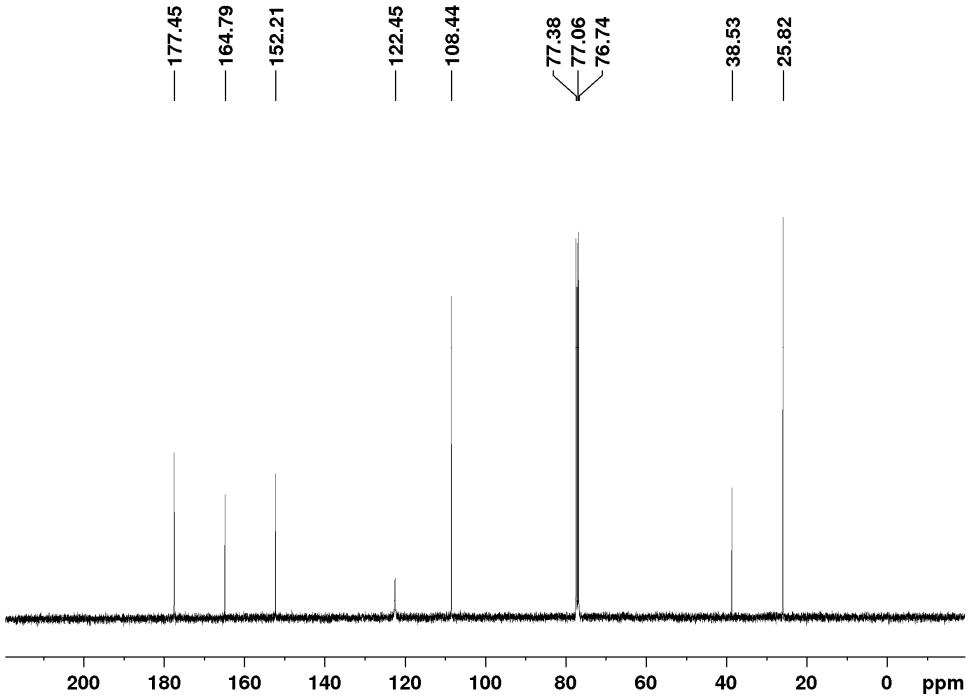

Figure A16. ^{13}C NMR Spectrum of 2,2-Bis(5-formyl-2-furyl)propane (**2.14**)

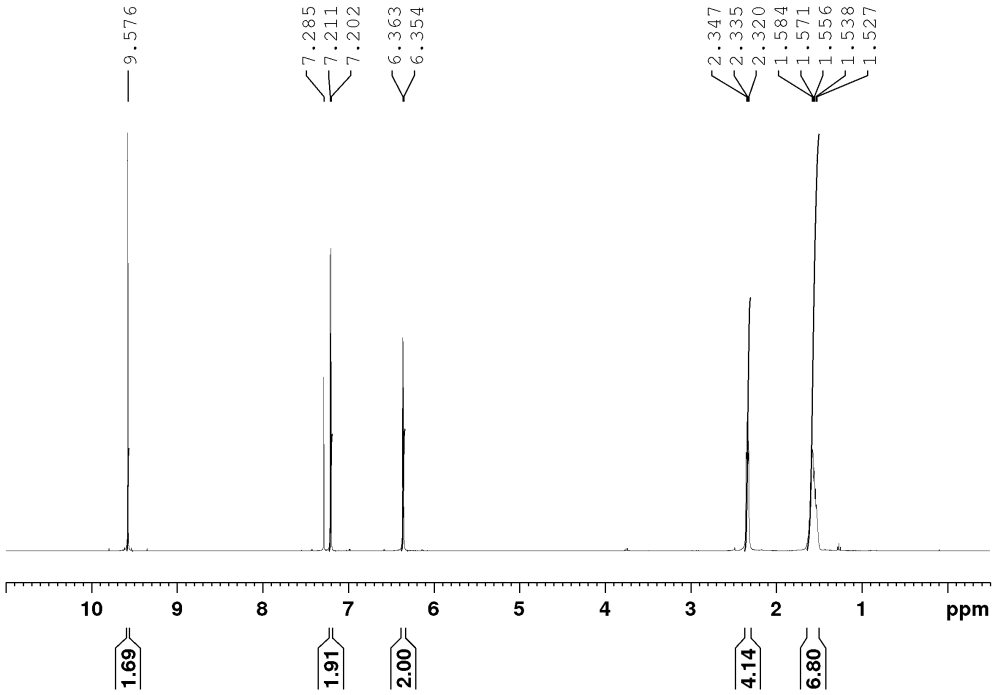

Figure A17. ^{1}H NMR Spectrum of 5,5'-Cyclohexylidenebis-2-furancarboxaldehyde (**2.15**)

