MECHANISTIC STUDIES OF CATALYTIC STOBBE CONDENSATION

By

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ABSTRACT

MECHANISTIC STUDIES OF THE CATALYTIC STOBBE CONDENSATION REACTION

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We report here the results of a series of mechanistic investigations of the condensation reaction between formaldehyde and dimethyl succinate, performed under catalytic conditions. The objective of the project was to understand the reaction pathway towards the final product, citraconic anhydride. To investigate the reaction course we performed a series of experiments using deuterium-labeled compounds such as CH_3OD, CD_2O and $CD_3OCOCH_2CH_2COOCD_3$. The hydrogen-deuterium exchange was monitored using mass spectrometry techniques. The experiments were performed in the vapor phase, at atmospheric pressure and high temperatures, using γ-alumina as the catalyst. Our results indicated that the reaction is catalyzed by the acidic sites on the alumina surface. Also, unexpected hydrogen-deuterium exchange between the reacting species was detected. Mechanistic routes for the condensation reaction and for the hydrogen-deuterium exchange processes are proposed.

To my parents and to Dr. Florian A. Urseanu

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I have passed through many pitfalls on my way to this degree and special thanks need to be given to those who helped me pick myself up and continue on.

First of all, I would like to thank Dr. James E. Jackson, my advisor, and Dr. Dennis J. Miller, my co-advisor, for their great guidance throughout the various steps of my research.

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Ancuta Cernat

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LIST OF ABBREVIATIONS

DMS	Dimethyl Succinate
TO	Trioxane
CA	Citraconic anhydride
TPD	Temperature-Programmed Desorption
H/D	Hydrogen/Deuterium
L-cat.	Lewis acid site on the catalyst surface

CHAPTER 1

Stobbe Condensation Reaction : A Review

1.1. INTRODUCTION

The Stobbe condensation is the reaction of carbonyl compounds with an ester of succinic acid to form alkylidenesuccinic acids (substituted itaconic acids) (Figure 1.1.1), or isomers formed by a tautomeric shift of hydrogen.

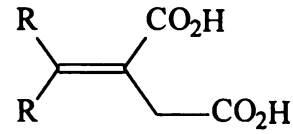


Figure 1.1.1. Alkylidenesuccinic acid

In the classic Stobbe condensation the condensing agent is a base and the primary product is the half-ester of the alkylidenesuccinic acid. In the recently reported catalytic Stobbe condensation, the main product is the anhydride of the alkylidenesuccinic acid.

The mechanism of the classic Stobbe condensation was thoroughly studied[1] and is well known today. In contrast, the mechanism of the catalytic Stobbe condensation has not been explored. The objective of this research project was to understand the pathway of the condensation reaction between formaldehyde and dimethyl succinate, performed at high temperature and atmospheric pressure, under γ-alumina catalysis. For this purpose, experiments involving deuterium-labeled compounds were performed.

1.2. Classic Stobbe condensation

1.2.1. General character and mechanism

In 1893 Hans Stobbe[2] demonstrated that when a mixture of acetone and diethylsuccinate was treated with sodium ethoxide, the expected acetoacetic ester type of condensation to give the following β-diketo compounds (Figure 1.2.1.)

Figure 1.2.1. β-Diketo-compounds

did not take place. Instead, the main reaction product was teraconic acid (Figure 1.2.2.),

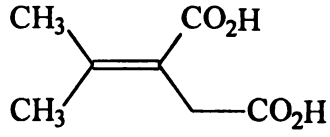


Figure 1.2.2. Teraconic acid

formed by an aldol type of condensation between the carbonyl group of the ketone and an α-methylene group of the ester. Stobbe and his collaborators undertook an extensive study which revealed that both aldehydes and ketones generally condense with succinic esters in this special manner.

Each mole of ester requires one mole of alkoxide. The lactone derivative is formed first, followed by the salt of the half-ester, which, upon acidic treatment, affords the alkylidenesuccinic acid, in the form of either the half-ester or the dibasic acid produced by hydrolysis (Figure 1.2.3.).

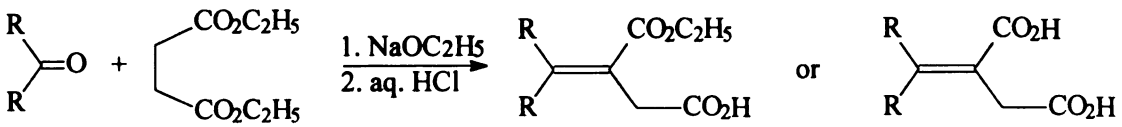


Figure 1.2.3. General representation of the classic Stobbe condensation

It is striking that this facile aldol type of condensation of esters with ketones is limited to succinic and substituted succinic esters. For example, benzophenone condenses with diethylsuccinate[3] to give pure β-carbethoxy-γ,γ-diphenylvinylacetic acid (Figure 1.2.4.)

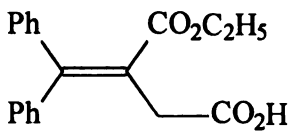
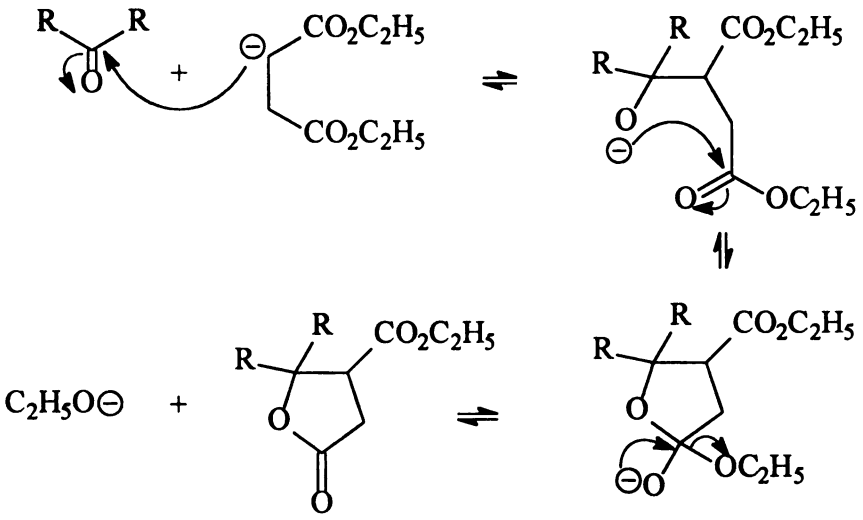


Figure 1.2.4. β- carbethoxy-γ,γ-diphenylvinylacetic acid

in 90% yield. In contrast, under the same conditions[4] this ketone fails altogether to react with ethyl or t-butyl acetate.

The success of the classic Stobbe condensation is not solely attributable to the high reactivity of the α-methylenes of succinic esters, as shown by the failure of diethyl malonate, which has a more reactive α-methylene group, to condense in any appreciable extent with benzophenone.[4]

The specificity of succinic esters in this reaction may be associated with the juxtaposition of a carbethoxy group with the newly formed alkoxide site, setting it up for ring formation, as indicated in reaction sequence (1), below (Figure 1.2.5.).



I

Figure 1.2.5. Mechanism for classic Stobbe condensation. Reaction sequence (1).

The postulation of an intermediary paraconic ester (I)[1,4] is reasonable in view of the fact that such substances are isolable,[6] particularly when shorter reaction periods are employed,[7] and that they are cleaved by alkoxides in excellent yield to give salts of the unsaturated half-esters.[8] This cleavage may be represented by reaction sequence (2), (Figure 1.2.6.).

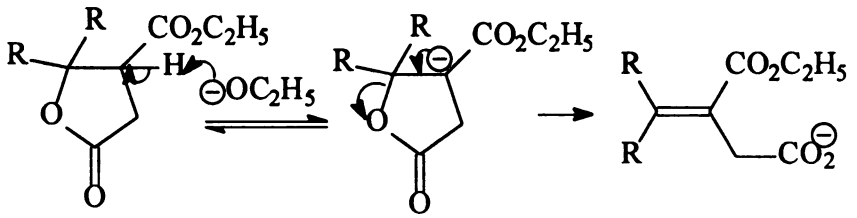


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Figure 1.2.6. Mechanism for classic Stobbe condensation. Reaction sequence (2).

The combined reaction sequences (1) and (2) thus constitute a satisfactory rationalization of the course of the classic Stobbe condensation, the irreversibility of the second step driving the reaction to completion.

The more obvious mechanism, in which the ketone first condenses with the succinate eliminating water which then reacts with the alkoxide to form hydroxide ion which in turn effects partial saponification of the diester, is not tenable in view of:

(a) the failure to isolate the postulated intermediary diester, even when a large excess of diethyl succinate was employed in the condensation, thus affording a highly competitive source of ester groups to react with the limited amount of hydroxide ion.[9]

(b) the failure of other esters[4] with comparably reactive methylene groups to condense readily.

