PRODUCTION OF VALUE-ADDED CHEMICALS FROM GLYCEROL VIA A SIX-MEMBERED CYCLIC ACETAL

By

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ABSTRACT

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The global growth in biodiesel production over the past decade has led to the availability of significant quantities of glycerol as a byproduct of the triglyceride transesterification process. Glycerol is a versatile feedstock for producing chemicals such as propylene glycol and epichlorohydrin. Another attractive application of glycerol is to convert it into cyclic acetals via direct condensation with aldehydes and ketones or transacetalization with another acetal compound. The product, glycerol acetal, can be used as fuel additives to improve viscosity and cold properties of biodiesel, and alleviate the pollution problems by reducing particulate emissions from fuel combustion.

In this work, glycerol acetal was synthesized via the acid-catalyzed reaction of glycerol with acetaldehyde or 1,1-diethoxyethane. Results show that at 25°C, the reaction gives nearly theoretical yield in 2 h if 1,1-diethoxyethane is used as the acetal forming reagent. The kinetics of this reaction was then investigated in batch reactors. The effect of solvent, reactant molar ratio, catalyst loading, and temperature were examined. A second order kinetic model is proposed to describe this reaction, and rate constants, activation energies, and equilibrium constants have been calculated based on the experimental results.

The product from glycerol transacetalization is a mixture of four glycerol acetal isomers. In the presence of acid catalyst, the isomers interconvert to form an equilibrated mixture with the same composition. Vacuum distillation was carried out to separate the four acetals into their purified forms. Result show that the cis-5-hydroxy-2-methyl-1,3dioxane (1) is the most volatile isomer among the four. When the distillation is carried out in the presence of an acid catalyst to promote interconversion, isomer (1) is obtained as a nearly pure distillate stream. This is further adapted to a continuous reactive distillation which produced 90-96% isomer (1) in a lab scale column.

With the availability of pure isomer (1), new synthesis pathways are developed to obtain valuable chemicals such as 1,3-propanediol and 1,3-dihydroxyacetone. For instance, by oxidizing the remaining free hydroxyl group in isomer (1) and hydrolyzing the corresponding ketone product, the tanning ingredient 1,3-dihydroxyacetone can be produced. The novelty and advantage of this method is that the cyclic acetal structure in isomer (1) blocks the primary hydroxyl groups of glycerol, thus can ensure a good selectivity of secondary alcohol oxidation and eliminate the byproduct generated from primary alcohol reaction.

To assess the feasibility of this concept, oxidation of isomer (1) to the corresponding ketone product was investigated using a variety of oxidants. Results show that a ruthenium tetroxide-based catalyst has the highest efficiency.

Based on the experimental results obtained in this study, a novel process to convert glycerol to the desired acetal (1) and then to 1,3-dihydroxyacetone is presented.

To My Family

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Chapter I. Background and Introduction

1.1. Introduction

The production of biodiesel from plant triglycerides leads to formation of by-product glycerol, a versatile feedstock for producing chemicals such as propylene glycol and epichlorohydrin. Glycerol obtained from biodiesel production usually contains a mixture of methanol, water, inorganic salts (catalyst residue), free fatty acids, unreacted and partly reacted triglycerides, methyl esters, and other compounds in varying quantities, depending on the biodiesel process [1].

The price of high purity glycerol in the U.S. dropped from \$1.00/lb to \$0.40/lb between 1995 and 2005 [2], but has since rebounded as chemical manufacturers developed new uses for the inexpensive feedstock instead of treating it as an environmental liability [3, 4].

Great effort has been made by scientists to search for new uses of glycerol. Suppes et al. developed a green process to convert glycerol into 1,2-propylene glycol [5, 6]. This new approach couples a copper-chromite catalyst with reactive distillation and uses hydrogen as coreagent to perform hydrogenolysis of glycerol. It first removes a water molecule from glycerol acetol, and then adds a hydrogen molecule. This process uses a lower temperature (220 °C) and lower pressure (<145 psi) than previous systems. In addition, the process converts glycerol to propylene glycol more efficiently (yield >90%), and produces less by-product (ethylene glycol < 1.5%) than do similar routes or catalysts. Propylene glycol made from this process is significantly cheaper than from petroleum.

Glycerol can also be used as a feedstock for the production of gaseous fuels [7]. Generally, the reforming of glycerol into H_2 or a syn-gas (H_2 +CO) stream can be carried out by 1) aqueous-phase reforming [7-10] over various metal catalysts, 2) reforming in supercritical water [7, 11, 12], or 3) steam reforming [13-15]. However, high temperature and high pressure are required in these processes to achieve a reasonable yield and selectivity.

Other uses of glycerol include converting it into alkanes, acetaldehyde, short chain alcohols, and acetone, etc. [11, 16-18]. Zhou and coworkers [19] reviewed the pathways for obtaining various useful chemicals from glycerol, summarized in Scheme 1-1.

In addition to chemicals, glycerol can be converted to effective fuel additives that improve combustion and emission properties and provide additional energy content. Fernando et al. [3] discussed the possibility of blending glycerol derivatives such as propanediol and propanol with gasoline as an automotive fuel. They obtained fuel blends with high energy value and with octane numbers exceeding 100. However, they did not investigate the cold weather properties of those fuel mixtures.

Noureddini developed a process to derive ether products from glycerol and isobutylene using acid catalyst [20]. He found that mixing these ethers with biodiesel decreased its viscosity and cloud point. Others [21] have reported that glycerol-ethers also to reduce particulate emission from diesel and biodiesel combustion. However, the drawback of this approach is that isobutylene is an expensive feedstock, which will increase the overall production cost.

Glycerol triacetate has been synthesized and tested as fuel additive [22]. The experimental results show that this acetate product could improve cold flow and viscosity properties of biodiesel. Delgado [23] described a procedure to make glycerol acetal (GA) and glycerol acetate mixtures, and blended them with biodiesel in concentrations of approximately 0.5-20 wt%. He found the mixture could reduce the pour point and viscosity of biodiesel at low temperatures.



Scheme 1-1. Processes of catalytic conversion of glycerol into useful chemicals [19].

It is well known that glycerol can be converted into cyclic acetals or ketals via reaction with aldehydes, ketones or another acetal compound [24-26]; for example, 2-methyl-4-hydroxymethyl-1,3-dioxolane and 2-methyl-5-hydroxy-1,3-dioxane (Scheme 1-2) are formed via reaction of glycerol with acetaldehyde. This class of compounds has been proven to have desirable properties as fuel additives via improving pour point and viscosity of biodiesel, and reducing particulate emissions from fuel combustion [23, 27, 28].

Scheme 1-2. Dioxane and dioxolane isomers of glycerol acetal





2-methyl-4-hydroxymethyl-1,3-dioxolane

2-methyl-5-hydroxy-1,3-dioxane

In 2008, a patent [29] filed by Dr. Miller's group at MSU proposed the concept of making glycerol acetals (GA) and biodiesel in large scale using a reactive-distillation (RD) technique. In the route they designed (Figure 1-1), the reaction mixture from a pre-reactor, which contains mostly transesterified oil and crude glycerol, is introduced to the top of the RD column. At the same time, a mixture of alcohol and GA forming reagent (aldehyde or acetal) is introduced to the column of the bottom. The reactive zone in this column is packed with solid catalyst packing. Residual oil and alcohol further react in this zone to achieve complete transesterification. Simultaneously, GA is synthesized in the reactive zone. During the operation, unreacted reagents are separated for recycling and the fuel mixture which consists of biodiesel and GA products are obtained at the bottom of the RD column.





In this study, effort was initially dedicated to assess and demonstrate the viability of the process proposed for continuous production of glycerol acetal with biodiesel. To achieve this goal, two synthetic routes were examined, i.e. glycerol acetalization with acetaldehyde and transacetalization with 1,1-diehtoxyethane. The latter approach, which is water-free and has a nearly 100% equilibrium yield, was selected for kinetic study and a kinetic model was then proposed to describe the reaction. At the same time, an elevated pressure reactive distillation column was designed and constructed for pilot scale demonstration of glycerol acetal production.

Under ordinary conditions, GA product obtained from either glycerol acetalization or transacetalization is a mixture of dioxane and dioxolane isomers. A continuous reactive distillation process was then developed to obtain the 6-membered dioxane isomer as the sole product of GA formation reaction. In the process of investigating the interconversion and separation of these isomers, we noticed that oxidizing the 6-membered dioxane GA isomer to its ketone product (2-methyl-1,3-dioxan-5-one) gives the precursor to 1,3-dihydroxyacetone (DHA) (Scheme 1-3), a high value specialty chemical that is the active ingredient in sunless tanning lotions.

Scheme 1-3. 2-methyl-1,3-dioxan-5-one and 1,3-dihydroxyacetone (DHA).





2-methyl-1,3-dioxan-5-one

1,3-dihydroxyacetone (DHA)

Because conventional DHA production from glycerol fermentation has low productivity and high production cost [32], we perceived an opportunity to develop a new, economical process and thus changed our focus from production of GA to DHA. Therefore, a variety of oxidation experiments were carried out to determine an efficient and green pathway to obtain the ketone precursor from cis-6. This work forms the basis for the development of a novel process to produce DHA from glycerol in yields of 90+%. References

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Chapter II. Formation of Cyclic Glycerol Acetals from Acetaldehyde or 1,1-Diethoxyethane

2.1. Introduction and background

Glycerol acetals can be synthesized by condensation with aldehydes or ketones, or by –OH exchange with other acetal compounds. The direct condensation of glycerol with aldehydes or ketones is known as acetalization [1-4], and the exchange of alcohols from another acetal is called transacetalization [5]. These two reactions are demonstrated in Scheme 2-1.





Early investigations indicated that the acetal product of glycerol formed via either process are composed of two cyclic compounds, a 5-membered 1,3-dioxolane and a 6-membered 1,3-dioxane [4, 6-8].

In this work, we present results of glycerol acetal synthesis using acetaldehyde or 1,1diethoxyethane (DEE). With each of the reactants, the synthesized 4-hydroxymethyl-2-methyl-1,3-dioxolane and 5-hydroxy-2-methyl-1,3-dioxane products contain cis- and trans isomers, giving a total of four conformational isomers as shown in Table 2-1 [4, 9].

Structure	IUPAC name	Abbreviation
ООН	cis-4-hydroxymethyl-2-methyl-1,3-dioxolane	cis-5
O O O O O	trans-4-hydroxymethyl-2-methyl-1,3-dioxolane	trans-5
OH 0	cis-5-hydroxy-2-methyl-1,3-dioxolane	cis-6
HO	trans-5-hydroxy-2-methyl-1,3-dioxolane	trans-6

Table 2-1. cis- and trans- conformational structures of glycerol acetal

In contrast to direct acetalization, the transacetalization reaction of glycerol with another acetal does not produce water (Scheme 2-1) and has a higher equilibrium constant than the direct

route. Because biodiesel production and subsequent purification are best accomplished in a water-free environment [10], transacetalization provides the opportunity to combine glycerol acetal formation with biodiesel production in an integrated operation without water formation.

In order to assess the viability of converting glycerol to its acetal products and provide a theoretical basis for designing the reactive distillation process proposed in Dr. Miller's patent [11], it is necessary to better understand the transacetalization reaction. Since very few reports have been published regarding the kinetics of this reaction [4, 6, 8], we have undertaken here a kinetic study of glycerol transacetalization with DEE using Amberlyst-15 cationic exchange resin as the catalyst. Effects of various reaction conditions, including reaction temperature, molar ratio of reactants, and catalyst loading have been examined along with reactant miscibility and measurement of the reaction equilibrium constant. A kinetic model describing the reaction is presented; results are compared with acetal formation via direct condensation with acetaldehyde.

The results presented in this work provide information to understand similar transacetalization processes between glycerol and other acetals, and establish the theoretic basis for development of large-scale glycerol acetal production process.

2.2. Experimental section

2.2.1. Materials

Anhydrous glycerol (99.5%), 1-propanol (99.9%) and 1-butanol (99.9%) were obtained from J.T. Baker. Ethanol (99.5%) and 1,1-diethoxyethane (99%) were purchased from Pharmco and Aldrich, respectively. Acetaldehyde (>99.5%) and amberlyst-15 cationic exchange resin (16-50 mesh, 1.2g/cm³) was purchased from Sigma-Aldrich. Amberlyst-15 cationic exchange resin was investigated as the catalyst. Before being used in reactions, it was pretreated at 90°C in a vacuum oven for 2 hours. Hydrogen (99.999%) and helium (99.999%) were used for GC analysis; both were purchased from Linde Gas, Inc.

2.2.2. Experiments

Glycerol acetalization with acetaldehyde was carried out in a 500 ml glass reactor cooled with ice water bath. To initiate an experiment, 200 ml of reactants (acetaldehyde and glycerol) plus 5% (weight to glycerol) Amberlyst-15 cationic exchange resin were added. The mixture was then stirred for 4 h for glycerol conversion.

Glycerol transacetlization with DEE was carried out using a Parr 5000 Multireactor System (Parr Instrument Company, Moline, IL), which includes six 75 ml stainless steel autoclaves. To initiate an experiment, 60 mL of reactants (DEE, glycerol and solvent) plus catalyst were placed in an autoclave and the vessel was sealed. The autoclave was heated at 2°C/min to the desired temperature and held for 5 min before the stirrer was activated to begin the reaction. Essentially no reaction took place during this heating period.

One ml liquid aliquots were taken from a sample port for analysis during reaction using a disposable syringe. Catalyst taken up in samples was eliminated by filtration to prevent further reaction in the sample solution. The samples were then diluted and analyzed by gas chromatography using the method described below.

At the end of reaction, the material in the reactor was collected and the catalyst was removed by filtration. The solution was then evaporated in a rotary evaporator at 70°C under 25 mmHg to remove volatile compounds such as ethanol and DEE. The final product was then weighed and analyzed by GC.

2.2.3. Analysis

Gas Chromatography

1-Butanol and 1-propanol were used as the internal standard and solvent, respectively, for this analysis. To prepare samples for analysis, 0.16 ml 1-butanol and 0.2 ml of reaction sample were added to a volumetric flask and the mixture was diluted with 1-propanol to 10 ml of solution. A Perkin-Elmer Sigma 2000 gas chromatograph with FID and a DB-Wax capillary column ($15m \times 0.53mm \times 1.0 \mu m$) was used for analysis. Ultra high purity helium (30 mL/min) was used as the carrier gas; the column temperature program involved holding at 40°C for 3min, heating at a rate of 30°C/min to 220°C, and holding there for 1 min. The total program time was 10 min. On-column injection was applied to analyze the samples. Injector and detector chamber temperatures were set at 60°C and 300°C, respectively.

Gas chromatography – mass spectroscopy

The structure of the primary reaction products was identified using GC-MS analysis (GC-Agilent 6890, MS-Agilent 5973) by injecting a 1 μ L sample onto a DB-wax capillary column (30m × 0.25mm × 0.25 μ m). The column temperature for GC-MS analysis included holding at 40°C for 5 min, heating at 20°C/min to 250°C and then holding for 10 min. Total program time was 25.5 min. Injector temperature was set at 240°C. Electron impact (EI) mass spectra were monitored from 20 to 300 m/z. The MS source was set at 230°C.

2.3. Results and discussion

2.3.1. Direct acetalization versus transacetalization

Direct glycerol acetalization with acetaldehyde was carried out in an ice water bath at 0 °C because acetaldehyde has a boiling point of 21°C. Two reactions were carried out with Amberlyst-15 cationic exchange resin as catalyst; the reactant molar ratio of glycerol:acetaldehyde was 1:1 and 1:4, respectively. After 4 h of reaction, the yields of glycerol acetal were 54% and 84%, respectively.

On the other hand, glycerol transacetalization with 1,1-diethoxyethane (DEE) using Amberlyst-15 cationic exchange resin as catalyst is a much faster reaction. At 25°C, a reaction with molar ratio of glycerol:DEE = 1:1 gives nearly theoretical yield of glycerol acetal after 2 h. More importantly, DEE is much easier to use than acetaldehyde because it is much less volatile and no special handling is required. Further, no water is formed in the reaction of DEE with glycerol. Thus, it can be concluded, as the two main approaches to synthesize glycerol acetals, glycerol transacetalization with DEE is a much better choice for reaction than acetalization with acetaldehyde. Therefore, DEE was chosen as the glycerol acetal forming reagent for the following kinetic study.

2.3.2. Identification of products

Glycerol transacetalization with DEE produces ethanol and glycerol acetals. However, some by-products were also obtained in this reaction. Figure 2-1 presents a GC analysis result of a typical reaction mixture. Structures of these compounds were identified using mass spectroscopy and are listed in Table 2-2. The detail of structure determination is presented in Appendix I.

The desired products include 2-methyl-4-hydroxymethy-1,3-dioxolane (peaks E and J) and 2-methyl-5-hydroxy-1,3-dioxane (peaks H and I). The two peaks corresponding to each of them are the cis- and trans- conformational structure of the isomers. This result is in agreement with Ferreira [4] and Camara's work [9]. The authors obtained the same glycerol acetals in their study of glycerol acetalization with acetaldehyde, and also detected the four GC peaks of the conformational isomers.



Figure 2-1. GC analysis of glycerol acetalization products

Peaks						
Α	В	С	D	E, J		
1,1-diethoxyethane (DEE)	ethanol (solvent)		anol 1-propanol 1-butanol (internal standard)			
	ОН	∕∕он	ОН			
F, G	Н	, I	K, L	М		
byproducts GAA	cis- (H, top) and trans- (I, bottom) 4- hydroxymethy-2- methyl-1,3-dioxolane		hemi-acetals of glycerol	Glycerol		
and	OH		and HO OH	НО ОН ОН		

Table 2-2. Key to compounds detected by gas chromatography (Figure 2-1)

Byproducts obtained in this reaction include 1) the hemi-acetals (peaks K and L) of glycerol and DEE, which are generally accepted as the intermediates in acetal synthesis [12], and 2) two complex acetals of glycerol (peaks F and G, together denoted GAA). Formation of GAA

arises from the reaction of the remaining free hydroxyl group in glycerol acetals (E, H, I, J) with DEE to form a second hemi-acetal and ethanol. This reaction is illustrated in Scheme 2-2.

Scheme 2-2. Formation of GAA from glycerol acetals and DEE.



The existence of these by-products reveals that glycerol transacetalization with DEE involves stepwise conversion of glycerol to hemi-acetal to glycerol acetal and then to GAA. In general, the amount of GAA formed is dependent on the initial reactant composition. The more DEE used, the more GAA obtained. This will be further discussed in the section discussing the of molar ratio section.

Another important side reaction is related to DEE disproportionation to ethyl vinyl ether (EVE). It has been reported [13] that at high temperature or in the presence of acid catalyst, vinyl ether can be formed by decomposition of acetal. As for DEE, the decomposition brings one molecule of ethanol and one molecule of EVE as shown in Scheme 2-3.





Temperature has a great influence on this reaction. Generally, with a certain amount of Amberlyst-15 loading, the higher the reaction temperature, the more vinyl ether is produced. In this study, no vinyl ether was found if the reaction was performed below 45 °C.