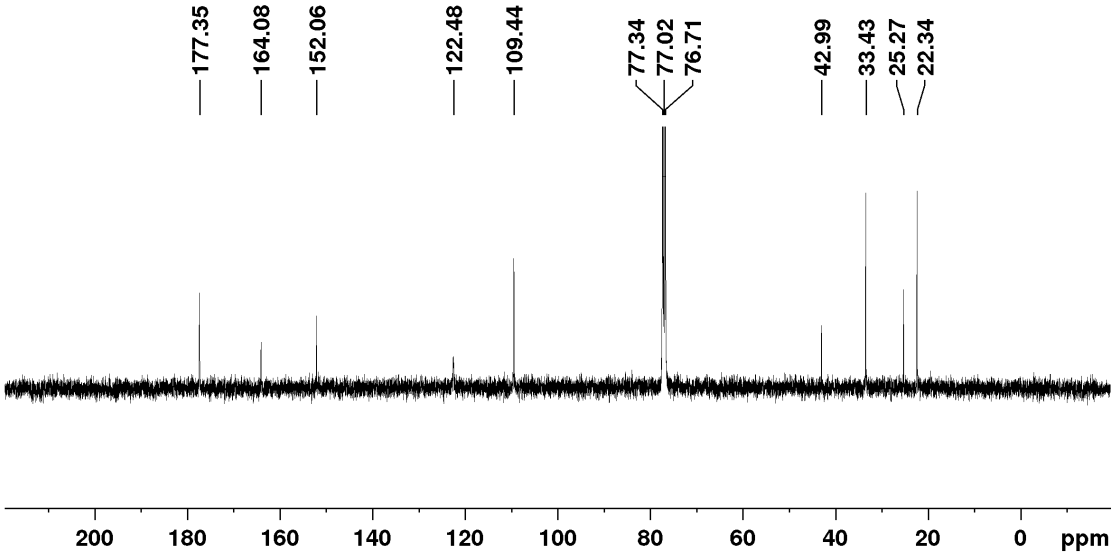

Figure A18. ^{13}C NMR Spectrum of 5,5'-Cyclohexylidenebis-2-furancarboxaldehyde (**2.15**)