(c) the failure of the appropriate unsaturated diester to give a good yield of half-ester on partial saponification.[10-12]

(d) the fact that isomers of citraconic and mesaconic acid type, which would be expected tautomers of certain alkylidenesuccinic diesters,[13] have never been found as products of the classic Stobbe condensation.

1.2.2. Scope and limitations

The carbonyl compounds that undergo the Stobbe condensation include members of the following classes of substances: aliphatic, aromatic, and α,β-unsaturated aldehydes; aliphatic, alicyclic, and aromatic ketones; diketones; keto esters and cyano ketones.[1]

The succinic esters that have been employed are diethyl, dimethyl and di-*t*-butyl succinate, and also α-substituted aryl-, alkyl-, and alkylidene-succinic esters.

Among the condensing agents used, sodium ethoxide, potassium *t*-butoxide and sodium hydride gave the best results.

1. 2.3. Side reactions

Several side reactions may accompany the classic Stobbe condensation reaction.

When aldehydes are used in the Stobbe condensation, the side reactions which have been observed are the Cannizzaro reaction[14-16] and the aldol condensation.[17,18] Aromatic and aliphatic aldehydes with no α-hydrogens, give the Cannizzaro reaction when treated with bases. In this reaction one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an α-hydrogen do not give the reaction, because when these compounds are treated with base the aldol condensation is much faster.

The failure of certain ketones containing highly active α-methyl or α-methylene groups to give good yields in the Stobbe condensation may be due in part to a tendency for these ketones to enolize. The anion produced may be relatively stable, as with dibenzyl ketone, in which event the ketone is recovered unchanged. On the other hand the anion may compete[1] with the ester anion in reaction with free ketone, in which case self-condensation of the ketone is effected.

When sodium ethoxide in ether (or ethanol) is used as the condensing agent, there is almost always a significant amount of reduction of the ketone to the corresponding

carbinol.[19] This reduction is effected by the ethoxide, which is converted to acetaldehyde, which in turn is largely responsible for the formation of resinous material and darkening usually observed with this procedure.

Sodium methoxide largely eliminates the oxidation-reduction complication, since metal methoxides are weaker reducing agents than ethoxides.[20] At the same time, sodium methoxide is a weaker condensing agent (since it is a weaker base) than sodium ethoxide and has therefore not found general use.

Potassium *t*-butoxide (in *t*-butyl alcohol) is a considerably stronger condensing agent than sodium ethoxide and affords better yields of pure products in much shorter reaction periods.[21] Even potassium *t*-butoxide and diethyl succinate, however, cause some reduction of the ketone. In this case the reduction is effected by the alcohol formed as a by-product in the Stobbe condensation and as a product of the self-condensation of the succinate to produce diethyl cyclohexane-1,4-dione-2,5-dicarboxylate (Figure 1.2.7.).

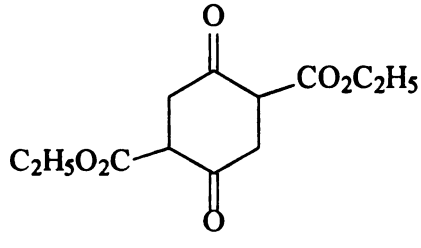

Figure. 1.2.7. Diethyl cyclohexane-1,4-dione-2,5-dicarboxylate

A significant amount of reduction[22] occurs only with ketones that react slowly in the classic Stobbe condensation, thus allowing a considerable concentration of ethoxide to build up by the competing self-condensation. This reduction could be almost completely eliminated by the use of dimethyl instead of diethyl succinate, a result that is

in accord with the comparative reducing properties of methoxide and ethoxide considered above. Dimethyl succinate is therefore useful in conjunction with *t*-butoxide for condensation with slowly reacting ketones.

A solution to the problem of the competing self-condensation of the esters lies in the use of an ester like di-*t*-butyl succinate.[9] which reacts in this way relatively slowly. The Stobbe condensation itself, however, is considerably slower with di-*t*-butyl than with dimethyl or diethyl succinate, presumably owing to steric resistance of the carbo-*t*-butoxy group to participation in the lactonization step. Therefore, longer periods of heating are required.

Sodium hydride has the advantage of being inexpensive and easy to use as a condensing agent. A small amount of alcohol[23] corresponding to the succinate is usually required to initiate the reaction. The alcohol reacts rapidly with the sodium hydride to produce sodium alkoxide, the true condensing agent. As the reaction proceeds, more alcohol is formed as a by-product. This reacts rapidly with the sodium hydride, producing additional sodium alkoxide; and, as the concentration of the latter gradually increases, there is a corresponding increase in the rate of condensation as evidenced by the rate of hydrogen evolution.

1.2.4. Applications of classic Stobbe condensation

Besides the obvious general use for preparing many varieties of unsaturated and (by hydrogenation) saturated substituted succinic acids, the classic Stobbe condensation

has found wide application[1] in the synthesis of other types of substances, including substituted lactones, naphthols, tetrahydroindanones, and tetralones.

Fulgides (Figure 1.2.8.) are derivatives of dimethylene succinic anhydride.

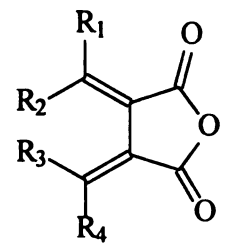

Figure 1.2.8. Fulgide

These compounds were first investigated by Stobbe[24] and he coined their name (from the Latin fulgere - to glisten and shine) because they were frequently obtained as beautiful reflective colored crystals. Typically, fulgides are yellow or orange crystalline compounds which change to orange, red, or blue upon irradiation with ultra-violet light, if at least one aryl group is present in the molecule, to participate in a photochemical ring closure (Figure 1.2.9.).

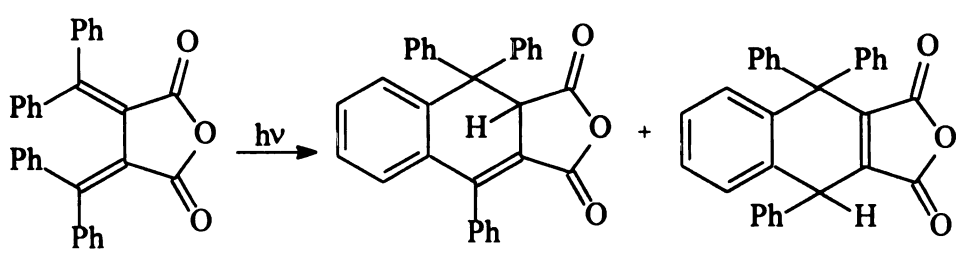

Figure 1.2.9. Photochromism in fulgides

Photochromism has been observed in crystals, solutions, polymers and glasses over a wide range of temperatures and conditions.

Fulgides have various uses: chemical actinometers[25] for the near u.v. region, optical data storage, sunlight active variable density optical filters (sunglasses are an obvious potential commercial application of these compounds). New applications of fulgides are in spatial light modulation,[26] optical waveguide construction,[27] and non-linear optical switching.[28]

1.3. Catalytic Stobbe condensation

1.3.1 Introduction

Recently chemists have become interested in performing the Stobbe condensation reaction in a catalytic fashion. Several heterogeneous catalytic processes have been patented, all claiming the preparation of citraconic (methyl succinic) anhydride, citraconic acid and/or its isomer, itaconic (methylidene succinic) acid. Hydrolysis of citraconic anhydride allows the formation of citraconic acid which upon thermal isomerization forms itaconic acid.

1.3.2. Scope and limitations

In 1974 B. E. Tate and R. G. Berg (Pfizer Inc.)[29] patented for the first time a catalytic procedure for the preparation of citraconic anhydride. Formaldehyde (from trioxane, or a heavy slurry of paraformaldehyde in mineral oil, heated to liberate CH_2O gas) is reacted in the vapor phase with dimethyl or diethyl succinate or with succinic anhydride at a temperature between 280-410 °C. The reaction time varies inversely with the temperature and ranges from 10 to 25 seconds. Best results are obtained at

temperatures of 340-410°C. Lower temperatures require longer contact times between the reagents and the catalyst and result in lower yields. The catalyst is selected from a group consisting of thorium sulfate, potassium diacid phosphate, lithium carbonate on alumina support, and lithium phosphate. An inert gas, such as nitrogen, hydrogen, helium, carbon dioxide, carbon monoxide, was used as a carrier gas. The molar ratio of formaldehyde to starting compound is preferred to be about 3.5:1 to 5:1 for best results. At molar ratios close to 1:1 the yields are low and accompanied by a sharp decrease in catalyst efficiency, while at molar ratios much above 5:1 little further improvement is obtained. Citraconic anhydride, recovered from the gaseous effluent from the reactor by trapping in a series of cold traps followed by distillation, is obtained in 60- 80% yield at 90-98% conversion.