EVE is reactive and volatile; Shostakovsky and coworkers [14] report that in the presence of HCl, EVE could also react with glycerol and stepwisely form the same glycerol acetals as DEE and glycerol (Scheme 2-4).

Scheme 2-4. Reaction between glycerol and ethyl vinyl ether.



If acetal formation is the only consequence of EVE formation, no loss of reactant would be realized. Unfortunately, in the presence of Amberlyst-15 cationic exchange resin, EVE readily oligomerizes and forms a viscous compound with deep color. In a control experiment in which pure EVE was stirred with 1 wt% of Amberlyst-15 at room temperature, the colorless liquid quickly turned green and then dark brown in color rapidly, along with an accompanying sharp increase in viscosity.

The production of this viscous compound has been noticed in the transacetalization experiments. Figure 2-2 displayed the transacetalization reactions after 24 h performed at different temperatures. The color of the reaction mixture changed from transparent to dark as the

reaction temperature increased from 40 °C to 70 °C. Therefore, to minimize loss of DEE via this route and limit the by-product formation, the glycerol transactetalization reaction with DEE is best carried out at low temperature ($< 45^{\circ}$ C).



Figure 2-2. Glycerol transacetalization products after 24h. Reaction temperature, 1) 40 °C; 2) 50 °C; 3) 70 °C. Molar ratio of reactants, DEE:glycerol= 1:2. Amberlyst-15 cationic exchange resin loading = 1 wt% of glycerol. For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this thesis (or dissertation.

2.3.2. Reaction conditions

2.3.2.1. Reagent miscibility and use of ethanol as the reaction solvent

When mixed, pure glycerol and DEE forms two liquid phases. In order to examine the influence of this partial miscibility on reaction rate, experiments were carried out with and without ethanol as a solvent at conditions. Table 2-3 reports the number of phases present and the apparent reaction rate constant at several times for several reaction mixtures.

Without ethanol present, there is an initial period of low rate as a result of the presence of two liquid phases. As reaction proceeds, formation of acetals and liberation of ethanol solubilizes

the reactants, greatly accelerating the reaction such that equilibrium conversion is nearly achieved in 40 min. This is consistent with a previous report [6] in which reaction products were observed to homogenize the two reactant phases.

Denations	Molar Ratio		Rea	iction	time (min)
Reactions	glycerol:DEE:EtOH		0	2	5	10
Α	1:1:0		2	2	2	1
В	1:2:0	Number of phones	2	2	2	1
С	1:2:0.78	Number of phases	2	2	1	1
D	1:2:3		1*	1	1	1
А	1:1:0		-	-	-	1.9
В	1:2:0	constant min ($\times 10^5$	-	-	-	0.5
С	1:2:0.78	$L^2/mol \cdot g \text{ cat} \cdot s)$	-	-	4.5	3.4
D	1:2:3	2 (mor g.out b)	-	9.0	5.2	4.3

Table 2-3. Effect of ethanol as solvent for glycerol transacetalization reactions. Amberlyst-15 loading = 1 wt% based on glycerol, reaction temperature = 50°C.

* The mixture is in two phases at room temperature, but forms single phase at the reaction temperature.

From the apparent reaction rate constant calculated from a differential analysis of the concentration versus time profile, it is seen that the 1:1 glycerol:DEE mixture (no ethanol added) reacts more rapidly than the 1:2 glycerol:DEE mixture, because the reactants form a single phase earlier in reaction.

Solubility measurements at room temperature showed that for a mixture with 1 mole glycerol and 1 mole DEE, it requires 2.5 moles of ethanol to form a single liquid phase; while for

a mixture with 1 mole glycerol and 2 moles DEE, the amount of ethanol required to form a single phase is 3.7 moles.

Adding ethanol to the reactant mixture increases rate substantially because reaction takes place in a single phase from the beginning of reaction. Even with dilution of reactants because of the ethanol added, glycerol conversion exceeded 80% in both Reactions C and D after 10 minutes (versus ~35% in Reaction B without ethanol addition). These results are reflected in the apparent rate constants in Table 2-3.

It is worth noting that addition of ethanol, a reaction product, lowers the equilibrium glycerol conversion slightly, from 99.6% to 98.9% and 98.3% for Reactions B, C and D, respectively. Despite this, further experiments in this study were carried in ethanol as a co-solvent to obtain intrinsic transacetalization kinetics in a single reaction phase.

2.3.2.2. Molar ratios of reactants/GAA production

One of the most important variables affecting yield and selectivity of glycerol transacetalization is the glycerol:DEE molar ratio. Table 2-4 shows the equilibrium conversions of glycerol and DEE for glycerol:DEE reactant molar ratios from 1.5:1 to 1:2.

Table 2-4. Comparison of equilibrium conversion for reactions with various reactant molarratios

Reactant molar ratio			Amberlyst-15 loading (wt to	Time (h)	Temperature (°C)	Equilit conver	orium csion
Glycerol	DEE	Ethanol	glycerol)			Glycerol	DEE
1.5	1	4				64.3%	89.2%
1	1	4	1%	24	40	78.6%	81.5%
1	2	4				92.7%	50.1%

Although the presence of excess DEE improves glycerol conversion, it also leads to production of more by-product GAA. Figure 2-3 displays the GC analysis of the final products from the reactions listed in Table 2-4. As can be seen, the production of GAA is low if DEE is the limiting reactant. When DEE is in excess, however, the yield of GAA increased substantially, such that GAA concentration in the final product increases by a factor of ten when the initial DEE:glycerol molar ratio is increased from 1:1 to 2:1.



Figure 2-3. GC analysis of glycerol acetalization products. Reactions were carried out at 40°C with 1 wt% Amberlyst-15 loading (based on glycerol). Molar ratio, glycerol:DEE:ethanol = A) 1.5:1:4; B) 1:1:4; C) 1:2:4. Reaction time = 24 h.
2.3.3. Mass transfer effects

2.3.3.1. Effect of agitation speed

In order to minimize external mass transport resistances during reaction, several reactions were carried out at different stirring speeds. Figure 2-4 shows that reaction rate is essentially constant when stirring speed exceeds 800 rpm, indicating that external mass transfer resistances can be neglected. All kinetics experiments were thus performed at a stirring speed of 850 rpm.



Figure 2-4. Effect of stirring speed. Glycerol:DEE:ethanol = 1:1:12, catalyst loading = 1wt% (based on glycerol), temperature = 40°C.

2.3.3.2. Effect of catalyst loading & Internal Mass Transfer Resistances

Acid catalyst is essential for the transacetalization reaction to proceed. Control experiments showed negligible formation of cyclic acetals after 24 h without catalyst present. Experiments were carried out with several loadings of Amberlyst-15 cationic exchange resin (0.5

wt% to 3 wt% of the initial mass of glycerol present) using a 1:1 glycerol:DEE feed ratio in ethanol (glycerol:DEE:ethanol = 1:1:12) to avoid GAA formation and at 40°C to avoid DEE decomposition.

As shown in Table 2-5, the observed reaction rates per unit volume of catalyst are almost identical (~0.06 mol/L.cat·s) in each experiment, signifying that all catalyst participates in the reaction and that external mass transport resistances do not affect rate.

Reactant molar ratio	temperature	cataly	st loading	observed reaction rate	Φ_{wn}	
glycerol:DEE: EtOH	(°C)	weight (g)	wt to glycerol	(mol/L cat/s)	wp	
1:1:12		0.1835	3%	бо 0.06		
	40	0.1249	2%	0.06	0.32	
	40	0.0608	1%	0.06	0.34	
		0.0314	0.5%	0.07	0.35	

 Table 2-5. Evaluation of internal mass transport resistances

Analysis of mass transport resistances within the Amberlyst resin particles was carried out by estimating the Weisz-Prater observable modulus (Φ_{wp}) at the reaction conditions of highest reaction rate (Table 2-5). Values of Φ_{wp} are in the range of 0.30-0.35, indicating that only mild mass transfer resistances are observed. Details of this calculation are presented in Appendix II.

2.3.4. Kinetic model

As discussed above, DEE decomposes and forms EVE at reaction temperatures above 50°C. To minimize DEE decomposition, all reactions performed for the kinetic model development were carried out at temperatures at or below 40°C. In addition, DEE was used as

the limiting reactant to minimize byproduct GAA formation. Finally, because the reaction is rapid, all experiments were carried out with large excess of ethanol (at least 12:1 EtOH:glycerol) to reduce intraparticle mass transport resistances.

2.4.4.1. Estimation of equilibrium constant

Experiments were carried out at 25°C and at 40°C for 24 h to determine the concentration-based equilibrium constant of the acetal formation reaction. In the relationship used for the equilibrium constant (Eq. 1), the 5-membered and 6-membered GA isomers are treated together as one compound (subscripted 'Acetal'). The decline in equilibrium constant with increasing temperature (Table 2-6) shows that acetal formation is exothermic, as increasing temperature has an unfavorable effect on reaction equilibrium.

$$K_{C} = \frac{C_{Acetal,Eq} \cdot C_{EtOH,Eq}^{2}}{C_{Glycerol,Eq} \cdot C_{DEE,Eq}}$$
(1)

Table 2-6. Equilibrium constant of glycerol transacetalization reactions (Amberlyst-15loading = 1 wt% based on glycerol)

Reactant molar ratio	Eq	uilibrium	convers	ion	Observed K a lnK a			Z a
	glyc	erol	D	EE	Observed KC		mixe	
glycerol:DEE:EtOH	25°C	40°C	25°C	40°C	25°C	40°C	25°C	40°C
1.5:1:4	62.3%	64.3%	93.0%	89.2%	1350	830	7.2	6.7
1:1:4	81.1%	78.6%	83.8%	81.5%	1390	890	7.2	6.8
1:1:8	77.1%	75.2%	77.2%	73.4%	1410	1030	7.2	6.9
1:1:12	67.9%	65.1%	69.5%	62.4%	1250	960	7.1	6.9
						Avg.	7.2	6.8

2.3.4.2. Formulation of model

It is generally believed [15, 16] that the first step of the reaction is initiated with the protonation of an oxygen in DEE followed by the substitution of the ethoxy group by glycerol. After that, the second protonation-substitution step cyclizes the product as a compound with ring structure (Scheme 2-5).

Scheme 2-5. Reaction mechanism of the 6-membered glycerol acetal formation.



According to the reaction stoichiometry, the elementary rate expression for the reaction of glycerol with DEE (Scheme 2-1) can be written as follows:

$$-\frac{dC_{DEE}}{dt} = \eta k W_C \left(C_{DEE} C_{Glycerol} - \frac{1}{K_C} C_{EtOH}^2 C_{Acetal} \right)$$
(2)

where η is the effectiveness factor, k is the reaction rate constant per mass of catalyst, W_C is the weight of catalyst per volume of solution.

The large values of the reaction equilibrium constant (Table 2-6) indicate that the forward reaction dominates over much of the reaction such that the rate expression can be expressed as

$$-\frac{dC_{DEE}}{dt} = \eta k W_C \cdot C_{DEE} C_{Glycerol}$$
(3)

2.3.4.3. Model fit over course of reaction

When initial concentrations of glycerol and DEE are different, the concentration of glycerol at any time can be expressed as

$$C_{Glycerol} = C_{Glycerol,0} - (C_{DEE,0} - C_{DEE})$$
(4)

Combining Eq. (3) with Eq. (4) and integrating gives the following equation

$$\frac{1}{C_{Glycerol,0} - C_{DEE,0}} \cdot \ln\left(\frac{C_{Glycerol} \cdot C_{DEE,0}}{C_{Glycerol,0} \cdot C_{DEE}}\right) = \eta k W_C \cdot t$$
(5)

As shown in Figure 2-5, a plot of the left-hand side of Eq. (6) vs. time gives a straight line, indicating that the model reasonably describes the experimental data.



Figure 2-5. Second order reaction kinetic plot for glycerol transacetalization with DEE at 40°C, glycerol:DEE:ethanol = 1.5:1:15, 1 wt% catalyst loading based on glycerol

For the case where initial glycerol and DEE concentrations are equal, the molar balance for DEE is integrated to give

$$\frac{1}{C_{DEE}} - \frac{1}{C_{DEE,0}} = \eta k W_C \cdot t \tag{6}$$

A plot of $1/C_{DEE}$ vs. time for reactions with molar ratio of glycerol:DEE:ethanol = 1:1:12 at 40°C at several catalyst loadings is given in Figure 2-6, again illustrating that the kinetic model adequately describes the experimental data. This is confirmed by a parity plot in

Figure 2-7 of experimental vs. predicted reaction rates for all experimental data; most predicted rates fall within $\pm 20\%$ of the experimental data at the same conditions.



● 0.5% ◆ 1% ▲ 2% **■** 3%

Figure 2-6. Second order reaction kinetic plot for glycerol transacetalization with DEE at 40°C, glycerol:DEE:ethanol = 1:1:12, catalyst loading based on glycerol; 0.5%, 1%, 2%, 3% respectively.



Figure 2-7. Parity plot between the reaction rates observed in experiments and the ones predicted by the model.

2.3.4.4. Temperature dependence and activation energy

The kinetic model was applied to the transacetalization reaction for temperatures in the range of 25°C to 40°C with a feed ratio of glycerol:DEE:ethanol = 1:1:12 (Figure 2-8). From the slope of the lines in Figure 2-8, values of ηkW_C were determined. Values of effectiveness factor values (η) were calculated using Eq. (7) and the effectiveness factor Thiele modulus diagram provided by Smith [17]. In this equation, Φ_{wp} is the Weisz-Prater value, and Φ_s is the Thiele modulus for a spherical pellet. The results are presented in Table 2-7.

$$\Phi_{wp} = \eta \Phi_s^2 \tag{7}$$



Figure 2-8. Kinetics plot for glycerol transacetalization reactions at different temperatures. Conditions: initial molar ratio glycerol:DEE:ethanol = 1:1:12; catalyst loading 1% (based on the weight of glycerol)

Reactant Molar ratio (glycerol:DEE:EtOH)	Reaction temp. (°C)	Catalyst loading (wt to glycerol)	Reaction rate constant (k) $(\times 10^5$ L ² /mol•g.cat•s	Initial reaction rate per unit mass of catalyst (×10 ⁵ mol/g.cat•s)	Weisz- Prater value (Φ_{wp})	Effectiveness Factor (η)
1.5:1:15	40	1%	17.3	15	0.39	0.74
		3%	9.7	9.5	0.30	0.81
	40	2%	10.6	10.2	0.32	0.79
	40	1%	11.4	10.7	0.34	0.78
1:1:12		0.5%	12.0	11.2	0.35	0.77
-	35		8.1	8.2	0.26	0.84
	30	1%	5.6	6.1	0.19	0.90
	25		3.1	3.4	0.10	0.91

Table 2-7. Rate constant and Weisz-Prater value at different reaction conditions

According to Arrhenius equation

$$\ln k = \ln A - \frac{E_a}{R} \left(\frac{1}{T}\right) \tag{8}$$

A plot of of ln(k) versus 1/T in Figure 2-9 gives an activation energy of $E_a = 66.50$ kJ/mol. And a pre-exponential factor of A = $1.5 \times 10^7 L^2$ /mol•g.cat•s.



Figure 2-9. Arrhenius plot of forward rate constant of transacetalization of glycerol with DEE.

2.4. Conclusions

Glycerol transacetalization with DEE is a complete reaction that at 25°C, equilibrium conversions of reactant can be achieved in 2 h. This reaction is described by a simple second order kinetic model. The major products formed in the reaction are the cis- and trans- forms of 5-membered and 6-membered cyclic acetals. The reaction is best carried out at low temperature to avoid formation of ethyl vinyl ether from DEE and with DEE as the limiting reactant to avoid over-acetalization of the primary acetal products. High selectivity of reactants to desired products are achieved at these conditions.

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Chapter III. Separation of Cyclic Glycerol Acetal Isomers & Continuous Production of the 6-Membered Isomer

3.1. Introduction and literature review

Cyclic acetal formation from glycerol has been demonstrated in Chapter II. This class of compounds has been shown to be good fuel additive as it can improve fuel combustion and reduce particle emissions [1-4]. In a 2008 patent, Miller et al. [5] proposed a continuous process to synthesize these compounds along with the formation of biodiesel to obtain a composition useful as a fuel. In addition, glycerol acetal can be used as flavour [6] and the building-block for surfactants [7]. Moreover, the six-membered dioxane isomer can serve as an important precursor for the production of value-added chemicals from glycerol, such as 1,3-dihydroxyacetone [8] and 1,3-propanediol [9].

As mentioned in Chapter II, under ordinary conditions, the acetal products formed via either acetalization or transacetalization pathway with glycerol are 2-substituted-5-hydroxy-1,3-dioxane and 2-substituted-4-hydroxymethyl-1,3-dioxolane compounds, which when formed from asymmetric ketones or aldehydes are produced as both cis- and trans- conformational isomers for a total of four products.

If desired, a 5-membered ring dioxolane compound (2,2-dimethyl – 4-hydroxymethyl-1,3-dioxolane) can be synthesized with high selectivity (> 99%) by reacting acetone with glycerol [10, 11]. The selectivity to the five-membered ring dioxolane is unique to acetone; with other acetal forming reagents, the 6-member ring dioxane compounds are always co-produced along with their 5-membered dioxolane counterparts in quantities determined by the kinetics and equilibrium constants of the interconversion isomerization reactions. Aksnes et al. [12] calculated the isomerization equilibrium constant and pointed out that the exchange between the two isomers only happens in the presence of acid catalyst. Deutsch et al. [10] investigated the influence of reaction parameters on the selectivity of cyclic glycerol acetal formation. They carried out acetalization and transacetalization reactions using various solid catalysts, temperature, solvents with reagents including aldehydes, ketones and linear acetals. In those reactions, the isomer ratio dioxane:dioxolane is usually 60:40. In addition, the equilibrium ratio can be achieved via isomer interconversion even after the initial conversion of reactant is over. For instance, in the experiments of glycerol acetalization with benzaldehyde using Nafion-H NR-50 or Montmorillonite K-10, the authors received 50:50 mixtures of dioxane and dioxolane isomers at reaction completion. However, when the mixtures were left at room temperature for a few days, the ratio shifted to 60:40. They further proposed a mechanism (Figure 3-1) for this interconversion as that in the presence of acid catalyst, the activated oxygen in the benzylic position is the intermediate for this ring transformation.



Figure 3-1 Mechanism of the interconversion between glycerol acetal isomers [10].

Lab-scale direct separation of the dioxane and dioxolane isomers was carried out by Aksnes and coworkers [12] in the 1960s using gas chromatography; large scale production of pure GA isomers, however, is still a challenge.

It was reported by Showler and Darley [13] in the review of condensation of glycerol with aldehydes and ketones that the most reliable method of obtaining the acetal isomers in their pure form was by organic synthesis, although the cis isomer of 6-membered glycerol acetal could be separated by crystallization.