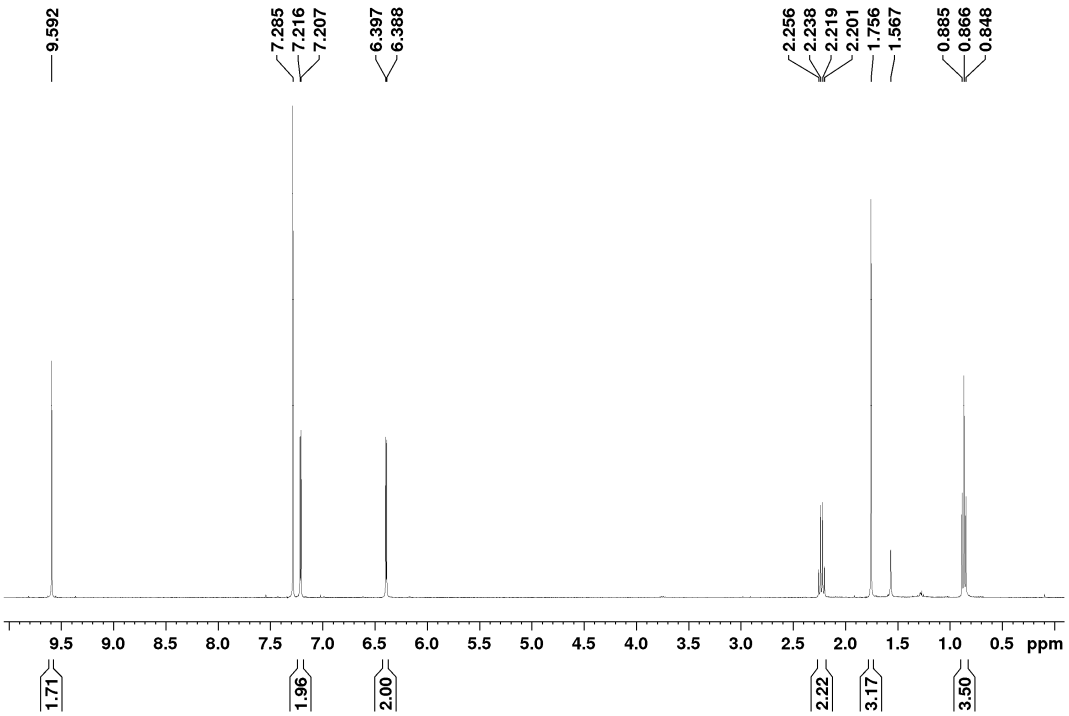

Figure A19. [1]H NMR Spectrum of 5,5'-(1-Methylpropylidene)bis-2-furancarboxaldehyde (**2.16**)

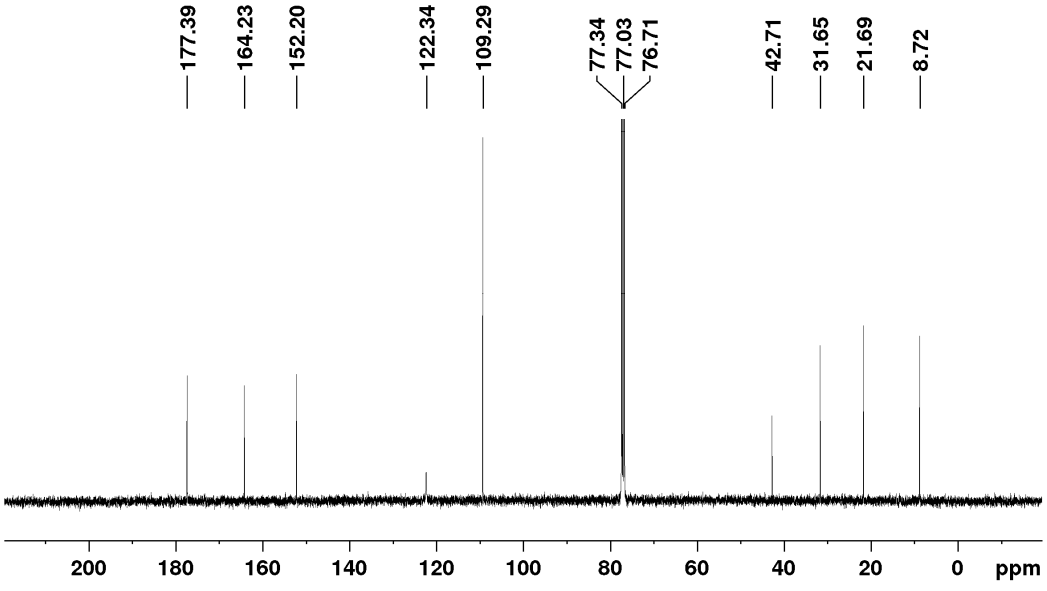

Figure A20. [13]C NMR Spectrum of 5,5'-(1-Methylpropylidene)bis-2-furancarboxaldehyde (**2.16**)