The Denki Kagaku Kogyo Inc.[30] also patented several processes for the synthesis of itaconic acid, citraconic acid and their ester derivatives. The catalysts used are zeolites, plain or impregnated with $PdCl_2$, or $MnCl_2$ (molecular sieves 10x), or impregnated with $La(NO_3)_3$, $Ni(NO_3)_3$, $CoCl_2$, (molecular sieves 13x) or silica-alumina plain or containing group IB or IIB metal salts, such as $ZnCl_2$, $CuCl_2$, $LaCl_3$, $MnCl_2$, and $NiCl_2$. The ratio of succinic acid (or succinate or succinic anhydride) to formaldehyde (from trioxane or formalin 37%) is preferred to be 2:1 ~ 5:1. The temperature ranges between 350 and 450°C.

Itaconic acid can be easily obtained from citraconic acid by isomerization. An aqueous 25% citraconic acid solution, autoclaved at 160°C for 8 hours, gives about 45% yield of itaconic acid easily recovered by evaporation and crystallization from water.[31]

There is no mention in the literature about a carbonyl compound other than formaldehyde being used for the catalytic Stobbe condensation. Also, no mechanistic study of this reaction has been reported.

1.3.3. Applications of catalytic Stobbe condensation

The interest in obtaining itaconic acid in a catalytic fashion rises from the methods presently used for its preparation and from its multiple uses.

Itaconic acid is currently manufactured[32] by the process of fermentation of sugars (from molasses). A 15-25% carbohydrate solution is sterilized and incubated with a culture of *Aspergillus terreus*. at 35-40°C for 3-7 days under a pressure of 10-15 psi. The pH is maintained at 5.0 by adding lime. Itaconic acid is separated from the broth by acidification, concentration and crystallization when the fermentation process is complete.

Itaconic acid is a valuable monomer for polymerization because of the presence of the two carboxyl groups and the methylene group (from the double bond). The methylene group is able to take part in addition polymerization forming polymers with many free carboxyl groups which confer advantageous properties on the polymer. Sodium polyitaconate or other alkali salts may be used in detergents to improve clarity and color, used in bleaches as a stabilizer, and used in metal cleaners for rust removal.[33]

Itaconic acid itself polymerizes very slowly to form low molecular weight polymers, so it is typically used in copolymerization. Itaconic acid is a specialty monomer that affords performance advantages to certain polymers when it is incorporated

in small amount. Styrene-butadiene latexes containing less than 10% itaconic acid are widely used in carpet backing[34-36] and paper coating.[37] Emulsion stability, clarity, water resistance of the coatings, and adhesion to substrates are improved by the inclusion of itaconic acid.

Dental cements made of acrylic-itaconic acid copolymers that are cured with polyvalent metal compounds such as aluminosilicates or oxides of zinc and magnesium possess a good compressive and adhesive strength as well as physiological compatibility.[38]

The dimethyl, diethyl and di-*n*-butyl esters of itaconic acid can also be used in copolymers, (e.g. for adhesives) and esters with long chain alcohols have been proposed as plasticizers.

With amines, itaconic acid produces N-substituted pyrrolidinones that can be used as thickeners for greases.[39] Other pyrrolidinones made from itaconic acid and a wide range of amines have potential uses in detergents, shampoos,[40] pharmaceuticals, and herbicides.

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CHAPTER 2

Experimental studies and results

2.1. Introduction

Stimulated by the great economic value of itaconic acid, our group started a project focused on the development of a continuous process for the production of itaconic acid via the catalytic Stobbe condensation. The reaction studied[1] was between dimethyl succinate (DMS) and formaldehyde, using γ-alumina as the catalyst. Reactions were run at 380°C and atmospheric pressure in a fixed bed tubular reactor placed in the center of a furnace to ensure even heating (Figure 2.1.1.).

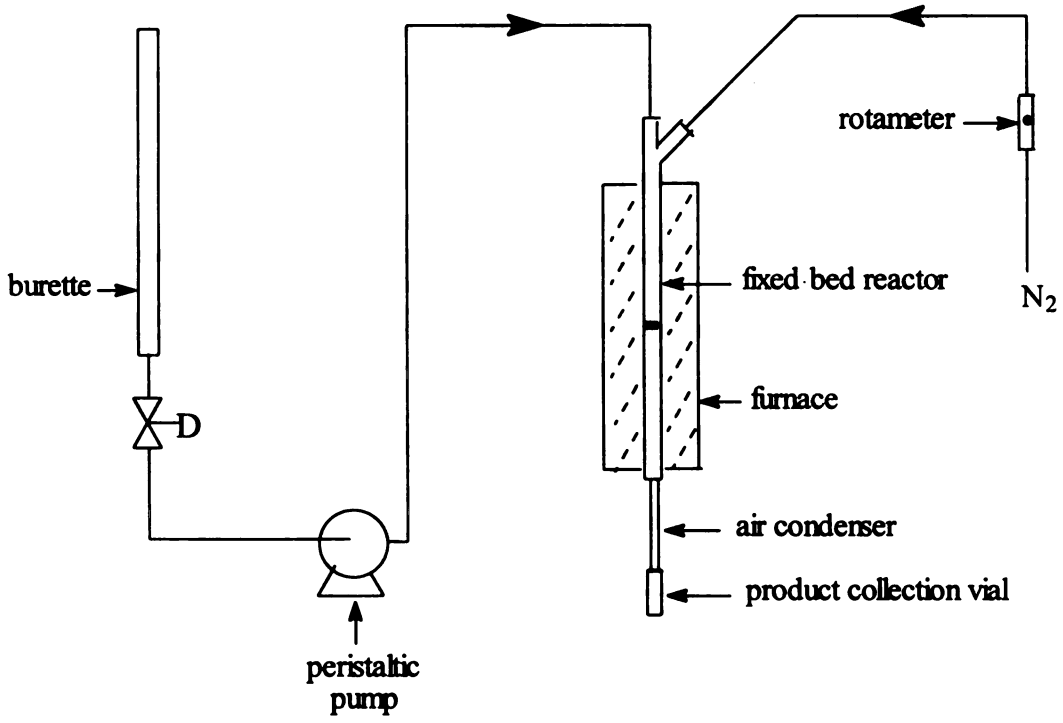


Figure 2.1.1. Set-up for catalytic Stobbe condensation between CH_2O (from trioxane) and DMS

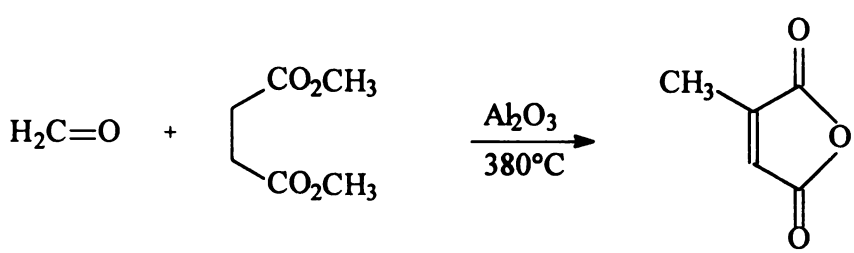
Trioxane, (99%, purchased from Aldrich Chemical Co.) which is soluble in DMS (solubility = 1 mol of trioxane/mol of DMS)[1] was used as the formaldehyde source. DMS (98%) was purchased from Aldrich Chemical Co. The molar ratio of the reagents was CH_2O : DMS = 2 : 1. The reagent mixture was stored in a burette and pumped

dropwise into the reactor at a rate of 0.3 mL/min., by means of a Masterflex (Cole-Parmer) peristaltic pump. Nitrogen was used as the carrier gas at a flow rate of 20 mL/min., controlled by a Cole-Parmer rotameter.

γ-Alumina (SA 3177, purchased as 1/8 inch pellets from Norton Inc.) was used in a fixed quantity of 5 grams. The pellets were ground and sieved to the size of 30 - 60 mesh. The catalyst was heated in the reactor at 380-400°C for at least 3 hours to eliminate moisture before the reagent mixture was added.

The product mixture was passed through an air condenser for cooling purposes and collected every 10 min. (up to four collections) in glass vials. Analysis by GC-Mass spectrometry used a Hewlett Packard 5890 Series II gas cromatograph (SPB-1 non-polar column) connected with a VG Trio-1 mass spectrometer.

The catalytic "Stobbe condensation" product of formaldehyde with DMS was obtained as citraconic anhydride, (Figure 2.1.1.).



citraconic anhydride

Figure 2.1.1. Catalytic Stobbe condensation between CH_2O and DMS

Citraconic anhydride is a double bond isomer of itaconic anhydride (Figure 2.1.2.).