The solubility of the cis-5-hydroxyl-2-phenyl-1,3-dioxane (cis-HPD) is significantly different from the other three isomers in a 1:1 benzene–ligroin solution, and the isolation of cis-HPD was accomplished by crystallizing it from this mixture [9, 14]. However, the yield of cis-HPD in those work was only 25%. Moreover, the product obtained was not 100% pure, it contained small amount of trans-HPD and very little the 5-membered isomers.

In another study, Carlsen et al. [8] isolated pure cis-HPD by crystallization in diethyl ether. They used acid catalyst to re-equilibrate the mother liquor to obtain more cis-PHD. After multi-step equilibration and crystallization, they achieved a yield of 46% of cis-HPD.

Recently, Deutsch et al. [10] discussed the feasibility of separating these isomers by converting them into their derivatives with sufficient difference in physical properties, such as boiling point, polarity, and solubility. However, these procedures require extra expensive purification steps and are always accompanied by significant loss of target product.

It has been reported by Hill et al. [15] that as a mixture, GA product boils in the range of 176-187°C at atmospheric pressure. However, under reduced pressure, the isomers demonstrate different volatilities. For instance, the authors collected two distinct products in a distillation

experiment with fraction I boiling at 86-88°C (21 mmHg) and fraction II boiling at 101-103.5°C (20 mm Hg). Therefore, it is possible to separate GA isomers via vacuum distillation.

In this chapter, the synthesis of GA isomers via glycerol transacetalization with DEE using Amberlyst-15 cationic exchange resin is described. The equilibrium compositions of the GA isomer mixtures formed in transacetalization are characterized, and the use of reactive distillation to produce the pure cis-6 dioxane isomer is presented. Based on these findings, a continuous process was developed to make cis-6 dioxane isomer as the sole product of glycerol condensation with acetaldehyde or DEE.

3.2. Material and methods

3.2.1. Materials

Anhydrous glycerol (99.5%), 1-propanol (99.9%), and 1-butanol (99.9%) were obtained from J.T. Baker. Ethanol (Pharmco, 99.5%), 1,1-diethoxyethane (DEE, Sigma-Aldrich, 99%), and sodium carbonate (Sigma-Aldrich, >99%) were used without further purification. Amberlyst-15 cationic exchange resin (16-50 mesh, Sigma-Aldrich), used as the catalyst, was pretreated at 90°C in a vacuum oven for 2 hours prior to use. Hydrogen (99.999%) and helium (99.999%) were used for GC analysis; both were purchased from Linde Gas, Inc.

3.2.2. Synthesis of GA isomers

Cyclic GA isomers were synthesized at 45°C in a 20 L round bottom flask by adding glycerol (3.1 kg, 33.9 mol), DEE (4.0 kg, 33.9 mol), and Amberlyst-15 cationic exchange resin (120 g) and stirring for 4 hours. After reaction, the mixture was filtered to eliminate catalyst and then subjected to evaporation in a rotary evaporator at 70°C under an absolute pressure of 25 mmHg to remove unreacted DEE, product ethanol, and any volatile byproducts or impurities.

The final mixture contained the four GA isomers and only trace amounts (less than 1 wt% total) of unreacted glycerol and byproducts.

3.3.3. Distillation of GA isomers

A glass batch vacuum distillation column was constructed to separate the four GA isomers (Figure 3-2). The column (height = 3.6 m, i.d. = 50 mm) was packed with 0.6 cm 316 Stainless Steel PRO-PAK protruded metal distillation packing (Scientific Development Co.). The column reboiler, consisting of a two-liter round-bottom flask, was heated with a 750 W electric heating mantle. Column pressure was adjusted using a Model RV8 vacuum pump (Edwards Vacuum, Ltd.). The column was equipped with a condenser and a dry ice-cooled cold trap to prevent loss of distillate through the vacuum pump. Vapor temperature was measured at the top of the column using a thermometer.

To initiate a distillation, a measured quantity of GA isomers and boiling chips were loaded in the reboiler. The column was then evacuated to a desired pressure, and the reboiler contents were heated slowly (2°C to 3°C/min initially) to generate GA vapor. When steady state was achieved throughout the column at total reflux (as indicated by steady temperatures in the reboiler and throughout the column), the top product was withdrawn slowly, at a rate of 1 to 2 ml/min, by controlling the power to the reboiler. In all experiments performed in the column, liquid reflux took place via condensation along the column wall; no external reflux was returned to the column from the distillate product stream.



Figure 3-2. Vacuum distillation apparatus.

3.2.4. Analytical methods

GC analysis: 1-Butanol and 1-propanol were used as the internal standard and the solvent, respectively, for the analysis. To prepare samples, 0.16 ml of n-butanol and 0.2 ml of reaction sample were added to a 10 ml volumetric flask and the flask was filled with 1-propanol. The analysis was carried out on a Perkin-Elmer Sigma 2000 gas chromatograph equipped with a

flame ionization detector. A DB-Wax capillary column $(15m \times 0.53mm \times 1.0 \ \mu m)$ with oncolumn injection was used for analyses with the following temperature program: hold at 40°C for 3min, ramp to 220°C at 30°C/min and hold for 1 min. Ultra high purity helium was used as the carrier gas at a flow rate of 30 mL/min. Injector and detector chamber temperatures were set at 60°C and 300°C, respectively.

Gas Chromatographic – Mass Spectroscopic Analysis: Structures of the reaction products were identified using gas chromatography – mass spectroscopy (GC-Agilent 6890, MS-Agilent 5973). A 1 μ L sample was separated in a DB-wax capillary column with a temperature program similar to that described above; electron impact (EI) mass spectra were monitored from 20 to 300 m/z. The MS source was set at 230°C.

3.3. Results and discussion

3.3.1. GA synthesis and analysis

The transacetalization of glycerol with DEE to produce the GA required for this study was carried out at a near-stoichiometric molar ratio and proceeded nearly to completion. In the final reaction mixture, only 3.8% of unreacted DEE and 1.5% of glycerol remained as unreacted compounds. The combined yield of GA isomers was greater than 95%, and no products other than GA isomers and ethanol were detected in the reaction mixture.

Following reaction and removal of volatile species (DEE and ethanol) by rotary evaporation, GC-MS analysis of the product mixture showed the presence of four different structures corresponding [16, 17] to the four GA isomers displayed in Table 2-1 of Chapter II.

3.3.2. GA isomerization equilibrium

In the presence of an acid catalyst, the four GA isomers interconvert and reach an equilibrated composition [10, 12, 16, 17]. Figure 3-3a presents three GA samples, obtained from

the distillation experiments below, with different isomer compositions: Sample 1 is rich in cis-6 isomer, Sample 2 is rich in cis-5 and trans-5 isomers, and Sample 3 is rich in trans-5 and trans-6 isomers.

After stirring each sample for 5 hours at 298 K in the presence of 5 wt% (relative to GA) Amberlyst-15 cationic exchange resin, identical isomer compositions were established for all three samples (Figure 3-3b). At this temperature, the equilibrated concentrations of cis-6, cis-5, trans-5 and trans-6 are $37\pm1\%$, $17\pm1\%$, $13\pm1\%$, and $33\pm1\%$, respectively. The molar percentages of 6-membered isomers and 5-membered isomers are approximately 70% and 30%, respectively, at equilibrium.

The concentration-based equilibrium constants of isomerization were calculated based on Scheme 3-1 and Equations (1) to (3). The values are $K_{1,2} = 0.46$; $K_{2,3} = 0.76$; $K_{3,4} = 2.54$. With these three values the equilibrium constants between any two isomers can be calculated.



Scheme 3-1. Equilibrium constants of isomer interconversion.

$$K_{1,2} = \frac{[cis-5]}{[cis-6]}$$
(1)

$$K_{2,3} = \frac{[trans-5]}{[cis-5]} \tag{2}$$

$$K_{3,4} = \frac{[trans-6]}{[trans-5]} \tag{3}$$



Figure 3-3. Isomer composition of three GA samples before and after equilibration at 25°C. a) – Before; b) – After equilibration.

Although equilibration of GA isomers was observed within a few hours in the presence of 5 wt% Amberlyst-15 catalyst, it is reported in the literature that isomerization can take many years to reach equilibrium without acid present [16, 17] and that isomerization rate remains very slow below a certain threshold concentration of acid [12]. Sufficient acid was therefore used in all experiments to drive the isomerization reactions rapidly to equilibrium.

In addition to requiring a sufficient quantity of catalyst present, rapid isomerization also requires vigorous agitation (to ensure mass transfer between solid catalyst and solution) and elevated temperature. For example, Sample 1 took 12 hr to reach equilibrium at 0°C, but only one hour at 80°C. Increasing temperature also shifts the equilibrium composition (Figure 3-4): for Sample 1, increasing temperature from 0°C to 80°C decreased the sum of (cis- + trans-) 6-membered isomers from 78% to 54%. However, the total quantity of cis- (cis-5 + cis-6) and trans- (trans-5 + trans-6) isomers remained essentially constant over all temperatures at $55\pm 2\%$ and $45\pm 2\%$, respectively.



Figure 3-4. Isomer equilibrium at different temperatures.

The higher concentration of cis- isomers at equilibrium has been attributed [18] to intramolecular hydrogen bond formation. The cis-6 isomer is stabilized by a relatively strong intramolecular hydrogen bond, with the corresponding trans-6 bond weaker and cis-5 and trans-5 bonds weakest and nearly identical. Therefore, the cis- isomers are slightly favored.

3.3.3. Separation of GA isomers

Two vacuum distillation experiments were carried out to obtain each of the GA isomers in their pure forms. In the first distillation, 896 g (800 ml) of a GA mixture containing 35% cis-6, 18% cis-5, 15% trans-5, and 32% trans-6 isomers was placed in the reboiler. To avoid isomer interconversion, the solution was maintained at a weakly basic state by adding 50 g of sodium carbonate to the mixture. This initial distillation was carried out at a pressure of 20.5 ± 1.0 mm Hg (except for Sample 1, where the pressure was temporarily reduced to 9.0 mmHg). Twelve 60-mL distillate samples were collected over the course of the distillation and analyzed by GC. Ninety percent of the initial charge to the still pot was recovered as distillate in these samples (Table 3-1). The material remaining in the still pot consisted primarily of the trans-6 isomer and glycerol; inclusion of this material gave essentially complete ($100\pm2\%$) closure of the material balance for the experiment.

	Initial GA charge		Product rec	Product recovery in distillate		
	Mass	Composition	Mass (g)	Percent of total	distillate	
	(g)	(wt%)	11111111111111		(%)	
Cis-6	311	35	288	36	93	
Cis-5	166	18	152	19	92	
Trans-5	132	15	120	15	91	
Trans-6	287	32	246	30	86	
Total	896	100	806	100	90	

Table 3-1. Summary of GA isomers recovered in the initial distillation

Figure 3-5 gives the reboiler liquid temperature, vapor temperature at the top of the column, and composition (via GC) of the distillate samples taken during the distillation. The results clearly show the order of decreasing volatility of the GA isomers as cis-6, cis-5, trans-5, and finally trans-6. As the more volatile isomers are removed from the still pot, liquid and vapor temperature gradually increase.



→ Cis-6 → Cis-5 → Trans-5 → Trans-6 --*-- Distillate vapor temp. --+-- Reboiler temp.

Figure 3-5. Initial distillation of GA isomer. Column pressure was 20.5±1.0 mmHg (except for the first sample, where the pressure was 9.0 mmHg).

The first three samples collected during the distillation contained high concentrations (>90%) of the cis-6 isomer, with the first one composed of 99% cis-6. Likewise, the last two samples contained >90% of the trans-6 isomer, with the final sample composed of 97% trans-6. Clearly, these species separate well from the other isomers present in the mixture.

In Figure 3-5, it can be seen that pure cis-5 isomer and trans-5 isomer were not obtained in the distillation experiment, as no sample contained more than 75 wt% cis-5 isomer or more than 60 wt% trans-5 isomer. A second distillation was therefore performed at a lower pressure $(7.7\pm0.3 \text{ mmHg})$ in order to separate and obtain pure samples of the 5-membered GA isomers. In this run, a charge of 914 g (816 ml) of a mixture of 17 wt% cis-6, 38 wt% cis-5, 43 wt% trans-5, and 2 wt% trans-6 isomers was fed into the reboiler along with 50 g of sodium carbonate. At the lower pressure, the liquid temperature was about 20°C lower than in the first distillation. From this distillation, a total of 744 g of distillate product (81% of that fed) was collected in 21 total samples with an average sample size of 31 mL (Table 3-2). Recovery of unseparated GA isomers from the reboiler again gave essentially 100% closure of the material balance.

	Initial GA c	harge	Product distillate	recovered in	Percent recovered in distillate	
	Mass (g)	Composition (wt%)	Mass (g)	Percent of total	(%)	
Cis-6	154	17	152	20	99	
Cis-5	351	38	336	45	96	
Trans-5	391	43	252	34	65	
Trans-6	18	2	4	1	21	
Total	914	100	744	100	81	

Table 3-2. Summary of GA isomers recovered in the second distillation

The lower pressure of this distillation significantly improved the quality of separation of the cis-5 and trans-5 isomers (Figure 3-6). Several samples contained more than 90% of a 5-membered isomer; among them, the sample at 201 min contained 93 wt% cis-5 isomer, and the sample at 559 min contained 97 wt% trans-5 isomer.



Figure 3-6. Second distillation of GA isomers. Column pressure: 7.7 ± 0.3 mmHg.

The above distillation experiments show that it is possible to achieve a good separation of GA isomers by optimizing operating conditions such as pressure in a packed distillation column.

3.3.4. Batch and continuous production and recovery of cis-6 isomer

As mentioned earlier, the 6-membered dioxane GA isomers are potential precursors for several valuable chemical products. In the above distillation of GA isomers, the maximum quantity of 6-membered isomers achievable is determined by the feed composition, since reactions are intentionally suppressed by base. However, if interconversion of GA isomers is catalyzed during distillation, it is possible to obtain high purity 6-member cis isomer at higher purity than in an equilibrium batch reaction. Removing the most volatile cis-6 isomer by distillation from an isomer mixture containing an acid catalyst provides a driving force toward re-equilibration in the reboiler, thus producing more cis-6 isomer. As long as the isomer interconversion rate is faster than the distillation rate, the charge in the still pot will approach its equilibrium composition and provide a stable cis-6 source such that cis-6 is the sole product recovered in the distillate.

To demonstration of this concept, a batch reactive distillation was carried out by charging 1344 g (1200 ml) of a mixture of 32 wt% cis-6, 26 wt% cis-5, 20 wt% trans-5, and 22 wt% trans-6 GA isomers along with 100 g of Amberlyst-15 cationic exchange resin to the reboiler pot of the glass column. For this experiment, the column pressure was maintained at 1.2 ± 0.2 mmHg. During the distillation, 16 distillate samples were collected with an average volume of 50 ml; the average distillate rate was maintained at approximately 2 ml/min.

As shown in Figure 3-7 and Table 3-3, the reactive distillation experiment produced a high concentration of cis-6 isomer (from 89% to 96%) in all samples; the total quantity of distillate produced (895 g) contained 93 wt% cis-6 isomer. The other species in the distillate was the cis-5 isomer; no trans- isomers were collected. The low pressure of this experiment (1.2 mm Hg) resulted in low reaction temperatures of 42–52°C. Some fluctuation in temperature, due to pressure fluctuation, was observed, but overall the reboiler temperature remained relatively constant over the course of the experiment. This is evidence that the interconversion rate is rapid relative to the distillation rate, as the reboiler composition and thus the liquid bubble point was essentially constant over the course of distillation.



Figure 3-7. Reactive-distillation of GA isomers. Column pressure was 1.2±0.2 mmHg.

	Initial GA charge		Produc	Product recovered in distillate		
	Mass (g)	Composition (wt%)	Mass (g)	Percent of total	distillate (%)	
Cis-6	430	32	836	93	194	
Cis-5	349	26	59	7	17	
Trans-5	269	20	0	0	0	
Trans-6	296	22	0	0	0	
Total	1344	100	895	100	67	

Table 3-3. Summary of GA isomers recovered in reactive-distillation

Although only about two-thirds of the initial charge to the still pot was distilled, results to that point indicate that if the reboiler pot is continuously charged with GA isomers to make up the consumption, continuous interconversion of GA isomers and recovery of cis-6 product is possible.

To demonstrate this, a continuous distillation experiment was therefore carried out. In this run, 504 g (450 mL) of a mixture of 36 wt% cis-6, 16 wt% cis-5, 14 wt% trans-5, and 34 wt% trans-6 GA isomers was charged to the reboiler pot of the glass column along with 50 g of Amberlyst-15 cationic exchange resin. For this experiment, the column pressure was maintained at 2.9 ± 0.2 mmHg. Once the distillate product started to condense at the top of the column, a continuous feed of the same GA isomer mixture was introduced to the column reboiler to maintain its liquid level constant. The feed rate was adjusted to match the distillate rate from the column, which was approximately 1.8 mL/min. During the distillation, 16 distillate samples were collected with an average volume of 59 mL.

As shown in Figure 3-8, this experiment produced samples with high concentration of cis-6 isomer (from 90% to 96%) continuously during operation of the column. The reboiler temperature and distillate vapor temperature were essentially constant during operation, indicating that the reboiler composition was constant and that the column was operating at steady state. The total quantity of distillate obtained was 1028 g, more than twice the amount of the initial charge to the reboiler, demonstrating that continuous production of the cis-6 isomer from the GA acetal mixture is feasible. Based on these results, it is fully expected that an appropriately designed commercial-scale column with sufficient separation capacity would provide essentially pure cis-6 isomer.



Figure 3-8. Continuous reactive distillation of GA isomers. Column pressure = 2.9 ± 0.2 mm Hg.

Discussion

A process concept to produce cis-6 isomer from glycerol is proposed in Figure 3-9. In this process, glycerol and aldehyde or dialkyl acetal are introduced to Reactor 1 to produce mixed GA isomers. Following Reactor 1, reaction mixture are heated to remove product ethanol, water, and acetaldehyde. The mixture of GA isomers is then introduced to the reboiler of a continuous reactive distillation column containing acid catalyst. The cis-6 isomer is produced as a continuous distillate stream from the column.



Figure 3-9. Process concept for continuous production of 2-methyl-5-hydroxy-1,3-dioxane (cis-6 isomer) from glycerol.

In this process, glycerol and acetaldehyde are inexpensive chemical substances that are readily available. However, the challenge of using acetaldehyde is the formation of water along with the acetals and the reaction is reversible. Shevchuk et al. [19] investigated the thermodynamic equilibrium of glycerol acetalization with paraldehyde. They found that the formation of GA is favored at high temperature, however, the highest equilibrium constant they observed was 1.3, corresponding to a yield of 54%. Therefore, this reaction is most advantageously conducted in a reactive distillation column with acetaldehyde in large amount excess as suggested by Miller et al. [6]. In the reactive distillation process they proposed, glycerol and acetaldehyde are introduced to the top and bottom of a reactive distillation column, respectively. The reactive zone in this column is packed with solid catalyst packing. GA isomers are synthesized in the reactive zone. During the operation, unreacted reagents and water are

separated for recycling from the top, and the product which consists of GA isomers can be obtained at the bottom of RD column.