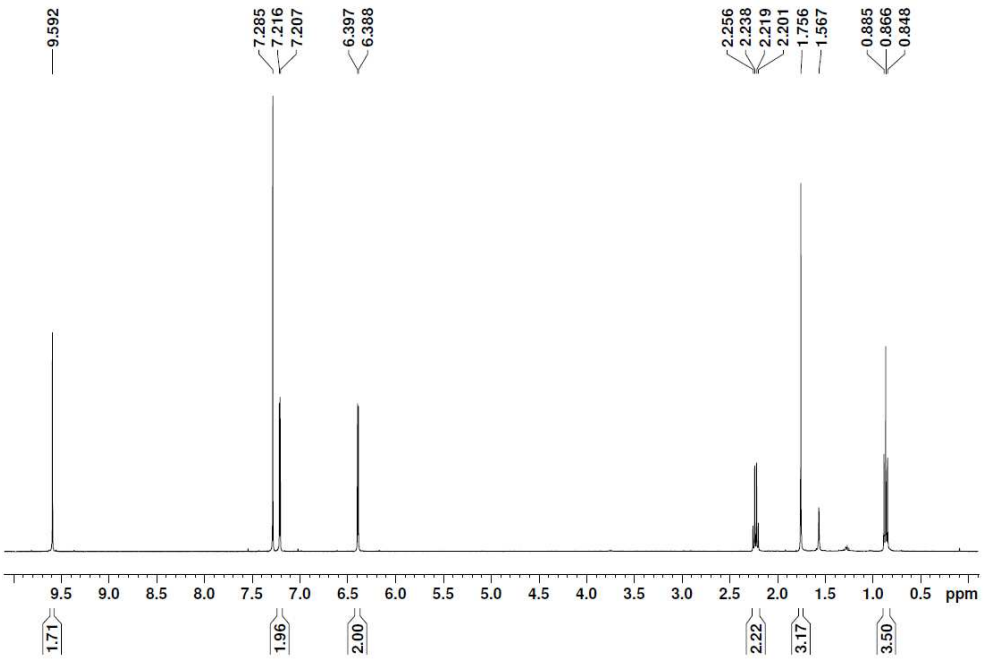

Figure A21. [1]H NMR Spectrum of 5,5'-(1-Bispropylidene)bis-2-furancarboxaldehyde (**2.17**)

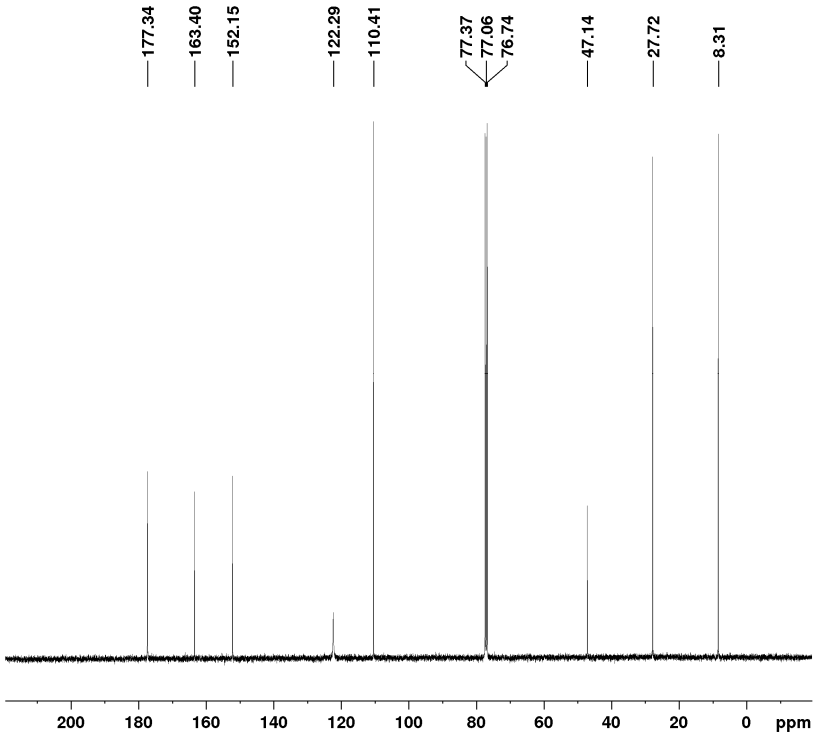

Figure A22. [13]C NMR Spectrum of 5,5'-(1-Bispropylidene)bis-2-furancarboxaldehyde (**2.17**)