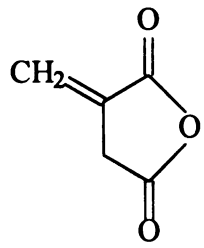


Figure 2.1.2. Itaconic anhydride

Beside citraconic anhydride, the product mixture contained monomethyl succinate, succinic anhydride, and unreacted DMS .

For a better understanding of the reaction, the catalyst was characterized by various methods. Exchange experiments involving deuterium-labeled reagents were performed to probe the mechanism of the reaction.

2.2. Catalyst characterization

As heterogeneous catalysis is a surface phenomenon, the determination of surface properties plays a large part in catalyst characterization. The investigated surface properties of alumina SA 3177 were total surface area, surface concentration of acidic sites, and surface concentration and strength of basic sites. The methods used for these investigations are all based on the physical adsorption of a gas (adsorbate) on the catalyst (adsorbent) surface.

2.2.1. Surface area

The BET dynamic method[2] is a rapid method of surface area determination. Nitrogen is used as adsorbate and helium (a gas not adsorbed significantly by most

solids) is employed as carrier gas and diluent. The volume of gas passed through the sample (adsorbent bed brought to 77 K in a liquid nitrogen bath) is adsorbed and equilibrium between gas phase and solid phase is rapidly established. The change in nitrogen concentration is recorded.

The main assumptions of this method[3] are:

- the adsorption is supposed to be localized on well defined sites; all of the sites have the same energy (homogeneous surface) and each of them can accommodate one adsorbate molecule.

- an adsorption-desorption equilibrium is established between molecules reaching and leaving the solid surface.

The surface area can be calculated with the formula: $s_{BET} = 4.37 \times 10^6 v_m$

where: s = specific surface area (surface area of the mass unit of solid) (m^2/kg)

v_m = the amount of adsorbate just sufficient to cover with a complete monolayer the whole surface developed by the unit mass of adsorbent

4.37×10^6 = constant which includes the surface area occupied by a N_2 molecule (at 77 K), the Avogadro constant (6.025×10^{23} $mole^{-1}$) and the molar volume of N_2 (22.414×10^{-3} $m^3 \times mole^{-1}$)

2.2.2. Acid-base properties

A complete description of acidic and basic properties on solid surfaces requires the determination of the acid and base strength, and of the amount and nature (Brönsted or Lewis type) of the acidic and basic sites.

2.2.2.1. Acidity

The acid strength of a solid is defined as the ability of the surface to convert an adsorbed neutral base into its conjugate acid. The amount of acid on a solid is usually expressed as the number or mmol of acid sites per unit weight or per unit surface area of the solid, and is obtained by measuring the amount of a base which reacts with the solid acid. The strength can be determined using indicators. For the determination of the density of acid sites, there are two main methods: an amine titration method using indicators and a gaseous base adsorption method.[3]

A. Amine titration method using indicators

The qualitative determination is easily made by placing the sample (0.5 grams) in powder form into a test tube, adding non-polar solvent, such as benzene, containing 1% indicator, and shaking briefly. The color of suitable indicators adsorbed on a surface will give a measure of its acid strength (expressed by the Hammett acidity function H_0). If the color is that of the acid form of the indicator, then the value H_0 of the surface is equal to or lower than the pK_a of the conjugate acid of the indicator. Lower values of H_0 correspond to greater acid strengths. This method determines the acid strength of a catalyst relative to that of the conjugate acid of the indicator. The amount of acid sites can be measured by titration of a solid acid suspended in benzene with *n*-butylamine using an indicator, immediately after the determination of the relative acid strength.

B. Gaseous base adsorption method

When gaseous bases are adsorbed on acid sites, a base adsorbed on a strong acid site is more stable than one adsorbed on a weak acid site, and is more difficult to desorb. As elevated temperatures stimulate liberation of the adsorbed bases from the acid sites, those at weaker sites will be released preferentially. Thus, the proportion of adsorbed base at various temperatures can give a measure of acid strength. The amount of a gaseous base which a solid acid can adsorb chemically from the gaseous phase is a measure of the amount of acid on its surface.

In temperature-programmed desorption (TPD) studies a solid previously equilibrated with a basic adsorbing gas (ammonia, pyridine etc.) under well-defined conditions is subjected to a programmed temperature rise and the amount of desorbing gas is continuously monitored in a spectrum. In the ammonia case, no distinction can be made between Brönsted and Lewis acidity, as the NH_3 coordinatively bondes to the catalyst giving only one peak in the spectrum. The distinction between Brönsted and Lewis acidity is possible when pyridine is used as a gaseous base, because pyridine coordinatively bonded to the catalyst gives peaks at different positions for Brönsted acid sites and for Lewis acid sites.

2.2.2.2. Basicity

The basic strength of a solid surface is defined as the ability of the surface to convert an adsorbed neutral acid to its conjugate base. The density of basic sites is usually expressed as mmol of basic sites per unit weight or per unit surface area of the solid.

There are two main methods for the measurement of strength and amount of basic sites: benzoic acid titration method using indicators and gaseous acid adsorption method[3].

A. Benzoic acid titration method using indicators

The principle of this method is similar to that for the determination of acidic strength, using acid indicators. This method determines the basic strength of a catalyst, relative to that of the conjugate base of the indicator. Similarly, the number of basic sites can be measured by titrating a catalyst sample with benzoic acid using an indicator.

B. Gaseous acid adsorption method

The principle of this method is the same as that of the gaseous base adsorption method. As adsorbates, acidic molecules such as carbon dioxide or nitric oxide can be used. The amount of carbon dioxide irreversibly adsorbed is a good measure of the amount of basic sites on solid surfaces.

2.2.3. Characteristics of γ-Alumina SA 3177

Hindin proposed a simple schematic description for the generation of acid and basic sites on the surface of alumina by dehydration[5] (Figure 2.2.1.).

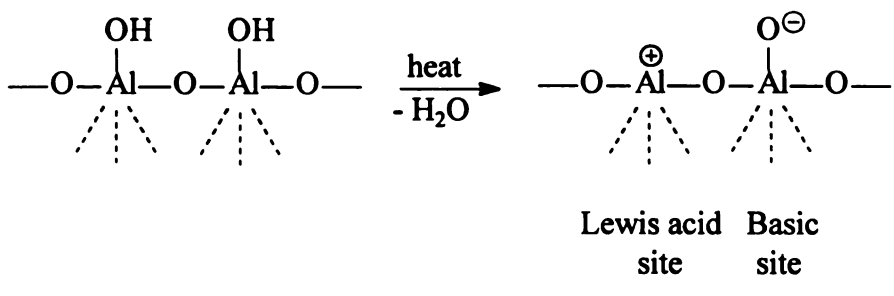


Figure 2.2.1. Lewis acid and basic sites on alumina

The Lewis acid site is visualized as an incompletely coordinated aluminum atom formed by dehydration while the basic site is considered to be a negatively charged oxygen atom.

γ-Alumina SA 3177 was tested by the TPD methods using NH_3, pyridine and CO_2 and the presence of acid sites of the Lewis type and of basic sites was proven.[4] The TPD experiments showed that the density of basic sites is 0.049 mmol/g and the density of acid sites is 0.232 mmol/g. The base indicator method showed that the acid sites on γ-alumina SA 3177 have a pK_a ranging between (+1.1) and (-0.2). The surface area determination by BET method showed that γ-alumina SA 3177 has a surface area of 106.94 m^2/g.

2.3. Hydrogen-deuterium exchange experiments involving CH_3OD

2.3.1. Introduction

The first step in the mechanism of the classic Stobbe condensation reaction is the formation of the enolate anion at C_2 in DMS by abstraction of a proton by a strong base. In order to determine whether the anion is also generated under heterogeneous catalytic conditions, experiments using DMS and CH_3OD as reagents were performed. The H/D exchange can be schematically represented as follows (Figure 2.3.1.).

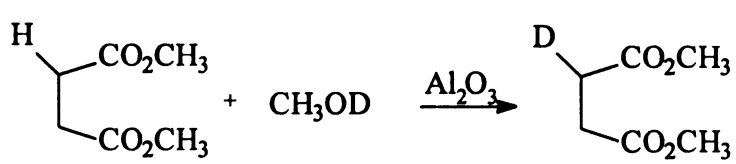


Figure 2.3.1. H-D exchange between CH_3OD and DMS

The experiments demonstrated the enolization of the DMS. Also, by performing the same experiments with a highly acidic catalyst and with a highly basic catalyst, it was shown that the reaction is catalyzed by the Lewis acid sites on the alumina surface.