On the other hand, if a dialkyl acetal substance is used as surrogate for acetaldehyde, it must be synthesized prior to the GA formation reaction. And then, the reaction of glycerol with the acetal compound can proceed to completion and thus a simple stirred tank or packed bed reactor suffices as Reactor 1.

It has been reported that such dialkyl acetals can be produced by the acid-catalyzed acetalization reaction with 2 mol of monohydric alcohol and 1 mol of aldehydes [20]. In case of formation of dialkyl acetal of acetaldehyde, recent research has been focused on using heterogeneous catalysts and the readily available alcohols, such as methanol [21, 22], ethanol [23-25] or butanol [26]. Thermodynamic and kinetic investigation indicates that with these alcohols, the acetalization reaction is slightly exothermic and equilibrium-limited (Table 3-4). Various solutions have been proposed to overcome this limit and improve the acetal productivity, e.g. using organic solvents to modify the equilibrium in a continuous flow reactor [24]; application of fixed bed adsorptive reactor [22], moving bed reactor (MBR) [22, 26] or simulated moving bed reactor (SMBR) [26] to integrate reaction and separation in a single unit apparatus, etc. With these technologies, the equilibrium can be shifted toward the desired product, and thus commercial scale production of dialkyl acetal from green natural resources is feasible.

Once the cyclic acetal forming reagent (acetaldehyde or its dialkyl acetal) is provided, the process proposed in Reactor 1, Figure 3-9 can be operated in a semi-batch mode or a continuous mode to match the distillation rate of the cis-6 isomer.

		Reaction Temperature (K)				
		293.15	303.15	313.15	323.15	333.15
Methanol / acetaldehyde = 2:1 [21]	Equilibrium conversion of acetaldehyde	71.3	69.1	69.0	66.5	65.3
	(%)					
	Equilibrium constant	5.35	4.03	4.01	2.92	2.55
Ethanol / acetaldehyde = 2.2:1 [23]	Equilibrium conversion of acetaldehyde	59.0	57.3	55.7		52.3
	(%) Equilibrium constant	2.20	1.92	1.66		1.21

 Table 3-4. Thermodynamic data of acetaldehyde acetalization reaction with alcohols [21, 23]

 (Equilibrium constants are based on mol fraction).

3.4. Conclusions

Four isomers are formed in the transacetalization of glycerol with 1,1-diethoxyethane. In the presence of acid catalyst, the isomers interconvert to form an equilibrated mixture that contains similar quantities of the four products. Distillation of the isomers shows that the cis-6 dioxane isomer (2-methyl-5-hydroxy-1,3-dioxane) is the most volatile, and is distilled preferentially such that nearly pure cis-6 isomer is initially produced. When an acid catalyst is added to the mixture of isomers such that interconversion can occur during distillation, it is possible to produce 90+% cis-6 isomer in quantitative yield from glycerol. A larger column or controlled reflux could lead to higher purities. This work demonstrates that a continuous process is possible.
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Chapter IV. Oxidation of 6-Membered Glycerol Acetal

4.1. Introduction and literature review

Chapter II demonstrated the feasibility of continuous production of pure cis-6 GA isomer from glycerol. With the availability of this substance, new synthesis pathways can be developed to obtain valuable chemicals. For instance, by oxidizing the remaining free hydroxyl group in cis-6 and hydrolyzing the corresponding ketone product, 1,3-dihydroxyacetone (DHA) can be produced [1]. Likewise, by dehydroxylation and hydrolysis, 1,3-propanediol can be synthesized from cis-6 [2].

DHA is a very important chemical product. Because of its non-toxic tanning effect, it has been extensively used in the cosmetics industry. DHA, as the active ingredient of sunless tanning lotions, has a growing market demand. In addition, DHA can be used as a versatile building block for the organic synthesis of a variety of fine chemicals (Figure 4-1) [3].

Currently, commercial synthesis of DHA is performed via glycerol fermentation approaches utilizing microorganisms [3, 4]. Although the microbial processes can provide high selectivity to DHA, they have some notable disadvantages such as low productivity and high production cost [5]. For example, in the glycerol fermentation with *Gluconobacter oxidans*, it takes ~32 h to obtain 87-94% yield of DHA [6]. Moreover, glycerol and DHA produced in these processes can cause inhibition of microorganism growth [7]. Thus, although biochemical technologies have increased the DHA production to a prominent level, the production rate has not reached the level yield to meet the desired commercial demand. A process for direct oxidation of glycerol is highly desirable.



Figure 4-1. DHA as the building block to other chemicals [3].

4.1.1. Direct oxidation of glycerol to DHA

Scientists have attempted conventional chemical oxidation processes to make DHA from glycerol using metal catalysts with air or molecular oxygen [8-12]. The goal is to achieve direct oxidization of the secondary hydroxyl group in glycerol to a carbonyl bond. Unfortunately, this reaction is always accompanied with primary alcohol oxidation and a variety of products (i.e. glyceroaldehyde, glyceric acid, etc.) are produced. For example, in a liquid phase batch reactor with Au/C or Au-Pd/C catalyst, glycerol was completely oxidized to a complex mixture after 5 h.

The main product was glyceric acid (45%); the selectivity to DHA, however, was only $\sim 10\%$ [8-10]. Platinum catalysts have also been tested in this application. Results show that they are more selective for oxidation of primary alcohols [11, 12]. Kimura and co-workers reported that by using 5 wt% Pt on carbon, it is possible to obtain DHA from glycerol, but the yield was only 4% for DHA at 37% conversion [13].

Recently, it was found that introducing Bi to a Pt/C catalyst could enhance the selectivity toward the oxidation of secondary hydroxyl groups [13]. With such catalysts, 50% selectivity to DHA was achieved at ~70% conversion of glycerol [5, 13, 14]. Hu et al. [6] examined the effect of various reaction parameters on Bi-Pt/C catalyzed DHA production from glycerol. They found the optimum reaction conditions for maximum DHA yield were using a catalyst of 3% Pt-0.6%Bi/C, reacting at 80°C, 30 psig O₂, and initial pH \approx 2. Under these conditions, a maximum yield of DHA of 48.1% was achieved.

Overall, direct conversion of glycerol to DHA is faster than fermentation approaches. However, such reactions always require expensive catalysts and harsh reaction conditions. In addition, the yield of DHA is not very high because of competition for primary alcohol oxidation product, and is thus not suitable to meet the requirements for large scale production.

Compared with glycerol, cis-5-hydroxy-2methyl-1,3-dioxane (cis-6) appears to be a much better substrate for DHA synthesis. Because in the molecule of cis-6, the primary hydroxyl groups are blocked by the cyclic acetal bonds, high selectivity of secondary alcohol oxidation can be expected. Therefore, if a suitable oxidation reagent is found for this purpose, a more productive process can be established to make DHA. The next section provides an overview of alcohol oxidation methods.

4.1.2. Alcohol oxidation to carbonyl compounds

The desired product from oxidation of the 6-membered GA isomer, as shown in Scheme 4-1, is a ketone compound, 2-methyl-1,3-dioxan-5-one (G-tone).

Scheme 4-1. From 6-membered GA isomer to its ketone counterpart.



In the last two centuries, various approaches have been developed to oxidize alcohols to their carbonyl products. Among them, the most commonly used reagents are the chromium-based chemicals. In 1946, Jones et al. [15] discovered the "Jones reaction" (Scheme 4-2). With the Jones reagent, which is chromium trioxide and diluted aqueous sulfuric acid in acetone solution, primary and secondary alcohols can be oxidized to carboxylic acids and ketones, respectively. In this reaction, alcohol is first converted into chromic acid ester, and then the ester evolves to the final product [16, 17]. The drawback of the Jones reaction is the use of sulfuric acid, which may cause side reactions in some acid-sensitive functional groups.

Scheme 4-2. Mechanism of Jones reactions [16].







In 1968, Collins reagent [18] was developed for alcohol oxidation. Collins reagent is the complex of chromium trioxide with pyridine in dichloromethane. Chromium trioxide derivatives are very strong oxidizing agents, however, the preparation procedure is quite dangerous in that it has the potential to explode in the presence of some organics [19].

Other chromium-based reagents include pyridinium chlorochromate (PCC) [20] and pyridinium dichromate (PDC) [21]. PCC is a yellow-orange solid, which is prepared from the reaction of pyridinium, chromic acid and concentrated hydrochloric acid. This oxidant is very effective in transforming alcohols to their carbonyl products in high yield at room temperature [19]. For primary alcohols, PCC selectively oxidizes the substrates to aldehydes and rarely does the over-oxidation to carboxylic acids.

PDC is produced by adding pyridinium into aqueous chromium trioxide solution. This bright-orange solid is a very efficient alcohol oxidant. Over-oxidation of primary alcohols into carboxylic acids can be prevented by controlling the amount of water in the reaction media [19].

In general, chromium-based reagents are cheap and easy to prepare. They can normally guarantee a good yield of oxidation product. However, one noticeable disadvantage of these reagents is that chromium compounds are highly toxic, corrosive, and carcinogenic. Large-scale application may cause serious environmental problems. In addition, they are strong oxidants that may lead to explosion under some conditions. Therefore, application of these reagents is usually limited to the lab-scale.

The Swern oxidation [22] is a widely used chromium free oxidation procedure. It uses oxalyl chloride-activated dimethyl sulfoxide (DMSO) and organic bases (i.e. triethylamine) as the oxidation reagent. This reaction can be performed under mild conditions and has a wide tolerance of functional groups [23]. The mechanism of this reaction involves the formation of a five-membered ring transition state and then the decomposition of the ring to dimethyl sulfide and the desired aldehyde or ketone products (Scheme 4-3) [19, 23]. Generally, Swern reactions must be carried out at very low temperatures because of the poor thermal stability of activated DMSO. Its application in organic synthesis is also somewhat limited by the stinky odor of the byproduct dimethyl sulfide [19].

Scheme 4-3. Mechanism of Swern oxidation [19, 23].



In 1983, Dess and Martin [24] developed the hypervalent iodine compound Dess-Martin periodinane (DMP, Scheme 4-4) reagent as the oxidant for alcohols. DMP has many advantages over chromium- and DMSO-based reagents. It offers rapid, complete, selective and mild oxidation of alcohols to aldehydes or ketones at room temperature [19, 25]. However, DMP has some disadvantages in application including its high price, the risk of explosion if decomposed, and the requirement of tedious purification steps after reaction [19].

Scheme 4-4: Alcohol oxidation by DMP [24].



TEMPO, 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl, or (2,2,6,6-tetramethylpiperidin-1-yl) oxidanyl, is broadly employed in organic synthesis as a catalyst for the oxidation of alcohols [19, 26]. This compound is prepared by oxidation of 2,2,6,6-tetramethylpiperidine. It is very efficient in alcohol oxidation reactions such that they can reach equilibrium in a few minutes [19]. A routine procedure of using TEMPO [19, 27] was established as mixing 1 mol% of a TEMPO related stable nitroxide radical with excess of bleach (NaClO), KBr, and NaHCO₃ in a biphasic medium of water and dichloromethane or tetrahydrofuran. In this process, NaOCl is the secondary oxidant that re-oxidizes the reduced TEMPO product. NaHCO₃ is used to adjust the pH value. The limitation of TEMPO related oxidation is the competing reactions by HClO produced from NaClO [19]. In addition, separation of the reaction mixture, which contains inorganic salts and organic substances, is quite a challenge for large-scale application.

Another classic and useful method for alcohol oxidation is Oppenauer oxidation [28, 29]. Oppenauer oxidation is the reverse process of Meerwein-Ponndorf-Verley (MPV) reduction. The mechanism of Oppenauer oxidation, as shown in Scheme 4-5, is believed to involve a sixmembered cyclic transition state in which both the carbonyl compound and the reducing alcohol are coordinated to the metal ion [28]. Generally, the oxidation reaction is performed with excess of a hydride acceptors (ketone or aldehydes) and catalytic amounts of Al(III) alkoxide such as aluminum t-butoxide, aluminum isopropoxide, or trimethyl aluminum. The advantage of Oppenauer oxidation over the traditional oxidation processes is that this reaction is highly selective for secondary alcohols and does not oxidize other sensitive functional groups such as amines and sulfides [30].



Scheme 4-5. Mechanism of Oppenauer oxidation [28].

Oppenauer oxidation has been proved to be extremely successful in the oxidation of sterols. However, its application in synthesis of ketones outside the field of steroids met a more limited success because of less favorable thermodynamics [19] and side reactions such as dehydration of alcohols and aldol condensations [28] which are induced by the basic character of the aluminum alkoxides. In addition, trimethyl aluminum is very sensitive to moisture, so if it is used as a catalyst, the reaction must be carried out under strictly anhydrous conditions [31]. Such drawbacks greatly limited the application of Oppenauer oxidation.

Ruthenium-based catalysts have great potential for catalytic oxidation of various organic compounds because of their wide scope of oxidation states (from -2, divalent to -8, octavalent)

and various coordination of geometries in each electron configuration [19, 32, 33]. A Latimer diagram of the reduction potentials of ruthenium species in base are given in Figure 4-2 below:

$$R_{uO_{2}} = -0.35 R_{uO_{4}} = -0.59 R_{uO_{4}} = -1.00 R_{uO_{4}} R_{uO_{4}} = -1.00 R_{uO_{$$

Figure 4-2. Standard reduction potential of Ru species at various oxidation states [34].

For alcohol oxidation, the Ru-based catalytic systems include $RuCl_2(PPh_3)_3$ with oxidants such as N-methylmorpholine N-oxide [35], iodosylbenzene [36], and peracetic acid [37], RuCl₃ with hydrogen peroxide [38], K₂RuO₄ with peroxodisulfate [39], and RuO₄ with sodium hypochlorite [19, 40], etc.

Ruthenium tetroxide (RuO₄), in particular, is a very powerful oxidant that can easily convert secondary alcohols, including very hindered ones, to ketone and primary alcohols to carboxylic acids very rapidly at room temperature [19].

Ruthenium tetroxide is a golden-yellow solid that has a high solubility in non-polar solvents such as carbon tetrachloride (CCl₄) and dichloromethane (CH₂Cl₂). The partition coefficient of RuO₄ in CCl₄-water system is in the range of 59-60 [19, 40]. Because it has high volatility (melting point = 25° C) and always reacts violently with common organic substrates, RuO₄ is generally dissolved in CCl₄ and handled as solution [19, 32, 40]. This solution can be easily prepared by stirring an aqueous solution of sodium metaperiodate (NaIO₄) [19], sodium hypochlorite (NaClO) [1] or sodium bromate (NaBrO₃) [41, 42] with a suspension of hydrated ruthenium dioxide [19, 32] or ruthenium (III) chloride [41, 42] in CCl₄.

In early experiments, a stoichiometric amount of RuO₄ was employed for oxidation of organic compounds [19, 43]. Later, the procedure was simplified to using catalytic amounts of RuO₄ in the presence of NaIO₄ as secondary oxidant in a biphasic water-CCl₄ system [44]. In 1965, Parikh and Jones further developed this method in that, rather than being prepared independently, RuO₄ is generated *in situ* by oxidation with excess of NaIO₄ of catalytic hydrated RuO₂ [45].

As shown in Scheme 4-6, the mechanism of RuO₄-catalyzed oxidation of secondary alcohols to aldehydes or ketones involves a two-electron transfer process [46-48]. It is generally accepted that the reaction rate is determined by the hydride transfer process from alcohol to the oxidant [49].

Scheme 4-6. Mechanism of the RuO₄-catalyzed oxidation of alcohols to aldehydes or ketones [46].



For secondary alcohol oxidations, one molecule of RuO_4 can oxidize two molecules of the substrates to the corresponding ketone product, while RuO_4 is reduced to RuO_2 [19]. The reaction is usually performed in a biphasic system (i.e. water-CCl₄) [33]. As shown in Figure 4-3, in such a system, the substrate is oxidized by RuO₄ in the organic phase. The co-product is a black precipitate of RuO₂, which can be re-oxidized to RuO₄ by the secondary oxidant (i.e. NaIO₄, NaBrO₃, NaClO) in the aqueous solution. The regenerated RuO₄ then enters the organic phase again for another cycle of oxidation. In this way, the alcohol substrate can be continuously oxidized to the desired product with catalytic amounts of RuO₄ while the secondary oxidant is consumed. When the reaction is finished, the residue RuO₄ species in the organic phase can be easily recovered by adding isopropanol to make it RuO₂ precipitate [19].



Figure 4-3. Phase-transfer oxidation with ruthenium oxide [33].

Phase-transfer reaction with ruthenium-based catalysts is very efficient in oxidizing many organic substrates. However, this process is much less effective for oxidizing alcohols with high polarity. Such alcohols have low solubility in organic solvent, thus cause a poor mixing with the oxidant. Another drawback of this reaction is that separation of the product from the solution with ruthenium oxides and oxidizing salts is always a problematic issue.

4.1.3. Alcohol oxidation using green oxidants

In the last a few decades, there was a growing demand for developing environmentally benign processes to eliminate the pollution problems encountered in conventional chemical industry. The requirement for "green chemistry" has led to extensive research in catalytic alcohol oxidation using clean oxidants such as air, molecular oxygen (O_2) [32], hydrogen peroxide (H_2O_2) [32], and ozone (O_3) [50, 51], etc. Such substances have many advantages over classical oxidation reagents that they are easy to get, inexpensive, and the sole byproduct generated in alcohol oxidation reactions is water. Thus the use of clean oxidants can greatly diminish the pollution problems caused by using conventional methods.

Homogeneous catalysts, in many circumstances, exhibited good performances in alcohol oxidation with these clean oxidants [33, 52, 53] However, industrial scale application of these catalysts may cause many corrosion problems and increase the difficulty of post-reaction separation and purification. Furthermore, the recycle of homogeneous catalysts is always a challenge.

Heterogeneous catalysts, on the other hand, are of significant interest to chemical engineers because of their easy handling, simple separation, and reusability. Therefore, in this study, the investigation was focused on using heterogeneous solid catalysts with clean oxidants.

Molecular oxygen and air

Heterogeneous catalysts for gas or liquid phase oxidation of alcohols using molecular oxygen or air as the oxidant has been broadly studied [54, 55-57]. Numerous types of materials containing transition metals such as Pt, Pd, Au, Ag, Ru, V and Mo etc. exhibited good catalytic activity in this application [55]. Among them, the most frequently used heterogeneous catalysts

usually consist of platinum group-metals, e.g. Pt, Pd and Ru, as the active components [12, 55]. It has been reported that these metals can activate the alcohol substrates and molecular oxygen under close to ambient conditions [55]. For instance, with Pt- or Pd-based catalysts, alcohol oxidation reactions can achieve close to 100% yields of carbonyl compounds or carboxylic acids at mild reaction conditions (e.g. 293K-363K, atmosphere pressure of O₂) [14, 55, 56, 58].