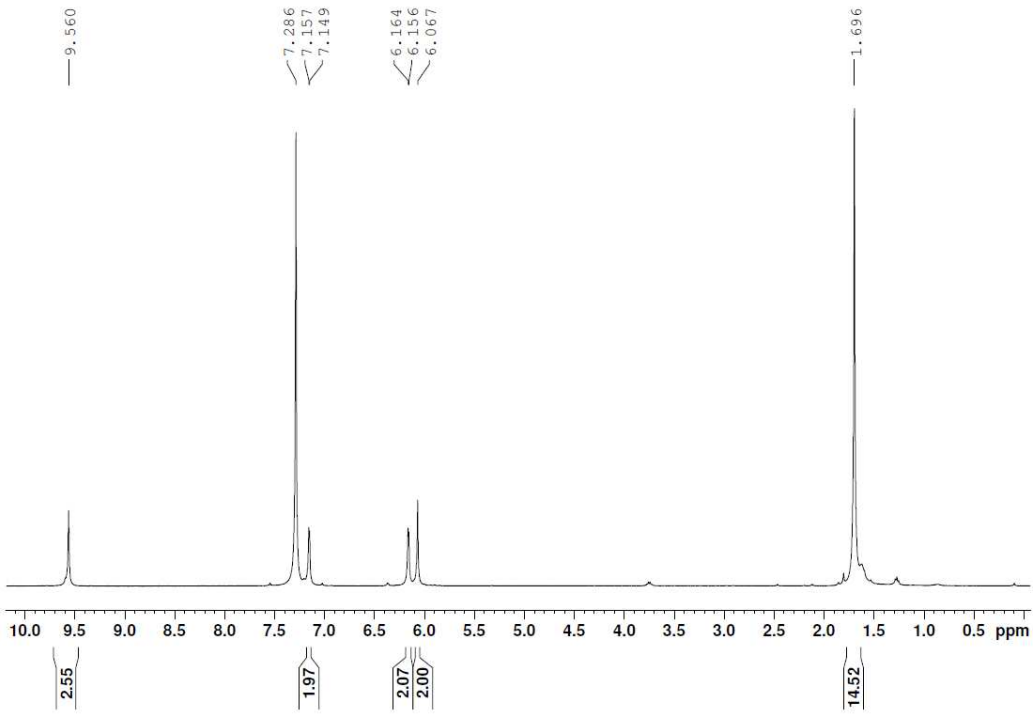

Figure A23. ^{1}H NMR Spectrum of 5,5'-[2,5-Furandiylbis(1-methylethylidene)]bis[2-furancarboxaldehyde](methyl-methyl trisfuran dialdehydes) (**2.18**)

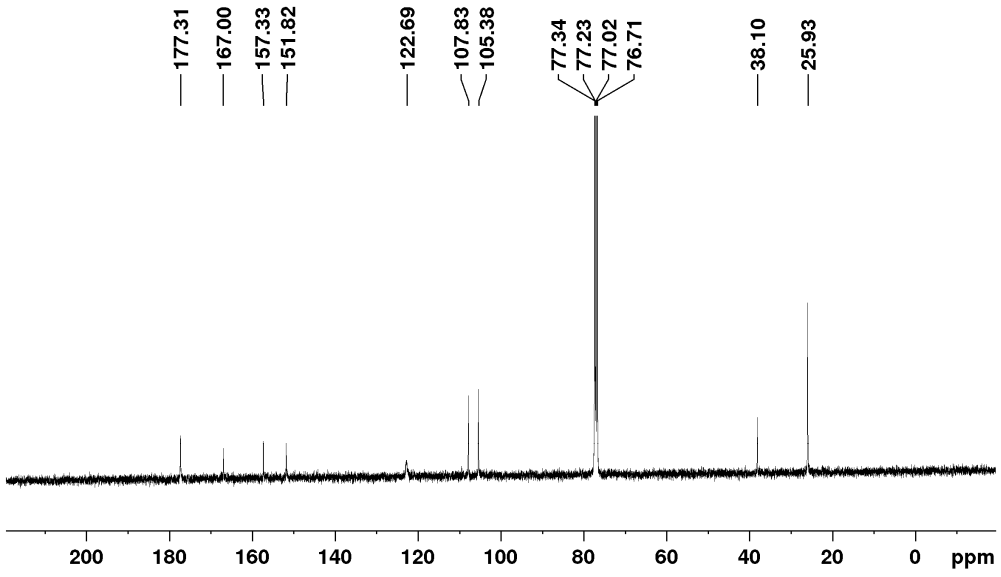

Figure A24. ^{13}C NMR Spectrum of 5,5'-[2,5-Furandiylbis(1-methylethylidene)]bis[2-furancarboxaldehyde] (**2.18**)