2.3.2. Experimental methods and results

The experiments were performed in the set-up presented previously. The molar ratio of the reagents was DMS : CH_3OD = 1 : 40 (exchangeable H : D = 1 : 10). CH_3OD (99.5%) was purchased from Aldrich Chemical Co.. The flow rate of the reagent mixture was 0.3 mL/min. Nitrogen was used as carrier gas at a flow rate of 20 ml/min, controlled by a Cole-Parmer rotameter. The catalyst, alumina SA 3177, 30-60 mesh in size, was heated in the reactor at 380-400°C for at least 3 hours to eliminate moisture before the reagent mixture started being added. The product mixture was passed through an air condenser for cooling purposes and collected in glass vials for 10 minutes at each temperature.

The experiments covered a large range of temperatures, from 190°C to 430°C, in increments of 40°C.

The gradual H/D exchange follows the scheme (Figure 2.3.2.) :

$$H_4\text{-DMS} \xrightarrow{CH_3OD} H_3D\text{-DMS} \xrightarrow{CH_3OD} H_2D_2\text{-DMS} \xrightarrow{CH_3OD} HD_3\text{-DMS} \xrightarrow{CH_3OD} D_4\text{-DMS}$$

Figure 2.3.2. Gradual replacement of hydrogen by deuterium

The product mixture was analyzed by GC-Mass spectrometry using a Hewlett Packard 5890 Series II gas cromatograph (SPB-1 non-polar column) connected with a VG Trio-1 mass spectrometer.

The monitored compound was DMS (M=146.14 g/mole), whose fragmentation pattern is[6] shown in Figure 2.3.3.

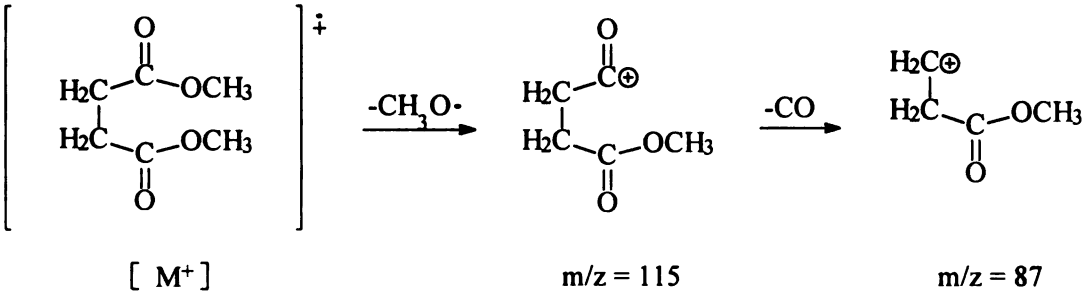


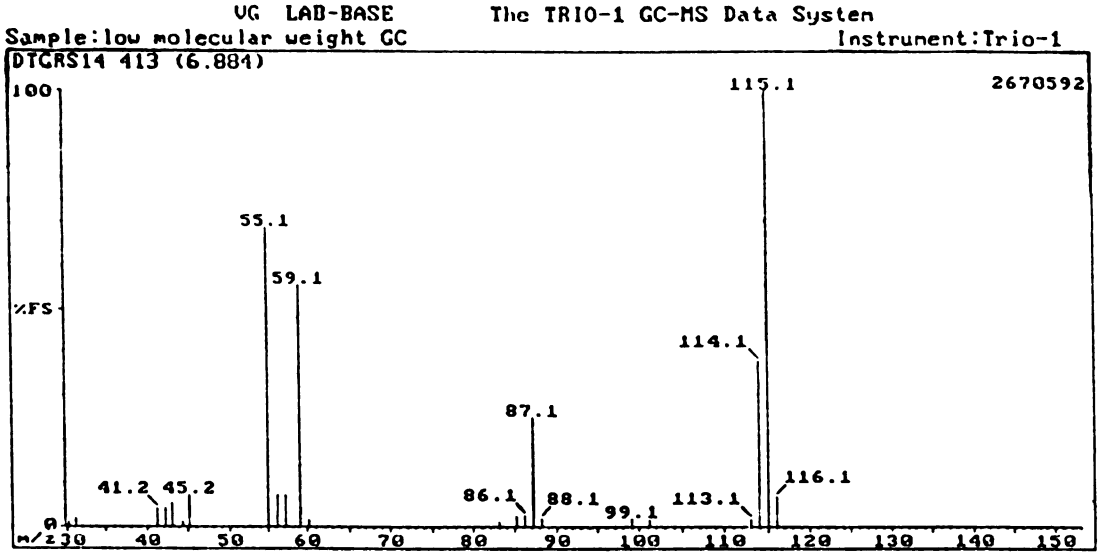
Figure 2.3.3. Fragmentation pattern for DMS

The EI^+ mass spectrum[6] of DMS does not show the molecular ion peak. The base peak is at m/z = 115, the fragment which corresponds to the loss of a methoxy group. The corresponding fragments containing 1, 2, 3 and 4 deuterium atoms will thus have m/z = 116, m/z = 117, m/z = 118 and m/z = 119, respectively. A comparison between the mass spectrum of standard DMS and of a product mixture containing mainly D_4-DMS is shown in Figure 2.3.4.

The fact that the m/z = 87 fragment in standard DMS mass spectrum corresponds to a fragment with m/z = 91 in the second mass spectrum proves that the four deuterium atoms in D_4-DMS are located at C_2 and C_3 and no deuterium is incorporated in the methoxy groups.[7]

Using[8] the mass spectra of recovered DMS with various degrees of deuteration, the change in the content of D_1-DMS, D_2-DMS, D_3-DMS, D_4-DMS and H_4-DMS with temperature was examined. The result is shown in Figure 2.3.5.

Over alumina, the extent of conversion of DMS to $D_{1,2,3,4}$-DMS, represented by the m/z = 115 curve, was quite rapid and it begins to equilibrate from 350°C.



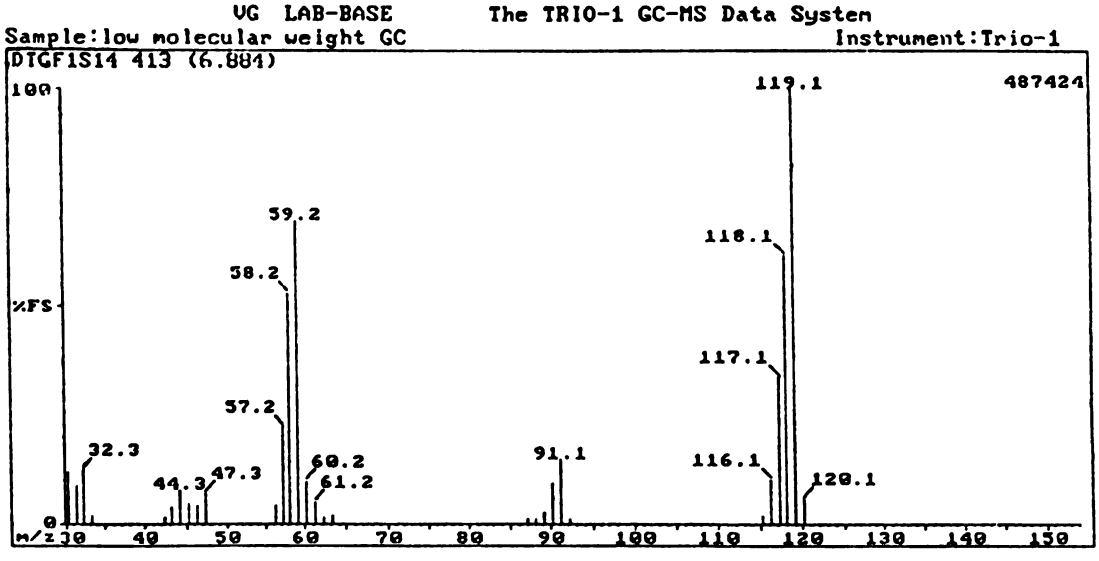


Figure 2.3.4. Comparison between the mass spectra of standard DMS (top) and of a product mixture containing mainly D_4-DMS (bottom)

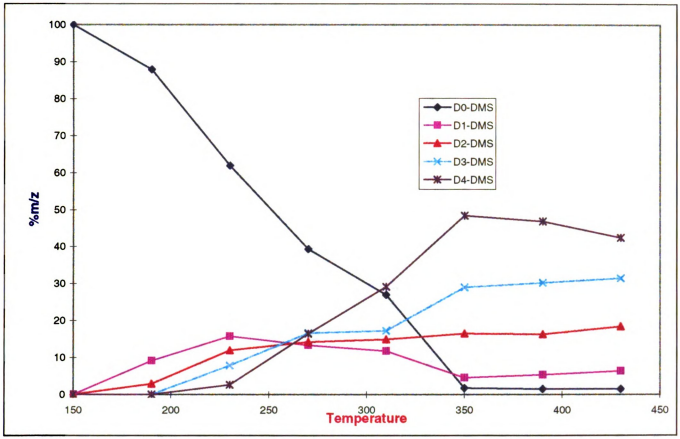


Figure 2.3.5. Extent of deuterium incorporation in DMS over alumina
CH_3OD/DMS Experiment

The D_1-DMS and D_2-DMS species started to appear at 190°C, but neither D_3-DMS nor D_4-DMS were detected at this temperature. At 230°C all four deuterated species were detected. As shown by the graph, the exchange seems to follow a certain pattern. At 230°C the relative concentrations of D_1-DMS and D_2-DMS are higher than D_3-DMS and D_4-DMS concentrations. From 310°C onwards the exchange appears to be rapid, with the D_3-DMS and D_4-DMS concentrations getting higher than the D_1-DMS and D_2-DMS concentrations, consistent with a sequential series of H/D exchanges.