Mallat and Baiker [55] reviewed the oxidation of alcohols with molecular oxygen on various solid catalysts in aqueous solutions. They concluded that the most accepted mechanism model of this type of reaction is the oxidative dehydrogenation procedure (Figure 4-4) [12, 55]. In this approach, alcohols adsorb and dehydrogenate on the metal surface in two steps, i.e. dehydrogenation of the O-H bond to a carbocation intermediate, and then dehydrogenation of the β -C-H bond to the carbonyl product. At the same time, the adsorbed oxygen molecule oxidizes the produced hydrogen atoms to shift the equilibrium toward carbonyl compound and accomplish a complete redox cycle. The rate-determining step of this reaction, which can be accelerated by bases, is generally believed to be the release of the β -C-H hydrogen [55, 59]. Recently, this model has been further developed. Experiments [55, 60] indicate that the primary effect of oxygen in this reaction is not oxidation of the produced hydrogen atoms, but regeneration of the deactivated catalyst sites via oxidative removal of the strongly adsorbed poisoning byproducts.



Subscript 'ad' refers to adsorbed species Figure 4-4. Oxidative dehydrogenation mechanism of alcohol oxidation over metal catalysts. [55].

In general, heterogeneous catalysts containing noble metals are very efficient in aerobic oxidation of a wide range of alcohol substrates, especially for activated alcohols such as aromatic, allylic or acetylenic species. However, the same catalysts were found to be much less effective for oxidation of non-activated alcohols such as aliphatic and alicyclic alcohols [53, 61, 62].Yamaguchi and Mizuno [63] investigated the Ru/ γ -Al₂O₃ catalyzed oxidation of benzyl alcohol and p-substituted benzyl alcohols with molecular oxygen. They found that the order of reactivity for such benzyl alcohols was in the sequence of p-CH₃O > p-CH₃ > p-H > p-Cl > p-NO₂, indicating that an electron-donating group can weaken the β -C-H bond and thus boost the reaction. On the other hand, an electron-withdrawing substituent plays a negative role in this reaction.

Recently, a few new catalysts have been developed to overcome obstacles for oxidation of non-activated alcohols with molecular oxygen. Such catalysts can be divided into two categories: homogeneous complex compounds [64, 65] and nano particles of noble metals such as Pt, Pd, Ru and Ir [62, 66]. However, these catalysts have some significant drawbacks. For example, oxidation with homogeneous catalysts is typically carried out in toluene solvent, which can cause many environmental problems [53, 64, 65]. The nanoparticle-catalyzed process requires an extended reaction time (20-40 h) to achieve a good yield of aliphatic ketone or aldehyde (78% to 99%) [62, 66]. In addition, the non-activated alcohols examined in these studies are aliphatic alcohols, the activity of those catalysts on alcohols with electron-withdrawing groups is unknown.

Although aerobic oxidation with noble metal catalysts is an extensively used synthetic approach, it is generally uneconomical because of the high price of the catalysts. In addition, the deactivation of the catalyst is always a problematic issue that decreases the efficiency and increases the production cost [12, 55].

Hydrogen peroxide

Metal-catalyzed oxidations with hydrogen peroxide (H_2O_2) can be divided into two categories including peroxometal and oxometal species, respectively, as the active oxidants (Figure 4-5) [67]. In the peroxometal pathway, the metal ion remains in the same oxidation state during the catalytic cycle. In contrast, oxometal pathways involve a two-electron change in oxidation state of the metal ion.

Peroxometal pathways are typically observed with early transition metal ions such as Mo(VI), W(VI), Ti(VI) and Re(VII). These metals have a d⁰ configuration and are relatively weak oxidants. On the other hand, oxometal pathways are characteristic of late transition elements and first row transition elements, e.g. Cr(VI), Mn(V), Os(VIII), Ru(VI) and Ru(VIII), which are strong oxidants in high oxidation states [32]. In addition, depending on the substrates, some metals can operate via both pathways. For instance, vanadium(V) operates via a peroxometal pathway in olefin epoxidations and via an oxometal pathway in alcohol oxidations [68].



Figure 4-5. Oxometal vs. peroxometal pathways in metal-catalyzed alcohol oxidations with hydrogen peroxide [67].

Alcohol oxidations using metal catalysts and hydrogen peroxide as the oxidant are usually carried out in a biphasic system for phase-transfer operation [69-71]. Recently, a microwave-assisted oxidation process using aqueous hydrogen peroxide was reported [72]. The experimental procedure involves a simple mixing of an alcohol, sodium tungstate (Na₂WO₄), and tetrabutylammonium hydrogen sulfate (TBAHS) followed by the addition of 30% aqueous H_2O_2 in a 25:1:1:125 molar ratio for primary and a 25:1:1:40 molar ratio for secondary alcohols in a monomode microwave reactor. Good yields (60%- 97%) of carboxylic acid or ketone products from primary or secondary alcohols can be obtained within 20 min. Commercial application of H_2O_2 in alcohol oxidation is always carried out using titanium silicate (TS-1) as the catalysts [73]. TS-1 is an isomorphously substituted hydrophobic molecular sieve and the progenitor of the so-called redox molecular sieves [74]. A major reason for the superior activity of TS-1 is that the hydrophobicity of the framework stimulates the adsorption of the relatively hydrophobic substrates and hydrogen peroxide from an aqueous medium [75]. However, the scope of alcoholic substrates that can be used in this process is limited by the pore size of TS-1. In addition, in the presence of allylic functionality, it gives a high selectivity for epoxidation products [67].

Ozone oxidation

Ozonation of organics in the absence of any catalyst is attracting more and more attention [76]. Ozone is well known as a powerful oxidant agent capable of oxidizing many organic compounds [50] such as alcohols [77, 78], olefins and aromatic substrates [79-81]. When ozone is used in organic synthesis, it can be simply decomposed back to oxygen and no special neutralization or separation is required at the end of the reaction. Moreover, since ozone is being produced *in situ*, complex logistics in transport, storage and disposal are not required.

For ozonation of secondary alcohols, it was found that the substrates could be rapidly and completely converted into the corresponding ketone products (Table 4-1) under mild conditions [51, 82].

Alcohol	Ketone Yield (%)	Alcohol	Ketone Yield (%)
2-propanol	83	2-nonanol	57
2-butanol	72	4-nonanol	68
2-pentanol	69	4-decanol	71
3-pentanol	81	5-decanol	65
2-hexanol	66	2,4-dimethyl-3pentanol	83
3-hexanol	74	cyclopentanol	53
2-heptanol	62	cyclohexanol	65
3-heptanol	82	cycloheptanol	74
4-heptanol	70	cyclooctanol	69
2-octanol	71	cyclododecanol	61
4-octanol	66		

Table 4-1. Ozone oxidation experiments of secondary alcohols at 0°C. [51]

In general, it is believed that ozone oxidation of organics in aqueous solution proceeds via two mechanisms: direct oxidation or radical decomposition [83]. The first mechanism involves the direct attack of ozone molecules on the substrate [76, 84]. This reaction usually occurs to some extent at any pH values for oxidation of alkene, alkyne compounds (Scheme 4-7) or the –CH bond of alcohols and ethers (Scheme 4-8).

Scheme 4-7. Direct oxidation of alkene by ozone [84].



Scheme 4-8. Direct oxidation of alcohols by ozone [76].



The second mechanism involves the decomposition of ozone into radical species (mainly hydroxyl radicals, ·OH). The hydroxyl radical, as shown in Table 4-2, is one of the strongest oxidants which reacts in a nonselective way with organic substrates at high reaction rates [83, 85].

In a low pH (0-4) solution, the formation of OH radicals is ascribed to the occurrence of the following reactions [86]:

 $O_3 \rightarrow O + O_2$

 $O + H_2O \rightarrow 2 \cdot OH$

At alkaline pHs, the radical decomposition mechanism can be accelerated by the following cycle [87]:

```
O_3 + OH \rightarrow O_3 + OH
O_3 + H_2O \rightarrow OH + OH + O_2
```

Redox reaction	E ^O (Volt) at 25°C
$F_2 + e^- \Leftrightarrow 2F^-$	2.87
$\cdot OH + H^+ + e^- \Leftrightarrow H_2O$	2.33
$O_3 + 2H^+ + 2e^- \Leftrightarrow O_2 + H_2O$	2.07
$H_2O_2 + 2H^+ + 2e^- \Leftrightarrow 2H_2O$	1.76
$Cl_2 + e^- \Leftrightarrow 2Cl^-$	1.36
$O_3 + H_2O + 2e^- \Leftrightarrow O_2 + 2OH^-$	1.24

Table 4-2. Standard reduction potentials of selected oxidation agents [85].

In the research of wastewater treatment, some new procedures have been discovered to improve the oxidative power of ozone and H_2O_2 . Experiments show that the combination of ozone (O₃) with hydrogen peroxide (H_2O_2) [88, 89], O₃ with UV radiation [90], or H_2O_2 with UV radiation gives rise to the formation of OH radicals and other reactive species. The related reactions [90, 91] are:

 $2 O_3 + H_2O_2 (HO_2^- + H^+) \rightarrow 2 \cdot OH + 3 O_2$

 $O_3 + hv + H_2O \rightarrow OH + other active species$

 $H_2O_2 + hv \rightarrow 2 \cdot OH$

With the ability to generate more hydroxyl radicals, the reactivity of O_3/H_2O_2 , UV/O₃ and UV/H₂O₂ system significantly exceeds that of using ozone or hydrogen peroxide alone [90].

Such technologies, termed as "advanced oxidation processes" (AOP), are extensively applied in waste water treatment to degrade some tough pollutants.

Recently, some metal oxides, such as γ -alumina and titanium oxide, were found to be effective catalysts in ozonation of organics [92]. Ni and Chen [93] investigated γ -Al₂O₃ catalyzed ozonation of 2-chlorophenol. They found that at an acidic pH value, the addition of γ -Al₂O₃ to the reaction medium increased the efficiency of the ozonation process by 83.7% compared to using ozonation alone. At neutral and basic pH, the increments of ozonation efficiency were 100% and 17%, respectively.

Generally, it is believed that the presence of catalyst increases ozone dissolution [92]. The proposed mechanism of catalytic ozonation on metal oxides [92, 93] assumes that the adsorption of both organic molecules and ozone takes place simultaneously on the surface of the catalyst. As the result of ozone adsorption and its conversion, OH and other radicals [92] are generated. Free radicals can initiate an oxidation reaction both on the surface of the catalyst and in the bulk of the aqueous phase. In this way, the catalysts improve the efficiency of ozonation.

Although ozonation is a very effective process for oxidizing various organic substrates, its application is usually limited to water treatment. It is rarely used for large scale organic synthesis, because its strong oxidative ability can over-oxidize the substrate and result in many undesired byproducts. In addition, the corrosion and damage caused by ozone is an important consideration.

4.1.4. Oxidation of dioxanol to the corresponding ketone product

In 1995, Majewski et al. [94] investigated the oxidation of the 6-membered cyclic acetal synthesized from glycerol and tert-butyraldehyde to the corresponding carbonyl product. The substrate, as shown in Scheme 4-9, has similar molecular structure as 5-hydroxyl-2-methyl-

dixoane (cis-6). The authors attempted a variety of oxidation methods including Swern, Collins, Fetizon's, PDC, and Jones reactions. They found that the reaction either failed or gave very low yield. The possible reason for this, they presumed, was due to the instability of dioxanone product.

Scheme 4-9. Structure of 2-tert-butyl-5-hydroxyl-1,3-dixane.



In this chapter, the oxidation of cis-6 to its ketone products is carried out with various oxidation methods. The efficiency of these methods was discussed and compared with literature. The experimental results provide a basis for further oxidant selection.

4.2. Experimental

4.2.1. Materials

Anhydrous diethyl ether (99.5%, ACS grade), acetone (99.7%), sodium hydroxide (> 99%), 1-propanol (99.9%), 1-butanol (99.9%), hydrogen peroxide (30% aqueous solution), toluene (99.7%, ACS grade) were obtained from J.T. Baker.

Anhydrous dichloromethane (99.8%), anhydrous o-dichlorobenzne (99%), sodium carbonate (> 99%), sodium bromate (> 99%), potassium bromate (> 99.8%), calcium hypochlorite (> 98%), sodium periodate (> 99%), sodium iodide (> 99%) were purchased from Sigma-Aldrich. Amberlyst-15 cationic exchange resin (16-50 mesh, 1.2g/cm3), purchased from

Sigma-Aldrich, was investigated as the catalyst. Before being used in reactions, it was pretreated at 90°C in a vacuum oven for 2 hours.

Pyridinium chlorochromate (98%), 3-nitrobenzaldehyde (> 99%), trimethyl aluminum (2.0 M in chlorobenzene), aluminum isopropoxide (> 99.99%), aluminum tert-butoxide (> 98%), ruthenium dioxide hydrate (99.9% trace metals basis, 28% water content), ruthenium trichloride hydrate (reagent plus, 46% Ru content), platinum on carbon (5% Pt absis), platinum on alumina (5% Pt basis), palladium on activated carbon (5% Pd basis), ruthenium on carbon (5% Ru basis), titanium silicate (99.8% trace metals basis) were obtained from Aldrich.

Bismuth modified platinum on carbon (5% Pt and 1% Bi) was obtained from Johnson Matthey. Sodium hypochlorite (15% aqueous solution) was purchased from Pharmco and Aldrich. Aluminum oxide (99.9%, γ -Al₂O₃) was obtained from Alfa Aesar. Cyclohexanone (> 99%) and 1,4-Benzoquinone (> 98%), were obtained from Fluka. Potassium bromide (ACS reagent, > 99.5%) was purchased from Spectrum.

Hydrogen (99.999%) and helium (99.999%) used for GC analysis, and oxygen (99.999%) used for oxidation experiment were purchased from Linde Gas, Inc.

4.2.2. GC and GC-MS analysis

The GC and GC-MS methods used in this investigation are the same as the ones described in Chapters I and II.

4.3. Results and discussion

4.3.1 Oxidation of cis-6 with pyridinium chlorochromate (PCC)

In a preliminary experiment, PCC was used to oxidize cis-6 to its ketone product. This experiment was carried out according to the procedure described by Piancatelli, et al [95]. In a 500 ml round bottomed flask fitted with a reflux condenser and magnetic stirrer, 32.5 g of

pyridinium chlorochromate (PCC) was suspended in 200 ml of anhydrous dichloromethane. Cis-6 isomer (11.8 g) in dichloromethane (20 ml) was added to the magnetically stirred suspension. After reaction at room temperature for 1.5 h, 200 ml of dry diethyl ether was added and the organic solution was decanted. Following the reaction, GC analysis showed the presence of Gtone in the final mixture. The conversion of cis-6 was 30%, and the selectivity to G-tone was nearly 100%.

This experiment illustrates the feasibility of producing the ketone precursor of DHA from cis-6. However, the production method must be improved because PCC and dichloromethane are toxic. Hence, further study was carried out with more environmentally benign catalysts and oxidants.

4.3.2. Oppenauer oxidation

Oppenauer oxidation proceeds via exchanging two hydrogen atoms between a ketone and an alcohol. In this study, the Oppenauer oxidation experiment of cis-6 was carried out in a dried 500 mL round bottom flask equipped with a condenser. Into this flask was introduced a measured quantity of cis-6 GA isomer, oxidizing reagent such benzoquinone and 3nitrobenzaldehyde, and anhydrous organic solvent, followed by the aluminum-base catalyst, i.e. aluminum tert-butoxide, aluminum isopropoxide, and trimethyl aluminum. If trimethyl aluminum (AlMe₃) is used, the reaction flask must be capped with septa and purged with nitrogen to maintain an anhydrous atmosphere. The chlorobenzene solution of trimethyl aluminum was transferred to the reactor with an oven dried syringe.

After loading of chemicals, the mixture was stirred and heated to the desired temperature (from 25°C to 113°C) using a heating mantle for reaction. Samples were taken after the reaction for GC analysis. The reaction conditions and results are presented in Table 4-3.

Reaction	Catalyst loading (wt to cis-6)	Oxidant	Solvent	Molar ratio (cis-6 : oxidant : solvent)	Temp. (°C)	Reaction time (h)	G-tone yield (%)
1	P (50%)	AT	Toluene	1:8:9	25	46	2
2	M (7.5%)	3-NB	Toluene	1:3:19	25	20	0
3	M (7.2%)	BQ	Benzene	1:2:15	25	24	0
4	B (22%)	СН	Toluene	1:5:30	113	24	0
5	B (25%)	BQ	Toluene	1:5:30	113	24	0
6	B (30%)	3-NB	Toluene	1:5:28	113	24	0
7	P (290%)	СН	-	1:100	100	24	0

Table 4-3. Oppenauer oxidation experiments of cis-6.

Catalysts: B = aluminum tert-butoxide, Al(t-BtO)₃, M = trimethyl aluminum, AlMe₃; P = aluminum isopropoxide, Al(i-PrO)₃.

Oxidants: AT= acetone; BQ = benzoquinone; CH = cyclohexanone; 3-NB = 3-nitrobenzaldehyde.

As shown, negligible product was produced via this pathway even after a long reaction period. Recalling the reaction mechanism (Scheme 4-5) that Oppenauer oxidation is the reverse process of Meerwein-Ponndorf-Verley (MPV) reduction, the poor yield indicates that the equilibrium is not favored towards the formation of G-tone.

The result can be explained by comparing the oxidation potentials of the reactants and product. Adkins and coworkers [96] calculated the relative redox potentials for a wide rage of carbonyl-alcohol systems via polarographic experiments. They found that under ordinary conditions, dialkyl ketones have the lowest oxidation potentials and, therefore, their corresponding secondary alcohols have the best reducing capacities. However, if the carbonyl bond of the ketone is on a ring structure or the α -hydrogen of the ketone is replaced by an alkoxyl group, its oxidation potential will increase remarkably. Accordingly, the alcohol

counterparts of such ketones have poor activity in Oppenauer reaction. The relation of ketone structure and its oxidation potential is well illustrated in Table 4-4 by comparing two series of ketone compounds.

IUPAC name of ketone	Structure	Oxidation potential (mV)
4-Heptanone		101
3-Pentanone	, o	110
Cyclohexanone	O O	162
2-Methoxycyclohexanone		218
Acetone	O 	129
Methoxyacetone		189
1,3-Dimethoxyacetone	_00	350

Table 4-4. Ketone compounds and their oxidation potentials [96].

From the theory developed by Adkins and et al., it can be anticipated that the oxidation potential of G-tone would be even higher than 1,3-dimethoxyacetone because it contains a ring

structure and two α -carbon connected methoxy groups. Hence, oxidation of its alcohol counterpart, cis-6, is expected to be extremely difficult via Oppenauer oxidation with other carbonyl compounds.

4.3.3. Ruthenium tetroxide catalyzed oxidation

A typical operation procedure for ruthenium tetroxide-catalyzed oxidation of cis-6 started with charging 10 ml of cis-6 solution (4 to 10 wt% in water) to a glass reactor with hydrated ruthenium dioxide (RuO₂·xH₂O) or ruthenium trichloride (RuCl₃·xH₂O) powder. The mixture was then agitated for 5 min with a magnetic stirring bar. After that, 10 to 20 mL of saturated solution of a secondary oxidant, such as NaClO, NaBrO₃, KBrO₃, NaIO₄, etc., was added to the well stirred reaction mixture at a rate of 5-10 mL/min. Ruthenium tetroxide (RuO₄) is then generated *in situ* by oxidation of RuO₂ or RuCl₃. A small amount of base, such as sodium carbonate (Na₂CO₃) or sodium hydroxide (NaOH), was added to maintain a slightly basic pH condition.