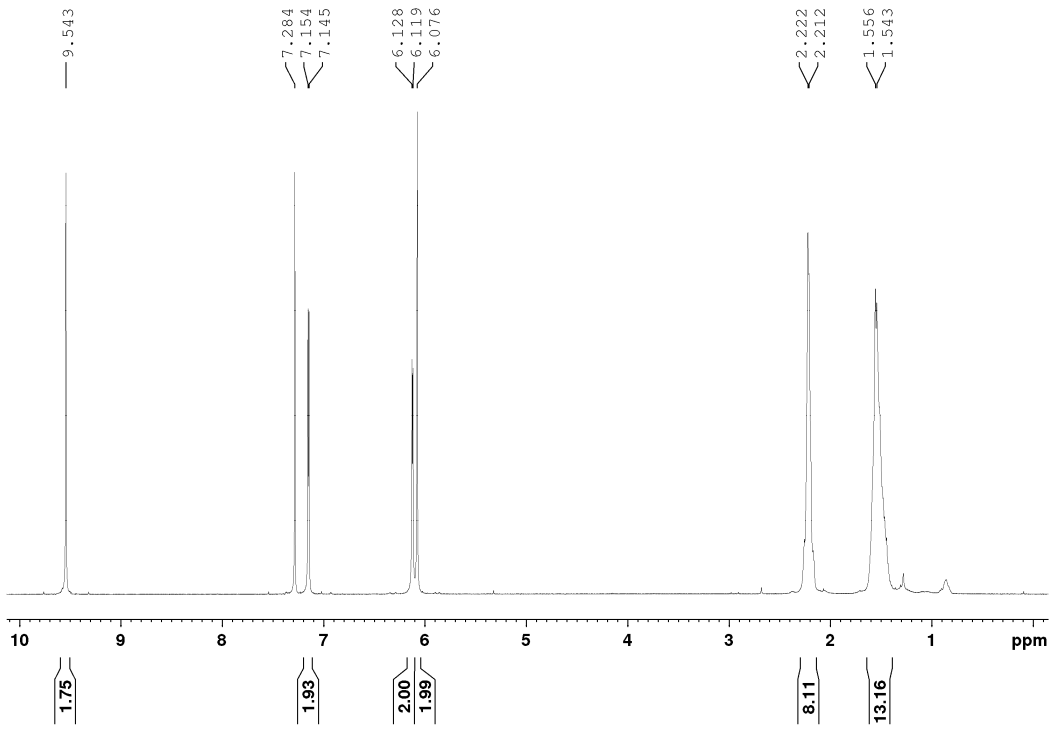

Figure A25. ^{1}H NMR Spectrum of 5-(1-{5-[1-(5-Formylfuran-2-yl)cyclohexyl]furan-2-yl}cyclohexyl)furan-2-carbaldehyde (**2.19**)

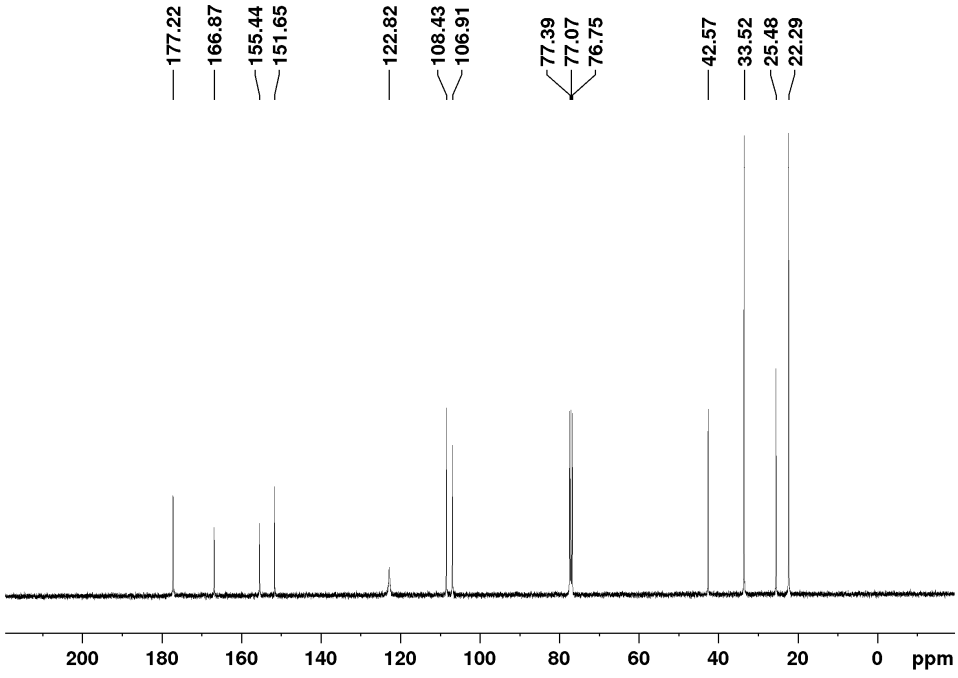

Figure A26. ^{13}C NMR Spectrum of 5-(1-{5-[1-(5-Formylfuran-2-yl)cyclohexyl]furan-2-yl}cyclohexyl)furan-2-carbaldehyde (**2.19**)