In order to determine whether the H/D exchange is due to the high temperatures or not, the experiment was repeated with no catalyst over the same range of temperatures. The mass spectra of recovered DMS showed no deuterium incorporation at any temperature, which proves that the H/D exchange between CH_3OD and DMS is due to the catalyst.

The next question that comes to mind is whether the deuterium exchange is acid or base catalyzed. As stated before, alumina has both acid and basic sites and the acid sites are characterized by Lewis acidity.

Zeolites are known to have highly acidic sites and no basic sites. The characteristics of zeolites 13-X were also determined[4] experimentally. The TPD experiments showed that the density of acid sites is 1.851 mmol/g.The base indicator method showed that the acid sites have a pK_a ranging between (-8.1) and (-9.3). The surface area is 435 m^2/g. The experiment was therefore repeated with zeolite 13-X in the H form as catalyst, over the same range of temperature, 190°C-430°C. The results are presented in Figure 2.3.6.

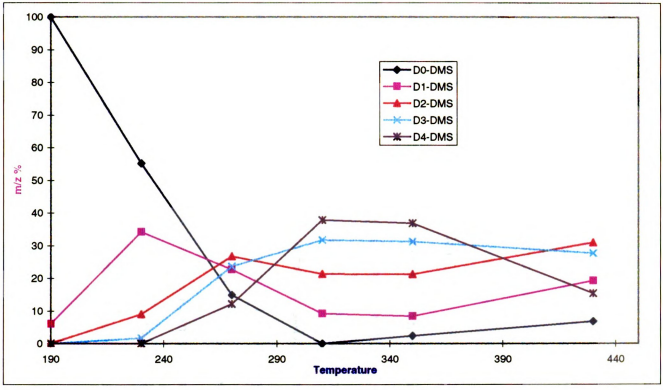


Figure 2.3.6. Extent of deuterium incorporation in DMS over zeolite
CH_3OD/DMS Experiment

Over zeolite 13-X, the extent of conversion of DMS to $D_{1,2,3,4}$-DMS was greater and more rapid than in the alumina case.

Since the H/D exchange occurred with a highly acidic catalyst, it must be considered that in the alumina case, the exchange may likewise be catalyzed by the acidic sites.

To verify whether the basic sites on alumina have any role in H/D exchange between CH_3OD and DMS, the experiment was repeated using a highly basic catalyst, hydrotalcite (MgO-Al_2O_3 cocatalyst) over the same range of temperatures, 190-430°C.

The characteristics of hydrotalcite (Mg : Al = 75 : 25) were determined[4] experimentally. The density of basic sites is 0.196 mmol/g. The surface area is 143.42 m^2/g. The pK_a of the basic sites is greater than (+4.8).

The results are presented in Figure 2.3.7. H/D exchange was observed, but to a much smaller extent, even at high temperatures. D_0-DMS is the main species at all of the temperatures. D_3-DMS and D_4-DMS species remain at a very low concentration all the time. Among the deuterated DMS species, D_1-DMS is predominant at all times.

Since a highly basic catalyst allowed only small extent of H/D exchange and since alumina has only slight basic character (much less than hydrotalcite), it can be considered that the contribution of basic sites on alumina to the H/D exchange is negligible.

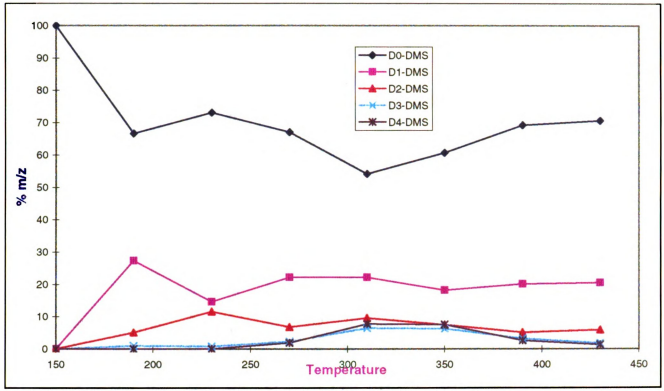


Figure 2.3.7. Extent of deuterium incorporation in DMS over hydrotalcite
CH_3OD/DMS Experiment

As a conclusion to the above experiments, the H/D exchange between CH_3OD and DMS in the alumina case can be considered as being effected by the Lewis acid sites. The mechanism for the hydrogen-deuterium exchange between CH_3OD and DMS is shown in Figure 2.3.8.

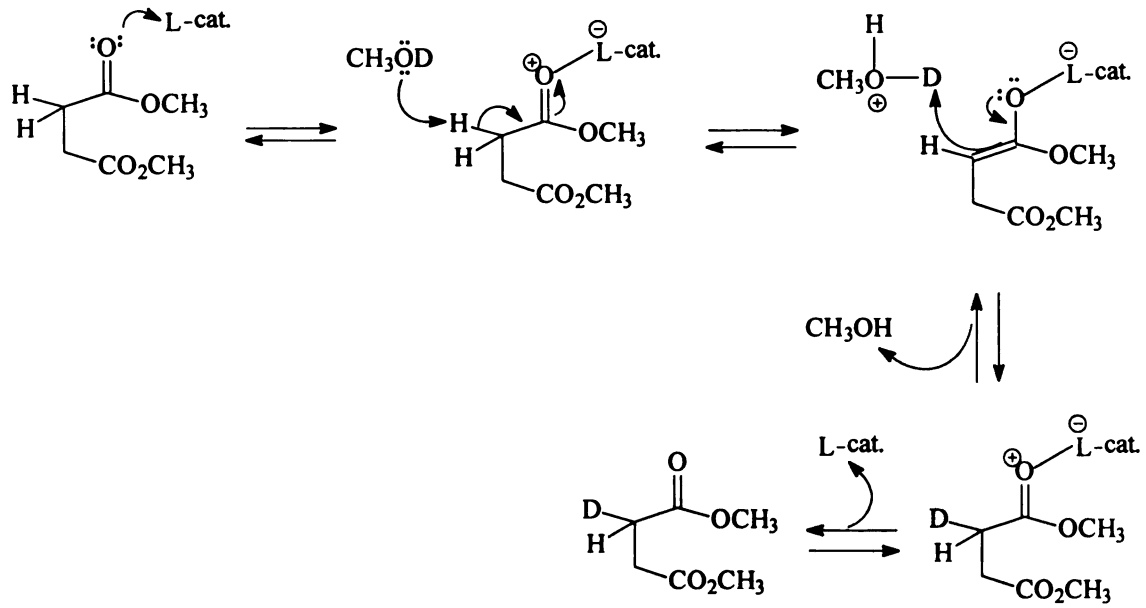


Figure 2. 3. 8. Mechanism for H/D exchange between CH_3OD and DMS on alumina

The oxygen from the carbonyl group in DMS coordinates the Lewis acid site on alumina surface by the means of a lone pair of electrons. This oxygen will thus have a positive charge. A methanol molecule abstracts a proton from C_2 in DMS, and the corresponding anion is stabilized as an enolate. The carbon-oxygen double bond in DMS is then reformed and a deuterium is abstracted from a CH_3OD molecule, followed by detachment from the Lewis acid site.

2.4. Experiments involving CD_2O and DMS

2.4.1. Introduction

In order to study the behaviour of the two hydrogen atoms from formaldehyde, experiments using CD_2O and DMS were performed. If no H/D exchange takes place, then deuterium should be present only in the methyl group of citraconic anhydride, according to the following scheme (Figure 2.4.1.) :

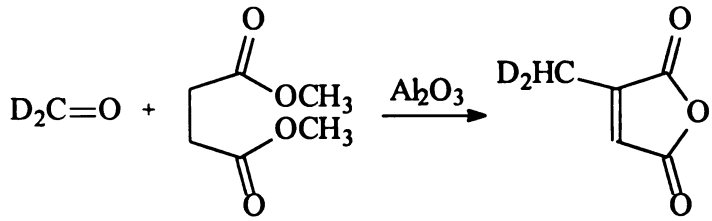


Figure 2.4.1. Formation of deuterated citraconic anhydride from CD_2O and DMS

The results showed deuterium incorporation both in citraconic anhydride and in the recovered DMS, which means that H/D exchange between deuterated citraconic anhydride and DMS took place.