Table 4-5 presents the results of cis-6 oxidation experiments catalyzed by rutheniumbased substances. It is clear that this type of reaction is highly exothermic and very efficient. In some reactions over 90% yield of G-tone was achieved within 30 min.

An important feature of this type of reaction is that it must be performed with a secondary oxidant (consuming oxidant), such as NaClO, NaBrO₃, NaIO₄, and KBrO₃. Such inorganic salts have strong oxidative ability in aqueous solution, however, they cannot oxidize cis-6 without the Ru catalyst present. As shown, negligible G-tone was produced in Reactions 1 and 2, indicating that the real oxidant which converts cis-6 to G-tone is a high-valent ruthenium species generated

in situ from $RuO_2 \cdot xH_2O$, or $RuCl_3 \cdot xH_2O$ with the oxidizing salts. This ruthenium species has been identified as RuO_4 [19, 45, 97].

Conventional RuO₄-catalyzed alcohol oxidation often employs a biphasic system, in which $RuO_2 \cdot xH_2O$ or $RuCl_3 \cdot xH_2O$ is reacted with the secondary oxidant in water and the RuO_4 generated is extracted into an organic solvent for alcohol oxidation [19, 97]. The most commonly used organic solvents are CH_2Cl_2 , CCl_4 , etc [19, 33, 44]. However, due to the poor cis-6 solubility in non-polar solvents, phase-transfer reaction cannot be applied. In this study, water was used as the only solvent.

The effect of water on this reaction is clearly illustrated by Reactions 10 and 11. Without water, no product was obtained in 24 h. However, if a small amount of water (0.4 g) is used, the yield of G-tone increased rapidly from 0 to 20% in 30 min.

Reaction	Cis-6 (g)	Water (g)	Catalyst (RuO ₂ ·xH ₂ O) loading (g)	Secondary oxidant solution/mass (g)/concentration	Time (min)	G-tone yield (%)
1	0.41	10	0	NaClO/4/10%	30	0
2	0.42	10	0	KBrO ₃ /10/saturated	1440	0
3	4.0	50	0.40	NaClO/100/10%	30	80
4	0.39	11	0.31	NaClO/4/10%	30	76
				NaClO/5/10%	60	95
5	0.45	10	0.05	Ca(ClO) ₂ /10/ saturated	20	87
6	0.40	10	0.30 ^a	NaIO ₄ /10/saturated	75	88
7	0.42	10	0.26	KBrO ₃ /10/ saturated	45	> 99
8	0.43	10	0.32 ^a	KBrO ₃ /10/saturated	75	95
9	4.1	10	0.40	KBrO ₃ /100/saturated	20	97
10	0.31	0	0.10	KBrO ₃ /0.31/powder	1440	0
11	0.31	0.4	0.10	KBrO ₃ /0.31/powder	30	20
12	0.30	10	0.41	NaBrO ₃ /10/10%	20	96
13	10.0	10	0.51	NaBrO3/100/20%	40	90
14	3.0	10	0.10	NaBrO ₃ /12.5/20%	20	95

 Table 4-5. Ruthenium tetroxide catalyzed oxidation of cis-6 at room temperature, atmospheric pressure. Catalyst was generated in situ with ruthenium dioxide.

a. RuCl $_3$ ·xH $_2$ O was used as catalyst.

Selection of an appropriate secondary oxidant is of significant importance for RuO_4 - catalyzed alcohol oxidation. In general, the five inorganic salts tested in this study are all good

options for lab scale experiments. However, for large scale production, fully consideration must be taken with respect to the stability, solubility and economic factors of the oxidizing salts. For instance, calcium hypochlorite is not stable in air, but reacts with carbon dioxide to form calcium carbonate and release chlorine.

$$2 \operatorname{Ca}(\operatorname{ClO})_2 + 2 \operatorname{CO}_2 \rightarrow 2 \operatorname{Ca}\operatorname{CO}_3 + 2 \operatorname{Cl}_2 + \operatorname{O}_2$$

Sodium hypochlorite loses its oxidation ability via decomposition to NaCl at elevated temperature. Since a large amount of heat is generated in the process of cis-6 oxidation to G-tone, if NaClO is used as the secondary oxidant it must be fed extremely slowly to avoid thermal decomposition.

Sodium periodate and potassium bromate have relatively better thermal stability than $Ca(CIO)_2$ and NaClO. However, they are much less soluble in water (Table 4-6). If they are chosen to be the secondary oxidant, more water is required to dissolve the salts, which will increase the separation cost after reaction.

Salt	Solubility in water at 20°C (g/100 mL)	Concentration of saturated solution (%)
NaClO	29.3 (0°C)	23
NaBrO ₃	36.4	27
NaIO ₄	8.0	7
KBrO ₃	6.9	6
Ca(ClO) ₂	21.0	17

Table 4-6. Solubility of the inorganic salts used as the secondary oxidant.

Last, sodium bromate, which has good thermal stability and the highest solubility in water, is the best option for this reaction.

Another parameter, pH value of the reaction medium, is of paramount importance for this reaction, because it can influence the stability and catalytic activity of RuO₄ [47]. In this study, it was noticed that during the course of some reactions, especially the ones with NaClO, the reaction mixture turned into dark orange or green in color. This is because RuO₄ generated in the aqueous phase is unstable. It can be reduced by OH⁻ ions to perruthenate (RuO₄⁻), a green species, which in turn, is reduced more slowly by OH⁻ ions to an orange species, ruthenate (RuO₄²⁻). [98, 99]. Thus, in sodium hypochlorite solution, which typically has a pH higher than 11, RuO₄ is readily reduced to the coloring ionic species.

The formation of perruthenate and ruthenate is highly dependent on the pH value. Figures 4-7 display the distribution of $\text{RuO}_4^{2^-}$, RuO_4^- , and RuO_4 as a function of pH in aqueous solutions with Ru concentration = 0.00038 M. The plots are obtained via electrochemical calculations for soluble ruthenium species (see in Appendix III for details). As can be seen, RuO₄ is only stable up to pH = 8, RuO₄⁻ regime is dominant between pH of 8 and 11.5, and above 11.5, RuO₄²⁻ is the dominant species. The trends predicted by electrochemical calculation are in good agreement with the experimental data reported by Mills and Holland [99] (Figure 4-8).



Figure 4-7. Calculated population (%) of various ruthenium species at different pHs in an aqueous solution with [Ru] = 3.8×10^{-4} M. RuO₄ (\bullet), RuO₄⁻(\bigcirc) and RuO₄²⁻(\triangle).



Figure 4-8. Population (%) of various ruthenium species at different pHs of an aqueous solution with [Ru] = 3.8×10^{-4} M. Experimental results. RuO₄ (\bullet), RuO₄⁻(\bigcirc) and RuO₄²-(\triangle). [99]

Ruthenate and perruthenate species are much weaker oxidants than ruthenium tetroxide [98]. To ensure a good performance, most RuO₄ catalyzed oxidations generally require acidic conditions. However, it is still possible to conduct the oxidation in slightly basic condition via the disproportion equilibrium of perruthenate as shown in Scheme 4-10 [47, 100]. Because the reaction between RuO₄ and organic substrates is very fast, the more reactive RuO₄ species is consumed much faster than the more stable RuO₄⁻⁻ species. Thus, the equilibrium of RuO₄⁻⁻ disproportion is shifted to the right side. In the meanwhile, the secondary oxidant is able to reoxidize the ruthenate species to perruthenate, which can again disproportionate. Hence, even in a basic solution, the high reactivity of RuO₄ and the ability of RuO₄⁻⁻ to undergo a disproportion reaction can provide an efficient oxidation cycle for an organic substrate.

Scheme 4-10. RuO₄-catalyzed oxidation under slightly basic condition.



For cis-6 oxidation with RuO₄ catalyst, acidic conditions must be avoided, because in the presence of acid and large amount of water cis-6 readily hydrolyzes to glycerol and acetaldehyde. Furthermore, acetaldehyde produced can be oxidized by RuO₄ to acetic acid, which will further
increase the acidity of the solution and cause more cis-6 to decompose. Thus, to avoid loss of reactant, basic pH must be maintained in the reaction mixture.

High-valent ruthenium species can be reduced by isopropanol to RuO_2 hydrate, which is insoluble in water and precipitates as black solid [19]. This method can be used for catalyst recycling. In Reaction 14, 13 g of isopropanol was added to the final mixture; after stirring for 2 h and filtering, 97% of the Ru species was recovered as RuO_2 hydrate.

4.3.4. Aerobic oxidation of cis-6 with molecular oxygen

Aerobic oxidation of cis-6 was performed in vapor phase or liquid solution.

Vapor phase experiments were carried out under atmosphere pressure in a fixed bed reactor equipped with a downstream condenser. In a typical experiment, a measured quantity of catalyst, such as 5% Pt/Al₂O₃, 5% Pt/C and RuO₂, supported by glass wool was loaded into the reactor. The catalyst was purged with helium gas at 200°C for 1 h before reaction. After that, cis-6 vapor was generated in a round bottom flask heated by heating mantel and carried to the reactor by air (air flow rate = 25 mL/min). During reaction, the reactor temperature was maintained in the range of 210 to 214°C. The reactor effluent was collected in a tube connected to the downstream condenser and immersed in an ice water bath.

The experimental results of vapor phase aerobic oxidation of cis-6 are listed in Table 4-7. GC analysis of cis-6 vapor showed that no reaction occurred up stream of the reactor, indicating that the reactant is stable under the vapor conditions.

Catalyst	Loading (g)	Reaction temp. (°C)	Air flow rate (mL/min)	Reaction product
5% Pt/Al ₂ O ₃	0.61	212	25	Negligible yield of G-tone, other GA isomers produced.
5% Pt/C	0.83	210	25	Negligible yield of G-tone, other GA isomers produced.
RuO₂·xH₂O	0.49	214	30	No reaction occurred

Table 4-7. Vapor phase aerobic oxidation of cis-6 at atmospheric pressure.

Oxidation of cis-6 to G-tone was insignificant at the conditions listed in Table 4-7. At the same time, some undesired products, trans-6 and 5-membered GA isomers, were detected in the final product of Pt-catalyzed reactions, indicating that interconversion of GA isomers was catalyzed by Pt-based catalyst.

Table 4-7 also shows that ruthenium dioxide has no effect on cis-6 oxidation or GA isomer re-equilibration, indicating that RuO_2 was not oxidized to high valent RuO_4 at this reaction conditions.

Liquid phase aerobic oxidation of cis-6 at atmospheric or elevated pressure is summarized in Tables 4-8 and 4-9, respectively.

For atmospheric pressure oxidation experiments, a 500 mL three-necked round bottom flask was used. A typical run started with charging of 5 g of cis-6, 25 g of solvent, and a measured quantity of catalyst such as 5% Pd/C to the flask. Thereafter, air flow was introduced into the mixture at a rate of 20-30 mL/min via stainless steel tubing. The mixture was then stirred with a magnetic bar and heated to the desired temperature for reaction from 1.5 h to 24 h. Samples were taken after the reaction and subjected to GC analysis.

High pressure oxidation liquid-phase experiments were carried out in Parr reactors connected to an oxygen cylinder. A typical reaction occurred with an initial charge of 30 g of 1.8 M cis-6 solution and a measured quantity of catalyst, such as 5% Ru/C and 5% Pt/C etc., in the reaction vessel. The system was stirred and purged with oxygen for 10 min before heating started. After reaching the desired temperature (from 60°C to 95°C), the oxygen pressure in the reactor was increased to the set point (from 30 psi to 250 psi) by adjusting the valve installed between the reactor and cylinder. When reaction is finished, the mixture was filtered and subjected to GC analysis.

In order to prevent isomer interconversion and hydrolysis of cis-6 in aqueous solution, small amount of bases, such as sodium hydroxide (NaOH), was added to the reaction mixture to maintain a slightly basic pH in the solution.

Cis-6 (g)	Catalyst loading (g)	Solvent (g)	Temp. (°C)	Time (h)	Result
10	5% Pd/C (0.40)	-	50	24	No oxidation occurred
1.5	5% Pd/C (0.48)	Water (9)	25	24	No oxidation occurred
5.9	5% Pt/Al ₂ O ₃ (0.59)	Toluene (40)	60	24	No oxidation occurred
6.0	RuO ₂ ·xH ₂ O (0.61)	Water (30)	60	22	No oxidation occurred
5.1	$RuO_2 \cdot xH_2O(0.28)$	o-DCB (26)	177	1.5	No oxidation occurred
4.1	5% Ru/C (1.25)	o-DCB (26)	175	23	No oxidation occurred
5.9	5% Pt/Al ₂ O ₃ (0.51)	Water (30)	65	18	4% G-tone yield, glycerol, acetic acid and other byproducts detected
4.0	1%Bi-5%Pt/C (0.25)	Water (36)	60	20	Over 90% cis-6 conversion, 30% G-tone yield, glycerol, acetic acid and other byproducts detected

Table 4-8. Aerobic oxidation of cis-6 using noble metal catalysts. Atmospheric pressure, airflow rate = 25-30 mL/min.

o-DCB: o-dichlorobenzene.

Cis-6 (g)	Catalyst loading (g)	Temp. (°C)	Pressure (psi)	Time (h)	Result
5.0	RuO ₂ ·xH ₂ O (0.51)	60	30	24	No reaction occurred
5.0	5% Ru/C (0.53)	60	30	24	No reaction occurred
5.0	5% Pt/C (1.06)	85	100	24	No G-tone produced, cis-6 decomposed to glycerol and converted to other GA isomers
5.0	5% Pt/Al ₂ O ₃ (0.75)	85	150	24	Cis-6 decomposed to glycerol and acetaldehyde which was further oxidized to acetic acid
5.0	RuO ₂ ·xH ₂ O (0.65)	75	150	22	Cis-6 decomposed to glycerol and acetaldehyde which was further oxidized to acetic acid
5.0	5% Pt/C (0.87)	95	250	24	No G-tone produced, isomer equilibrium shifted and acetic acid produced

 Table 4-9. Aerobic oxidation of cis-6 using noble metal catalysts at elevated pressure.

 Oxygen was used as oxidant.

Under atmospheric pressure, cis-6 was inert in the Pd and Ru catalyzed reactions even at a temperature of 177°C. It indicates that cis-6 is more difficult to oxidize than other alcohol substrates. In aqueous solution, Pt-based catalysts exhibited low catalytic activity. In one reaction, a small amount of cis-6 (4%) was oxidized to G-tone in the presence of 5% Pt/Al₂O₃ catalyst in 18 h. The yield of G-tone increased markedly to 30% when Bi promoted Pt/C catalyst was used.

It was reported that addition of Bi to Pt catalyst could improve its performance for secondary alcohol oxidation [6, 13]. However, in the Bi-Pt/C catalyzed reaction presented in Table 4-8, the improved yield of G-tone could be the result from the oxidation of the secondary

hydroxyl group of glycerol instead of cis-6 dehydrogenation. Because a large amounts of cis-6 was decomposed to glycerol and acetaldehyde in this reaction. Acetaldehyde was then oxidized to acetic acid which further promoted cis-6 decomposition.

Side reactions were more prevalent at elevated pressure and temperature (Table 4-9). In some reactions, especially those catalyzed by Pt-based compounds, although base was initially added to the solution to obtain a slightly basic pH, the reactant was completely decomposed before oxidation occurred.

The results from the aerobic oxidation experiments indicate that under special conditions, Pt catalyst has low activity for cis-6 oxidation. However, it also catalyzes isomer interconversion and decomposition of cis-6. Recalling the reaction mechanism [55] and the order of alcohol reactivity discovered by Yamaguchi and Mizuno [63], it can be assumed that the presence of oxygen in the heterocyclic structure of cis-6 may have the same effect as electron-withdrawing groups and thus strongly suppress the reactivity of alcohol.

4.3.5. Oxidation with hydrogen peroxide

The initial oxidation experiments using hydrogen peroxide solution as oxidant was carried out at room temperature with $RuO_2 \cdot xH_2O$ and $RuCl_3 \cdot xH_2O$ catalysts. In these experiments, hydrogen peroxide decomposed immediately upon addition to the reaction mixture. It was reported [101] that $RuCl_3$ can facilitate the decomposition of H_2O_2 and the concentration of H_2O_2 in aqueous $RuCl_3$ solution can only be sustained at the mmol/L level. Thus, more than 90% of H_2O_2 was consumed via unproductive decomposition. Further experiments were carried out in Parr reactors. In one of them, 5 g of cis-6 was mixed with a 30 g of 30% aqueous H_2O_2 solution and stirred at 60°C for 22 h using a magnetic bar. However, no reaction occurred under this condition.

The other reaction was conducted with H_2O_2 and 0.5 g of titanium silicate (TS-1) as catalyst. The vessels were then well sealed and heated to 60°C. Alcohol oxidation with TS-1 and H_2O_2 is a commercialized technology [73]. However, the reagents did not exhibit any oxidation effect on cis-6. In this experiment, no oxidation product was detected in 22 h. Moreover, cis-6 was slightly decomposed to glycerol and acetaldehyde under this reaction condition.

4.3.6. Ozone oxidation

Ozonation of cis-6 was carried out in a self-designed reactor (Figure 4-6) constituting of a glass tube with a fritted disc at the bottom. To initiate an experiment, a measured quantity of cis-6 and solvent (water or 30% aqueous H_2O_2 solution) were added to the reactor and maintained room temperature in a water bath. Ozone-oxygen mixture was produced *in situ* by passing dry oxygen (5-8 L/min) through a Trailigaz ozone generator (model number OZC-1001; Praxair, Cicinnati, OH); the mixture contains of 8-9 wt% of O₃. During reaction, O₃ was introduced into the reaction medium as small gas bubbles by passing the ozone-oxygen stream through the fritted disc. The formation of these small gas bubbles improved the dispersion of ozone within the reaction mixture. A dry ice-cooled trap was used to collect the volatile product in the reactor effluent. Any unreacted ozone was decomposed by venting the exhaust gas through aqueous KI solution.



Figure 4-6. Ozone oxidation of cis-6 solution.

Table 4-10. displays the result of a series of ozone oxidation experiments. In Reaction 1, ozone gas was used as the only oxidizing reagent. The yield of G-tone in this reaction is less than

1%, indicating that ozone alone has poor activity for cis-6 oxidation.

Table 4-10. Ozone oxidation experiments. Substrate: 20 g of 20% cis-6 solution; ozone (8-9wt% in oxygen): 5-8 L/min; room temperature; reaction time: 20 min.

Reaction	Reagent (g)	Solvent	рН	G-tone yield (%)
1		Water	7	< 1
2		Water	10	< 1
3		$30\%\mathrm{H_2O_2}$	7	1
4		$30\%\mathrm{H_2O_2}$	10	1
5	γ-Al ₂ O ₃ (1.0)	Water	7	< 1
6	$RuO_2 \cdot xH_2O(0.2)$	Water	7	< 1
7	RuCl ₃ ·xH ₂ O (0.2)	Water	10	1
8	RuCl ₃ ·xH ₂ O (0.2) + KBr (0.5)	Water	7	13

Reactions 2 to 5 examine the activity of hydroxyl radicals on cis-6 oxidation. The hydroxyl radical is a very strong oxidant with a redox potential of 2.33 V [85]. It was reported that increasing pH [87] or adding hydrogen peroxide [88, 89] to aqueous ozone solution can promote the formation of OH radicals. However, in Reactions 2 to 4, no improvement of G-tone yield was observed when base or hydrogen peroxide was added to the reaction medium. The result indicates that formation of OH radical in the solution is not essential for cis-6 oxidation. The mechanism of G-tone formation is more likely to be from the direct attack of ozone on the substrate, as described by Canterino et al [76].

In Reaction 5, γ -Al₂O₃ was used as a catalyst for ozonation. It is believed that on the surface of metal oxides, ozone can be adsorbed and decomposed to OH and other radicals to initiate oxidation reactions on both the catalyst surface and in the bulk of the aqueous phase. However, in Reaction 5, the ozonation efficiency was not increased by addition of γ -Al₂O₃. This result further reinforces the conclusion that oxidizing radicals have no effect on cis-6 oxidation, but that formation of G-tone is the result of ozone direct attack.

Early in this chapter, ruthenium tetroxide was proven to be an excellent reagent for cis-6 oxidation. In this section, two experiments (Reactions 6 and 7) were designed to test whether ozone or OH radical can be used as the secondary oxidant for RuO₄ formation. Unfortunately, this goal was not accomplished. As shown, at pH = 7 or 10, addition of RuO₂ and RuCl₃ to the reaction mixture made no difference to the yield of G-tone, indicating that RuO₄ was not generated in the solution.

In Reaction 8, potassium bromide and ruthenium trichloride were added to the reaction mixture. As a result, yield of G-tone increased significantly to 13%. This is because ozone is able

to oxidize bromide to bromate in aqueous solution [102, 103]. Consequently, in this solution, RuO_4 was able to be generated from $RuCl_3$ and bromate produced *in situ*. Therefore, cis-6 was oxidized to G-tone by RuO_4 . The rate of this reaction is likely to be controlled by the oxidation of bromide to bromate, because formation of RuO_4 and oxidation of cis-6 have been proven to be very fast reactions.

It is reasonable to presume that bromide can be recycled and continuously oxidized to bromate in this solution. Thus, if the reaction time is extended to long enough, it can be expected that conversion of cis-6 to G-tone will proceed to completion.

When ozone and bromide salt are used in RuO_4 -based oxidation, the oxidizing salt required can be reduced from stoichiometric ratio to catalytic amount. This improvement will greatly help the separation operation after reaction.

4.4. Conclusions

Oxidation of cis-6 GA isomer to the corresponding ketone product provides a new synthesis route for DHA production. A broad range of catalysts and oxidizing reagents including green oxidants such as molecular oxygen, hydrogen peroxide and ozone have been examined for this purpose. However, due to the heterocyclic ring structure and high oxidation potential of cis-6, most of the reagents exhibited poor activity.

Ruthenium tetroxide based oxidation appears to be the most effective method for this reaction. With this reagent, complete conversion of cis-6 to G-tone can be achieved very rapidly. However, separation of the desired product from the reaction mixture which contains water, soluble ruthenium species and oxidizing salts such as bromate, periodate and hypochlorite is a big challenge. An improvement of this method was found to be using bromide salt and ozone as

the oxidant. In this way, bromate salt can be generated *in situ*, and only catalytic amount of salt is required for reaction.

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Chapter V. Design and Construction of Reactive Distillation Column

5.1. Overview

In 2008, a patent [1] filed by colleagues in our research group at MSU proposed the concept of making glycerol acetals and biodiesel in large scale using a reactive-distillation technique. To demonstrate the viability of this process, an elevated pressure reactive distillation column was constructed for pilot scale test. In this chapter, the advantage of reactive distillation operation over conventional biodiesel process is discussed, and the parameter design and construction of this column is presented.

5.2. Introduction

Continuous oil transesterification to make biodiesel was proposed as early as the 1940s [2, 3] and has been studied continuously since [4-8]. Current biodiesel production primarily uses batch reactors with alkali-catalysts and downstream separation units. In such a process, raw materials and catalysts react in the batch reactor and produce a two-phase mixture. The upper phase consists of esters, alcohol and catalysts; the lower phase is rich in glycerol and residual transesterified triglycerides. The mixture is further separated in a flash chamber or distillation column to obtain qualified biodiesel product. This process is continuous and fast, but needs labor and intense energy. Because, in this process, excess alcohol must be used to improve oil conversion, thus a large amount of energy is required to recover the excess alcohol and byproduct glycerol, and catalyst waste in the solution requires treatment.

A prospective alternative to the classic process is using reactive distillation (RD). RD is a unit operation that integrates reaction and separation in a single vessel. It is increasingly being applied to various chemical systems, i.e. etherification, esterification, ester hydrolysis and acetalization, etc [9].

Recently, in our lab, colleagues have successfully demonstrated the use of reactive distillation to recover propylene glycol and ethylene glycol from aqueous solution [10], and to form ethyl lactate from aqueous lactic acid solution and ethanol [11].

RD holds a promising potential to reduce investment and operating costs by overcoming chemical equilibrium, achieving energy integration and performing difficult separations. These features are appropriate solutions for the problems encountered in biodiesel industry today. However, very few studies on RD in biodiesel production have been reported, especially for acid-catalyzed processes. In one of these studies, He developed a RD system for biodiesel synthesis using an alkali-catalyst [12]. He found that 1) short reaction time and high unit productivity can be achieved in this unit, and 2) much lower excess alcohol is required for the reaction. Yet, this process cannot avoid saponification problems caused by alkali-catalysts. Thus, as described in Chapter I, a more comprehensive RD process is proposed with the application of heterogeneous acid catalysts.

To demonstrate the viability of this process, an elevated pressure reactive distillation column was designed and constructed for pilot scale test.

5.3. Column construction

The pilot-scale reactive distillation column at MSU was designed with a maximum capacity of producing 3 L of glycerol acetal per hour. The temperature and pressure allowed are 190° C and 2 MPa (300 psi), respectively.

As shown in Figure 5-1, the main body of the column consists of six sections. Five of them are 3 ft (91.5 cm) in length; the top section is 1 ft (30.5 cm). On the top, there is an elbow

connecting the column and the condenser. The material of the column is 304 stainless steel (2 inch, schedule 40).

At the bottom of the column, there is a reboiler with a 2.4 kW heating system. The reboiler working volume is around 1.5 L. It is equipped with a level sensor and solenoid valve to maintain a constant level and allow product withdrawal.

On the top of the column, there is a total condenser with a chiller capable of achieving a condenser temperature of -20° C. A stainless steel reservoir is used to collect the condensed chemical and allow product withdrawal. Between the condenser and reservoir, there is a solenoid valve which adjusts the column pressure by releasing or accumulating condensed chemical in the condenser. In addition, the reservoir has an overflow outlet to maintain the liquid level inside.

The column is equipped with three pumps, one reflux pump which returns condensed chemical to the column, and two feed pumps which dispense feed solutions to the column at a controlled rate.

The column has several ports along its length allowing internal temperature measurement, introduction of feed, and sample withdrawal. The column is wrapped with electric heating tapes that are controlled by surface thermocouples and Omega controllers to a temperature just below the internal column temperature to minimize the heat loss. Heat loss is further minimized by insulating the column with bands of glass wool.



Figure 5-1 Reactive distillation column constructed for this project

Inside the column, there are three sections: top non-reactive stripping section (45.7 cm), a reactive section, and a non-reactive enriching section (73.7 cm). The reactive section, 360 cm in height, is packed with Katapak-S structured packing elements (Sulzer chemtech Ltd.) filled with 0.3 mm Aberlyst-70 cationic exchange resin as the catalyst. Empty Katamax structured packing (Koch-Glitsch, Ltd.) is used to fill non-reactive column sections.

In addition, safety relief valve and rupture disk are installed on the top to protect the column against over pressure.

5.4. Design and calculations

5.4.1. Temperature and pressure limit

The operation temperature of the column cannot exceed 190° C which is the maximum operation temperature of Amberlyst-70 cationic exchange resin. In addition, saturated pressure of the distillation compound at the operation temperature must be less than the designed column pressure (300 psi).

The relation of saturated pressure and operation temperature can be estimated using Antoine's Equation:

$$\log P = A - \frac{B}{C+T} \text{ or } T = \frac{B}{A - \log P} - C$$
(1)

Table 5-1. presents the values of Antoine coefficients [13] and the calculation of operation temperature allowed at 300 psi. For different systems, the smaller number between 190° C and T_{max} must be used as the temperature limit of the column.

Chemical	А	В	С	$T_{max} \stackrel{(^{O}C)}{=} @P_{sat} = 300 \text{ psi}$
Acetaldehyde	7.31377	1175.27	244.272	132
Ethanol	8.13484	1662.48	238.131	183
Methanol	8.09126	1582.91	239.096	166
Water	8.05573	1723.64	233.076	212

Table 5-1. Antoine coefficients of some chemicals and temperature allowed at $P_{sat} = 300$ psi.

5.4.2. Pipe thickness

The formula [14] used to calculate minimum pipe thickness t_m required for a designed pressure (t < D/6) is

$$t_m = \frac{PD_0}{2(SE + PY)} + C \tag{2}$$

Values of the parameters used in Eq. (2) are listed in Table 5-2.

For 2 inch SS 304 schedule 40 pipe, the calculated value of t_m at 300 psi is 0.132 inches. It is less than the standard wall thickness of this pipe which is 0.154 inches. Thus, this pipe was selected for the column construction.

	Nomenclature	Unit	Values for 2 [°] SS 304 schedule 40 pipe
Р	design pressure	Psi	300
D_0	outside diameter of pipe	Inch	2.375
С	Sum of allowance (corrosion, thread depth)	Inch	0.085
S	Basic allowable stress at maximum temperature	Psi	10,000 (at 315 °C)
Е	Longitudinal weld joint factor		0.8
Y	Coefficient		0.4

Table 5-2. Parameters used for minimum wall thickness calculation.

5.4.3. Reboiler

The reboiler (Figure 5-2) of the reactive distillation column is purchased from Pope Scientific Inc., Saukville, WI. The working volume is around 1.5 L. It is equipped with a level sensor and solenoid valve to maintain a constant level and allow product withdrawal.



Figure 5-2. Reboiler of reactive distillation column.

Initially, two 1.5 kW cartridge heaters (14 inches in length, 1.25 inches diameter) were equipped with the reboiler to generate chemical vapor. The heaters, mounted on a blind flange, were kept in the lower half of the reboiler to ensure constant immersion in liquid when the reboiler is half full. However, during operation, the blind flange was heated to red hot due to its direct contact with the heaters. To solve this problem, the cartridge heaters were replaced by two 304 stainless steel coil heaters (1.2 kW, 12 feet total length, 0.125 inches diameter). The coil heaters have 5 inches of transition piece (cold zone) at the end to avoid overheating of the flange.

5.4.4. Condenser

The condenser equipped with the column was purchased from Exergy, LLC. It is a 316 stainless steel tube-in-tube heat exchanger (Figure 5-3). The diameters of inside and outside tubes are 0.25 and 0.5 inches, respectively. The total heat exchange surface area is 44.5 square inches. During operation, vapor condensed in the inside tube, while cooling water flows in the outside tube. The designed capacity of this condenser is 3000 W.



Figure 5-3. Condenser used for the reactive distillation column. 5.4.5. Sensor wiring

Temperature profile along the column is monitored manually by thermocouple controllers installed on a control box. Other sensors including pressure transducer, level sensor, relay and solenoid valves are connected to a data acquisition system (purchased from National Instruments Corporation, model number: USB 6259) and controlled by Labview software.

Pressure control

The major components of the pressure control system include pressure transducer, relay, 24V DC power and solenoid valve. The pressure transducer (model number: PX41T0-500AI) and relay (model number: SSR330DC10) are purchased from Omega.

Figure 5-4 displays the wiring diagram of the pressure control system. During operation, the data acquisition unit measures the amplitude of the signal generated from the pressure transducer. A Labview program computes the amplitude measured by the data acquisition unit to determine a reflectivity. When the signal is higher than the setpoint, the program triggers the DC power channel of the data acquisition unit, and then the relay turns on the solenoid valve to release pressure from the column.



Terminals of data acquisition unit

Analog input	19. Analog ground		
69. Digital output	82. Digital ground		

Figure 5-4. Wiring diagram of the pressure control system of the column.

Liquid level control

The magnetic sensor used to control the liquid level in the distillate collector is purchased from National magnetic sensors, Inc (model number: BB212OO43OO510-11S2S). As shown in Figure 5-5, the level sensor is an on-off type float switch that when the liquid level reaches the setpoint, it closes the circuit and turns on the solenoid valve to drain liquid from the distillate collector.



82. Digital ground

Figure 5-5. Wiring diagram of the liquid level control system of the column

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Chapter VI. A Novel Process Concept to Make 1,3-Dihydroxyacetone from Glycerol

Using 5-hydroxyl-2-methyl-1,3-dioxane as intermediate provides relatively quick, environmentally safe and economical routes for production of 1,3-dihydroxyacetone (DHA) from glycerol. Based on the experimental results presented in the previous chapters, a novel process of making DHA from glycerol is developed and described here.

Figure 6-1 presents the overall scheme of a novel DHA production process based on acetaldehyde as the glycerol acetal forming reagent. In fact, this reagent can be any aldehyde, ketone and acetal (eg. 1,1-diethoxyethane, DEE). For practical operation, selection of this reagent is dependent on its price, availability and reproducibility. As shown in Figure 6-1, the new concept of DHA production involves three major steps: 1) formation of glycerol acetal (GA) and reactive distillation to get the 6-membered GA isomer 5-hydroxyl-2-methyl-1,3-dioxane (cis-6); 2) oxidation of cis-6 GA isomer to the corresponding ketone product 2-methyl-1,3-dioxane (G-tone); 3) conversion of G-tone to DHA via hydrolysis. Acid-catalyzed hydrolysis of G-tone (Scheme 6-1) is a very fast and complete reaction. In this reaction, a molecule of acetaldehyde is produced with DHA. In one experiment, 5 wt% (weight to substrate) of Amberlyst-15 cationic exchange resin was added to the final mixture of Reaction 14 in Table 4-5. When the mixture was heated to 30°C, complete hydrolysis of G-tone was achieved in 10 min.



 \sim

$$H_2O$$
 $\xrightarrow{\text{Acid}}$ H_2O $\xrightarrow{\text{Acid}}$ H_3CHO



Figure 6-1. Design of new DHA production process.



Figure 6-1. Cont'd

In the first stage of this process, glycerol and acetaldehyde are introduced to Reactor 1 to form cyclic glycerol acetals. The reaction mixture, which contains four isomers of glycerol acetal, is then evaporated to get rid of water and unreacted acetaldehyde for recycling. After that, the mixture of glycerol acetal isomers is introduced to a vacuum distillation column, in which the cis-6 GA isomer can be separated and obtained from the top of this column. At the same time, other isomers, which have higher boiling points, react in the reboiler to re-establish isomerization equilibrium. The continuous recycling of the less-volatile glycerol acetal isomers through the
equilibration-distillation procedure can transform all of the products into the desired 6-membered structure.

In the second stage of this design, cis-6 GA isomer is introduced to the oxidation Reactor 2 to form 2-methyl-1,3-dioxan-5-one (G-tone). A preferred operation for this stage is to use ruthenium tetroxide-related oxidation.

In the last stage, G-tone and an excess amount of water are reacted, perhaps in a reactivedistillation column, to hydrolytically decompose G-tone to the desired product DHA and acetaldehyde, which can be recycled or reformed into DEE. The possible application of reactive distillation along with a large amount of water will overcome any chemical equilibrium limitations of this reaction, such that a high yield of DHA can be achieved from this process.

Storage and handling of DHA have some special requirements [1]. DHA presents as monomer in aqueous solution, but can gradually tautomerize into glyceraldehydes in alkaline environment (Scheme 6-2). Under alkaline conditions, various isomerization and condensation reactions occur and ultimately lead to the formation of brown colored oligomers [1].

Scheme 6-2. Interconversion between DHA and glyceraldehydes [1].

Acidic environment

Alkaline envrionment



DHA content can be dramatically reduced if stored at temperature higher than 40° C. Via decomposition or rearrangement reactions, aldehydes and ketones e.g. methyl-glyoxal can be formed [1]. The recommended storage temperature for DHA is 4° C.

Overall, the novel process developed in this study is a green and environmentally friendly process that no polluted gas is generated. After reaction, catalysts and organics, which are acetaldehyde or ethanol, can be easily recovered and recycled from the aqueous solution. From this point of view, the entire process only consumes glycerol and oxygen (Scheme 6-3). These features make it a more economical approach than current DHA production technologies; and it holds great promise of achieving commercialization.





1. http://www.dihydroxyacetone-dha.com/

Chapter VII. Summary and Conclusions

Glycerol transacetalization with 1,1-diethoxyethane (DEE) in the presence of Amberlyst-15 cationic exchange resin gives the cis- and trans- forms of 5-membered and 6-membered cyclic acetals. At 25°C, equilibrium conversion of reactants can be achieved in 2 h. The reaction is best carried out at low temperature to avoid formation of ethyl vinyl ether from DEE, and with DEE as the limiting reactant to avoid over-acetalization of the primary acetal products. A kinetic study was carried out to understand the transacetalization process and establish the theoretical basis for large scale glycerol acetal production. The result shows that the reaction can be described by a second order kinetic model.

Further investigation of glycerol acetal product from the reaction shows that in the presence of acid catalyst, the four isomers interconvert to form an equilibrated mixture that contains similar quantities of the four products. Vacuum distillation can be used to obtain each individual isomer with a purity in excess of 90%. The distillation experiments also indicate that the cis-6 dioxane isomer (2-methyl-5-hydroxy-1,3-dioxane) is the most volatile, and is distilled preferentially such that nearly pure cis-6 isomer is initially produced. When an acid catalyst is added to the mixture of isomers such that interconversion can occur during distillation, it is possible to produce the cis-6 isomer in nearly quantitative yield from glycerol. Based on these results, a reactive distillation process is proposed to produce pure cis-6 isomer as the sole product from glycerol continuously.

Oxidation of cis-6 GA isomer to the corresponding ketone product (2-methyl-1,3-dioxan-5-one) provides a new synthesis route for 1,3-dihydroxyacetone (DHA) production. A broad range of catalysts and oxidizing reagents including green oxidants such as molecular oxygen, hydrogen peroxide and ozone were then tested for this purpose. Due to the heterocyclic ring structure and high oxidation potential of cis-6, most of the reagents exhibited poor activity. However, ruthenium tetroxide-based oxidation demonstrated high activity toward oxidation of cis-6. With this reagent, complete conversion of cis-6 to its ketone product was achieved in 1 h at room temperature.