2.4.2. Experimental methods and results

Paraformaldehyde-d_2 (99%, purchased from Merck&Co., Inc.) was used as a formaldehyde source. Since paraformaldehyde is not soluble in DMS, the set-up described previously was modified (Figure 2.4.2.). Paraformaldehyde-d_2 (4 grams) was stored in a glass tube having a frit in the middle and was heated with a heating tape at 185-190°C to decompose paraformaldehyde-d_2 into CD_2O gas. The tube was attached directly to the reactor. The carrier gas, nitrogen (20 ml/min, controlled by a Cole-Parmer rotameter), was passed through the tube, thus carrying the CD_2O gas into the reactor. The

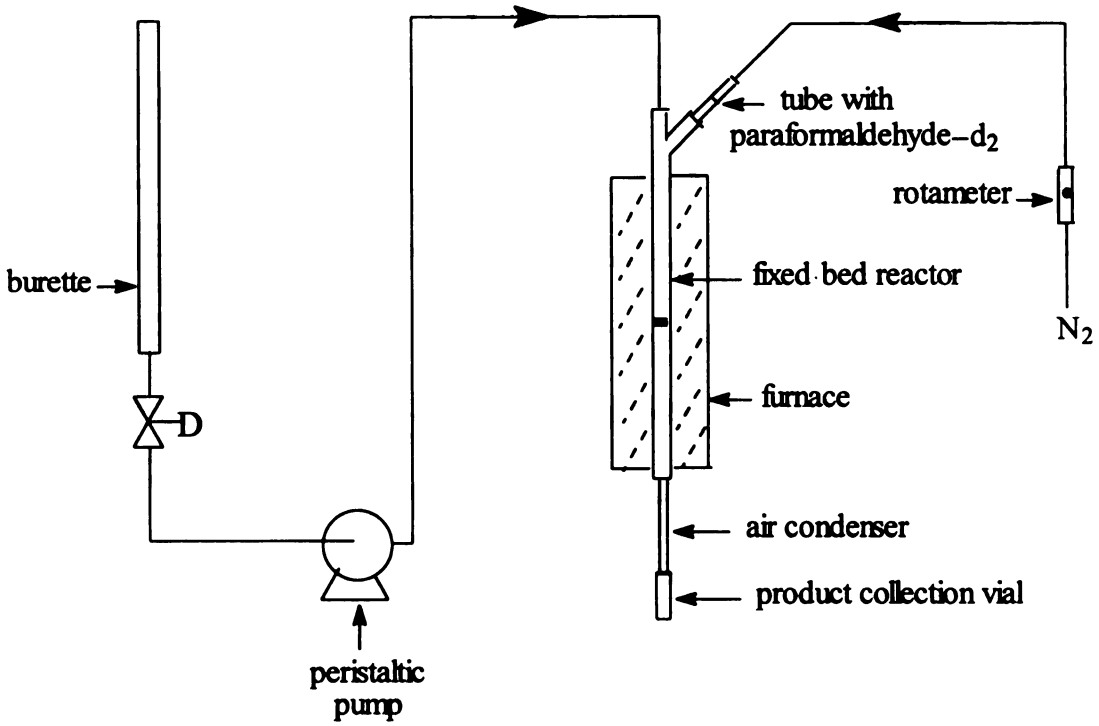


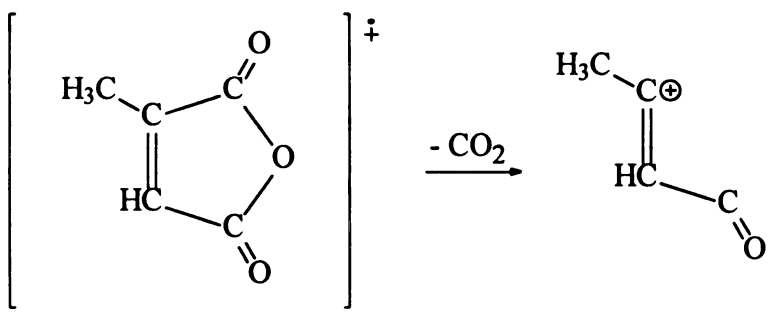
Figure 2.4.2. Set-up for the reaction between CD_2O and DMS

feed of CD_2O gas was regulated by the nitrogen flow. A quantity of 1.1 grams of paraformaldehyde-d_2 was recovered in the tube, so only 2.9 grams (0.097 moles) were consumed during the reaction, which gives a feed of 0.0725 g/min of CD_2O. DMS was stored in a burette and fed at a flow rate of 0.15 ml/min into the reactor by means of a Masterflex (Cole-Parmer) peristaltic pump. The catalyst, alumina SA 3177, 30-60 mesh in size, was heated in the reactor at 380-400°C for at least 3 hours to eliminate moisture before the reagents were added. The reaction was run at 380°C and atmospheric pressure for 40 minutes. The product mixture was passed through an air condenser for cooling purposes and collected every 10 min (up to four collections) in glass vials. The molar ratio of the reagents, based on DMS feed (0.046 moles total) and the quantity of CD_2O

consumed, was CD_2O : DMS = 2.11 : 1. Due to the small amount of feed, the first sample was not analyzable.

The product mixture from samples 2, 3, and 4 was analyzed by GC-Mass spectrometry using a Hewlett Packard 5890 Series II gas cromatograph (SPB-1 non-polar column) connected with a VG Trio-1 mass spectrometer. Two compounds were monitored: citraconic anhydride (M = 112.09 g/mole) and DMS (M = 146.14 g/mole).

The fragmentation pattern for citraconic anhydride is presented in Figure 2.4.3.



[M^+] m/z=68

Figure 2.4.3. Fragmentation pattern for citraconic anhydride

The EI^+ mass spectrum[9] of citraconic anhydride shows the molecular peak at m/z = 112. The peak corresponding to the m/z = 68 fragment (resulting from the molecular fragment by the loss of a CO_2 molecule) was considered for calculations because this fragment contains all four hydrogen atoms of the citraconic anhydride molecule, so any deuterium incorporation is followed by an increase in m/z value of this fragment. A comparison between the mass spectra of standard citraconic anhydride and of a product mixture containing deuterated citraconic anhydride species is presented in Figure 2.4.4.