Based on this discovery, a novel process is designed for DHA production. In this route, glycerol is first converted to cis-6 glycerol acetal isomer. After that, the cis-6 isomer is oxidized to its ketone product and followed by a hydrolysis process to the final DHA product.

This new method has many advantages over the current DHA production technologies. Comparing to the conventional microbial approaches, this method does not require expensive microorganisms for fermentation; and has much shorter reaction time. Comparing to direct oxidation of glycerol, oxidation of the cis-6 substrate, with the primary alcohols blocked by a cyclic acetal structure, gives a much higher oxidation selectivity towards the secondary hydroxyl group. We estimate that a DHA yield in excess of 90% can be achieved from glycerol using this technology. Thus, the new method holds a good potential for commercial success.

Chapter VIII. Suggestions for Future Work

In this study, the experimental results indicate that preparation of the 6-membered GA isomer (cis-6) and hydrolysis of 2-methyl-1,3-dixoan-5-one (G-tone) to the final product 1,3-dihydroxyacetone (DHA) can be carried out continuously with high yield (over 90%). The biggest challenge to accomplish DHA production via the process proposed in the previous chapter is oxidation of cis-6 and separation of G-tone from the reaction mixture.

Cis-6, with heterocyclic structure and high oxidation potential, is beyond the capacity of many conventional oxidation reagents. The most effective methods we discovered so far is using ruthenium based catalyst and oxidizing salts as consuming oxidant. Although complete oxidation of cis-6 can be achieved using this method, separation of G-tone product from the reaction mixture which contains soluble ruthenium species and inorganic salts is quite a challenge.

Thus, a more convenient oxidation method is highly desirable to make this process eligible for commercialization purpose. As for future work recommendation, I would suggest the following research directions for consideration.

First, development of new catalysts for vapor phase oxidation of cis-6. Comparing with liquid phase reaction, vapor phase oxidation has a big advantage that it employs only pure cis-6 and air or molecular oxygen as reactant. Hence, the tedious separation operations encountered in conventional oxidation processes can be eliminated. Copper [1] and nickel catalysts [2] that have been used for aerobic oxidation of methanol and other alcohol substrates to their carbonyl products could be good candidates for this purpose.

Second, application of electro-catalytic method for cis-6 oxidation. In 2005, Ciriminna et al. [3] reported an electro-catalytic oxidation method to make DHA from glycerol. They obtained

an oxidation mixture with 25% DHA yield in 20 h. If an electro-catalytic process can be developed for direct cis-6 oxidation or ruthenium tetroxide catalyzed cis-6 oxidation, the following separation process can also be considerably simplified.

Third, dehydroxylation of cis-6 to a 1,3-propanediol precursor. As discussed in the Chapter III, cis-6 has a high oxidation potential and is less likely to be oxidized. From the opposite point of view, it may be a good substrate for reduction reaction such as dehydroxylation. Thus, if an appropriate method is found to reduce cis-6 to 2-methyl-1,3-dioxane, cis-6 can serve as a good intermediate for 1,3-propanediol synthesis.

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Appendices

Appendix I. Mass Spectra of the Glycerol Transacetalization Products

GC and GC-MS analysis of the reaction mixture from glycerol transacetalization with DEE is presented in Figures A1-1 to A1-9.



Figure A1-1. Gas chromatogram of transacetalization product mixture.



Figure A1-2. Mass spectrum of Peak E



Figure A1-3. Mass spectrum of Peak F



Figure A1-4. Mass spectrum of Peak G



Figure A1-5. Mass spectrum of Peak H







Figure A1-7. Mass spectrum of Peak J



Figure A1-8. Mass spectrum of Peak K



Figure A1-9. Mass spectrum of Peak L

Glycerol acetal isomers were identified by their retention index and mass spectrum as compared with Ferreira's report [1]. Comparing the experimental result and the reported mass spectrum [1], we can conclude that the isomers of the glycerol acetal obtained in this study are cis-5-hydroxy-2-methyl-1,3-dioxane (Peak E), cis-4-hydroxymethyl-2-methyl-1,3-dioxolane (Peak H), trans-4-hydroxymethyl-2-methyl-1,3-dioxolane (Peak I) and trans-5-hydroxy-2-methyl-1,3-dioxane (Peak J).

Structure analysis of species F, G, K, and L is presented in Table A1-1 and A1-2.

m/z		Fracture
189	M-1	
175	M-15	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \\ \end{array} \\ 0 \end{array} \\ \begin{array}{c} \\ 0 \end{array} \\ 0 \end{array} \\ 0 \end{array} \\ \begin{array}{c} \\ 0 \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ 0 \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ 0 \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ 0 \end{array} \\ \begin{array}{c} \\ 0 \end{array} \\ \end{array} \\$
145	M-45	O O CH O CH O O O O O O O O O O O O O O
117	M-73	$CH_3 O O O O O O O O O O O O O O O O O O O$
101	M-89	$CH \xrightarrow{O} CH_3 CH \xrightarrow{O} O$
85	M-105	$\begin{array}{ccc} CH & CH CH_3 & CH_2 \\ O - C & CH CH_3 \\ H_2 & OH CH_2 \\ O - C & CH CH_3 \\ O - C & CH CH_3 \\ H_2 & OH CH CH CH_3 \\ H_2 & OH CH CH CH_3 \\ H_2 & OH CH CH CH CH_3 \\ H_2 & OH CH CH CH CH_3 \\ H_2 & OH CH CH CH CH CH_3 \\ H_2 & OH CH CH$
73	M-117	-CHCH ₃ (OCH ₂ CH ₃)
58	M-132	-CHO CH ₂ CH ₃
45	M-145	-OCH ₂ CH ₃
29	M-161	-CH ₂ CH ₃

Table A1-1. Molecule fracture identification for species F and G.

So, the structures of species F and G are



They are 4-(1-ethoxy-ethoxymethyl)-2-methyl-1,3-dioxalane and 5-(1-ethoxy-ethoxy)-2methyl-1,3-dioxane, M.W. = 190.

m/z		Fracture	
163	M-1		
149	M-15	$HO \longrightarrow OH $	
133	M-31	CHOHOHOTO	
119	M-15	HO OH OT OH OT OH	
75	M-89		
73	M-91	-CHCH ₃ (OCH ₂ CH ₃)	
58	M-106	-CHO CH ₂ CH ₃	
45	M-119	-OCH ₂ CH ₃	
29	M-135	-CH ₂ CH ₃	

Table A1-2 molecule fracture identification for species K and L.

So, the structures of species K and L are



M.W. 164.

1. Ferreira, A, Barbe, J. and Bertrand, A. (2002). Heterocyclic acetals from glycerol and acetaldehyde in port wines: <u>Evolution with aging. Journal of agricultural and food chemistry</u>. 50, 2560-2564.

Appendix II. Calculation of Weisz-Prater Criterion for Ascertaining the Influence of Mass Transport on Transacetalization Kinetics

The equation used to calculate Weisz-prater criterion is

$$\Phi_{wp} = \frac{R_G \cdot L^2}{C_S \cdot D_{AB,eff}}$$

The values of the parameters used in this equation are listed in Table A2-1.

Parameter	Denotation	Unit
Φ_{wp}	Wiesz-Prater criterion	
R _G	observed reaction rate per unit catalyst	mol/L.cat•s
L	Catalyst size, L=R/3	m
C_S	bulk concentration of reactant	mol/L
D_{AB}	molecular diffusion coefficient	m ² /s
ε	porosity of catalyst	
τ	Tortuosity ($\tau \cong 1/\varepsilon$)	

Table A2-1. Parameters used to calculate Weisz-prater criterion

For reaction performed at 40° C with 1 wt% of Amberlyst-15 cationic exchange resin catalyst (0.0608 g, density = 1.2 g/cm³) and reactant molar ratio glycerol:DEE:ethanol = 1:1:12, the observed reaction rate constant is 9.0×10^{-5} L/mol·s. The initial concentration of glycerol and DEE is 1.1 mol/L (1:1:12 glycerol:DEE:EtOH); volume of solution is 60 ml. Catalyst

volume is 0.051 cm^3 when it is saturated with ethanol, the catalyst swells to twice its original size, so the volume to be used is 0.102 cm^3 . Then, the observed reaction rate per unit catalyst is

$$R_G = (9.0 \times 10^{-5} L / mol \cdot s) \times (1.1 mol / L)^2 \times 60 ml \div 0.102 cm^3 = 0.06 mol / L.cat \cdot s$$

The characteristic length L is related to particle size as L = R/3. For dry Amberlyst-15 catalyst, the average radius is 0.15 mm. Considering swelling by a factor of two in ethanol,

$$L = 0.15 \times 2^{\frac{1}{3}} / 3 = 0.063 mm$$

C_S is the bulk concentration of reactant,

$$C_S = 1.1 mol / L$$

 $D_{AB,eff}$ is the effective molecular diffusion coefficient, $D_{AB,eff} = \varepsilon \cdot D_{AB} / \tau$. Catalyst porosity (ε) for the dry catalyst is taken as 0.5; tortuosity, (τ) is taken as 1/ ε according to the classical random pore model. Considering catalyst swelling,

$$\varepsilon = 1 - 0.5/2 = 0.75$$
, $\tau = 1/0.75 = 1.33$

The molecular diffusion coefficient DAB can be evaluated using Wilke-Chang equation,

$$D_{AB} = 7.4 \times 10^{-12} \frac{T \cdot \sqrt{\varphi_B \cdot M_B}}{\mu_B \cdot v_A^{0..6}}$$

The values of the parameters used in Wilke-Chang equation are listed in Table A2-2.

Parameter	Denotation	Value	Unit
φ_B	association factor of solvent	1.5	
M _B	molecular weight of solvent	46	
Т	Temperature	313	K
μ_B	viscosity of solvent	1.2	mPa•s
v _A	molar volume of solute	73	cm ³

Table A2-2. Parameters used in Wilke-Chang equation [1]

$$D_{AB} = 7.4 \times 10^{-12} \cdot \frac{T \cdot \sqrt{\varphi_B \cdot M_B}}{\mu_B \cdot \nu_A^{0..6}} = 7.4 \times 10^{-12} \cdot \frac{313 \cdot \sqrt{1.5 \cdot 46}}{1.2 \cdot 73^{0.6}} = 1.22 \times 10^{-9} \, m^2 \, / \, s$$

$$D_{AB,eff} = \varepsilon \cdot D_{AB} / \tau = 0.75 \times (1.22 \times 10^{-9} m^2 / s) / 1.33 = 6.86 \times 10^{-10} m^2 / s$$

So, for this reaction,

$$\Phi_{wp} = \frac{R_{G} \cdot L^{2}}{C_{S} \cdot D_{AB,eff}} = \frac{0.06 mol / L \cdot s \times (0.063 \times 10^{-3} m)^{2}}{1.1 mol / L \times 6.86 \times 10^{-10} m^{2} / s} = 0.34$$

In the same manner, the Weisz-Prater criterion for other reactions is calculated. The value of ~ 0.3 indicates mild mass transport resistances in the kinetic experiments as noted.

1. Pryde, A. and Gilbert, M. (1979). <u>Applications of high performance liquid chromatography</u>. New York: Wiley.

Appendix III. Calculation of High-Valent Ruthenium Species in Aqueous Solution

The following reactions and equations are taken from Pourbaix's book 'Atlas of electrochemical equilibria in aqueous solutions' [1]. In these reactions, H_2RuO_5 is the dissolved form of RuO_4 species. $E_{0,x}$ represents the potential of the ionic solution.

$$H_{2}RuO_{5} + e^{-} \Leftrightarrow RuO_{4}^{-} + H_{2}O$$
(1)

$$E_{0,1} = 1.001 - 0.0591 \cdot \log \frac{[H_{2}RuO_{5}]}{[RuO_{4}^{-}]}$$
(2)

$$RuO_{4}^{-} + xH_{2}O + 4H^{+} + 3e^{-} \Leftrightarrow RuO_{2} \cdot xH_{2}O(s) + 2H_{2}O$$
(2)

$$E_{0,2} = 1.533 + 0.0788 \, pH - 0.0197 \cdot \log[RuO_{4}^{-}]$$
(3)

$$H_{2}RuO_{5} + 4H^{+} + 4e^{-} \Leftrightarrow RuO_{2} + 3H_{2}O$$
(3)

$$E_{0,3} = 1.400 + 0.0591 \, pH - 0.0148 \cdot \log[H_{2}RuO_{5}]$$
(4)

$$E_{0,4} = 0.590 - 0.0591 \cdot \log \frac{[RuO_{4}^{-}]}{[RuO_{4}^{2}^{-}]}$$
(4)

$$E_{0,4} = 0.590 - 0.0591 \cdot \log \frac{[RuO_{4}^{-}]}{[RuO_{4}^{2}^{-}]}$$
(5)

$$E_{0,5} = 2.005 + 0.1182 \, pH - 0.0295 \cdot \log[RuO_{4}^{2}^{-}]$$

The standard potential E^{0} for each reaction is the first item on the right side, i.e., for reaction 1, the standard potential is 1.001 V.

To calculate the equilibrium constant for a system containing $RuO_2 \cdot xH_2O$, RuO_4^- and H_2RuO_5 , we need to combine Reactions (1) and (2), or (2) and (3). For example,

$$(1) - 3 \times (2)$$

 $RuO_2 \cdot xH_2O(s) + 3H_2RuO_5 \iff 4RuO_4^- + (x+1)H_2O + 4H^+$
(6)

The standard potential of Reaction (6) is

$$3 \cdot E_6^0 = 3 \cdot E_1^0 - 3 \cdot E_2^0 = -1.596$$

According to Nernst equation, at equilibrium, the correlation between $[RuO_4^-]$ and $[H_2RuO_5]$ must satisfy Eq. (6),

$$E_6^{0} = \frac{RT}{nF} \log K = \frac{0.0591}{3} \left(\log \frac{[RuO_4^-]^4}{[H_2 RuO_5]^3} - 4pH \right)$$
(6)

Eq (6) can be simplified to

$$\frac{[H_2 R u O_5]^{0.75}}{[R u O_4^-]} = 10^{(6.751 - pH)}$$
(7)

Eq (7) can also be obtained by relating reactions (1) and (3). From Eq (7), it can be seen that RuO_4^- is favored in a basic pH, while H_2RuO_5 is favored in acidic pH.

In the same way, the correlation between $[RuO_4^-]$ and $[RuO_4^{2-}]$ can be calculated using Eq (2), Eq (4) and Eq (5), and the result is

$$\frac{[RuO_4^-]^{0.6667}}{[RuO_4^{2^-}]} = 10^{1.33 \cdot (11.9 - pH)}$$
(8)

Eq (8) indicates that RuO_4^{2-} is favored at even higher pH value.

With Eq (7) and Eq (8), the distribution of the three Ru species can be calculated for a given solution. For example, Figure A3-1 gives the distribution of Ru species between pH = 0 to 14 in an aqueous solution with total amount of [Ru] = 0.00038 mol/L. This result is in agreement with the experimental data reported by Mills (Figure A3-2) [2].



Figure A3-1. Calculated population (%) of various ruthenium species at different pHs in an aqueous solution with $[Ru] = 3.8 \times 10^{-4} \text{ M}$. $RuO_4 (\bullet)$, $RuO_4^- (O)$ and $RuO_4^{2-} (\triangle)$.



Figure A3-2. Population (%) of various ruthenium species at different pHs of an aqueous solution with [Ru] = 3.8×10^{-4} M. Experimental results. RuO₄ (\oplus), RuO₄ (O) and RuO₄² (\triangle). [2]

Electro-chemical calculation of RuO_2 and BrO_3 system

In a system containing RuO_2 and BrO_3^- , RuO_2 is oxidized to RuO_4 ; while BrO_3^- may be

reduced to BrO^- or Br^- . To understand the interactions between the species, the possible half reactions are listed below (taken from ref [1]).

$$H_2 RuO_5 + 4H^+ + 4e^- \Leftrightarrow RuO_2(s) + 3H_2O \tag{3}$$

$$E_{0,3} = 1.400 + 0.0591 pH - 0.0148 \cdot \log[H_2 R uO_5]$$

$$BrO_3^- + 4H^+ + 4e^- \Leftrightarrow BrO^- + 2H_2O$$
(9)
$$E_{0,9} = 1.341 - 0.0591pH + 0.0148 \cdot \log \frac{[BrO_3^-]}{[BrO^-]}$$

$$BrO_3^- + 6H^+ + 6e^- \Leftrightarrow Br^- + 3H_2O$$

$$E_{0,10} = 1.423 - 0.0591pH + 0.0098 \cdot \log \frac{[BrO_3^-]}{[Br^-]}$$
(10)

If BrO_3^- was reduced to BrO^- , the complete reaction can be expressed by combining Reactions (3) and (9).

$$(9) - (3)$$

$$BrO_{3}^{-} + RuO_{2}(s) + H_{2}O \Leftrightarrow H_{2}RuO_{5} + BrO^{-}$$

$$(11)$$

$$4 \cdot E_{11}^{0} = 4 \cdot E_{9}^{0} - 4 \cdot E_{3}^{0} = 4 \times 1.341 - 4 \times 1.400 = -0.236$$

$$E_{11}^{0} = -0.059$$

According to Nernst equation, at equilibrium, the equilibrium constant can be calculated from Eq. (12),

$$E_{11}^{0} = \frac{RT}{nF} \log K = \frac{0.0591}{4} \cdot \log \frac{[H_2 RuO_5] \cdot [BrO^-]}{[BrO_3^-]} = -0.059$$
(12)
$$K = 10^{-4}$$

It indicates that this reaction is not thermodynamically favored. Therefore, BrO^- is not the reduction product in the system.

Likewise, if BrO_3^- was reduced to Br^- , the complete reaction can be expressed by combining Reactions (3) and (10).

$$2 \times (10) - 3 \times (3)$$

$$2BrO_{3}^{-} + 3RuO_{2}(s) + 3H_{2}O \Leftrightarrow 3H_{2}RuO_{5} + 2Br^{-}$$

$$12 \cdot E_{13}^{0} = 12 \cdot E_{10}^{0} - 12 \cdot E_{3}^{0} = 12 \times 1.423 - 12 \times 1.400 = 0.276$$

$$E_{13}^{0} = 0.023$$
(13)

According to Nernst equation, at equilibrium, the equilibrium constant can be calculated from Eq. (14),

$$E_{13}^{0} = \frac{RT}{nF} \log K = \frac{0.0591}{12} \cdot \log \frac{[H_2 RuO_5]^3 \cdot [Br^-]^2}{[BrO_3^-]^2} = 0.023$$
(14)
$$K = 10^{4.67}$$

The large value of the equilibrium constant indicates that this reaction is thermodynamically favored. Therefore, Br^- is the reduction product in the system. Also, note that water is consumed in the reaction, which helps to explain why the reaction did not run without water present.

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