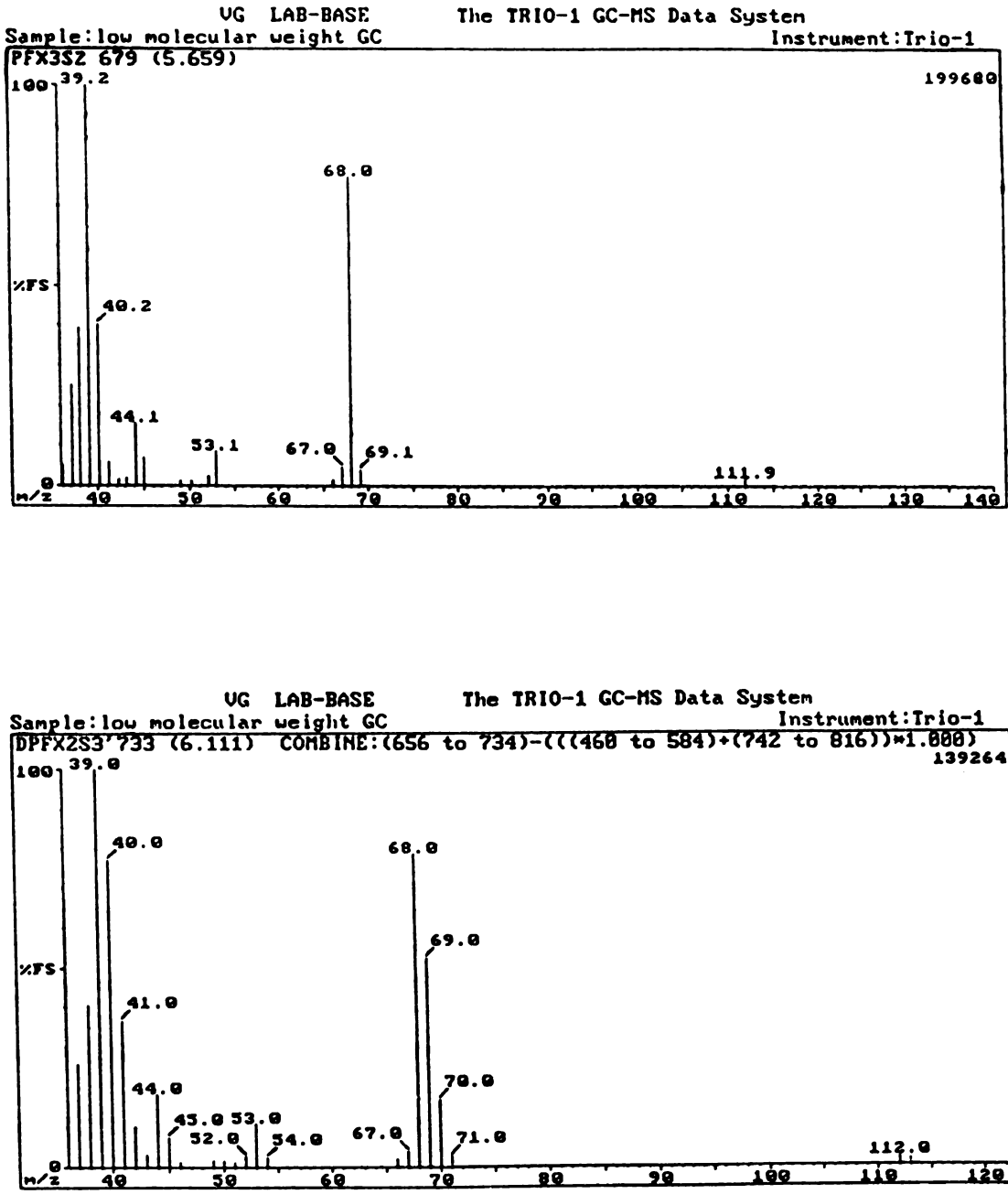


Figure 2.4.4. Comparison between the mass spectra of standard citraconic anhydride (top) and of a product mixture containing deuterated citraconic anhydride species (bottom)

Using[8] the mass spectra of citraconic anhydride (CA) with various degrees of deuteration, from the product, the change in the content of D_1-CA, D_2-CA, D_3-CA and D_0-CA (non-deuterated CA) with time was examined. The result is shown in Figure 2.4.5. Although the expected product should have contained only D_2-CA, the D_0-CA species was the most prevalent at all times (about 48-55%), followed closely by the D_1-CA species (about 35-40%). Surprisingly, the D_2-CA species has a low concentration, about 10%. The D_3-CA always has a very low concentration. No D_4-CA has been detected.

Using[8] the mass spectra of recovered DMS with various degrees of deuteration, as previously described (see 2.3.2), the change in the content of D_1-DMS, D_2-DMS, D_3-DMS, D_4-DMS and D_0-DMS (non-deuterated DMS) with time was examined. The result is shown in Figure 2.4.6. The D_0-DMS species, which should have been the only species present, has the highest concentration all the time (about 48-55%), followed closely by D_1-DMS (about 30-35%). The D_2-DMS species has a low concentration (about 10-15%), while D_3-DMS and D_4-DMS have a very low concentration.

Since the paraformaldehyde-d_2 was used directly from the box, without any drying, the detected H/D exchange was first suspected to have been the result of traces of water possibly present in the paraformaldehyde-d_2. Therefore, the experiment was repeated in a slightly modified set-up. The CD_2O gas was passed through a tube containing anhydrous P_2O_5 and a tube containing molecular sieves, previously dried at 400°C for 2 hrs. Both tubes were heated with heating tape. The molar ratio of the reagents was CD_2O : DMS = 2.17 : 1. All the other parameters were the same.

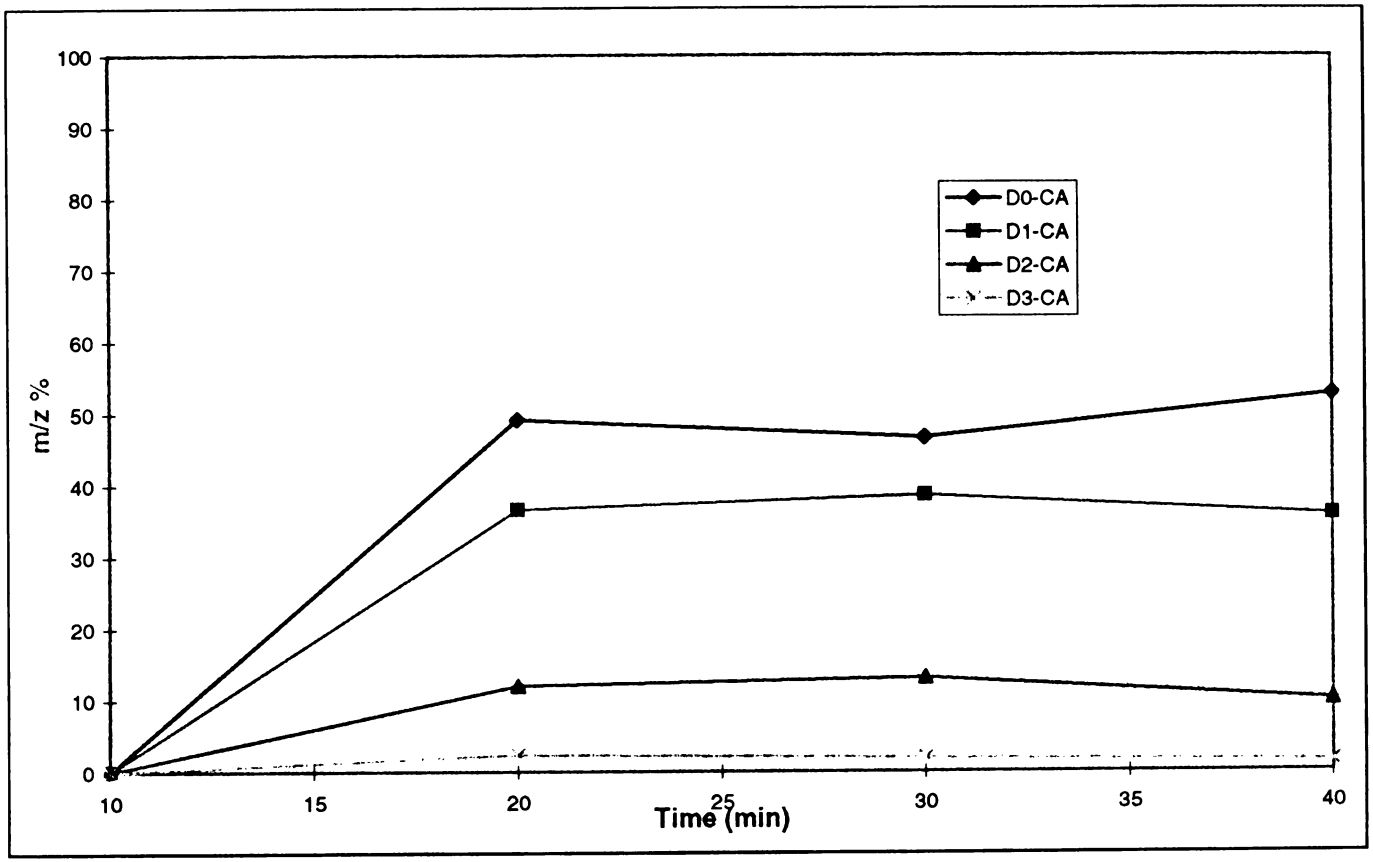


Figure 2.4.5. Extent of deuterium incorporation in CA
CD_2O/DMS Experiment 1

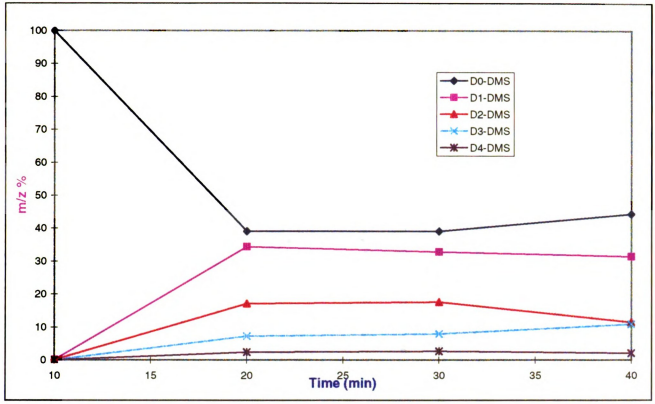


Figure 2.4.6. Extent of deuterium incorporation in DMS
CD_2O/DMS Experiment 1

The products were analyzed the same way as previously described and the results are presented in Figure 2.4.7. for citraconic anhydride, and in Figure 2.4.8. for DMS. As shown by the graphs, the H/D exchange took place again. In the citraconic anhydride case, the concentration of various deuterated species, especially D_0-CA and D_1-CA, varies over a larger range than in the previous experiment. In the DMS case, the variations are about the same, except for the D_0-DMS, which varies on a larger scale than previously.

Since any moisture from paraformaldehyde-d_2 was eliminated, and since the H/D exchange still took place, it is clear that the H/D exchange between CD_2O and DMS is mainly due to the catalyst. A possible explanation for the loss of deuterium from D_2-CA (Figure 2.4.9.) and for deuterium incorporation in DMS (Figure 2.4.10.) is proposed.

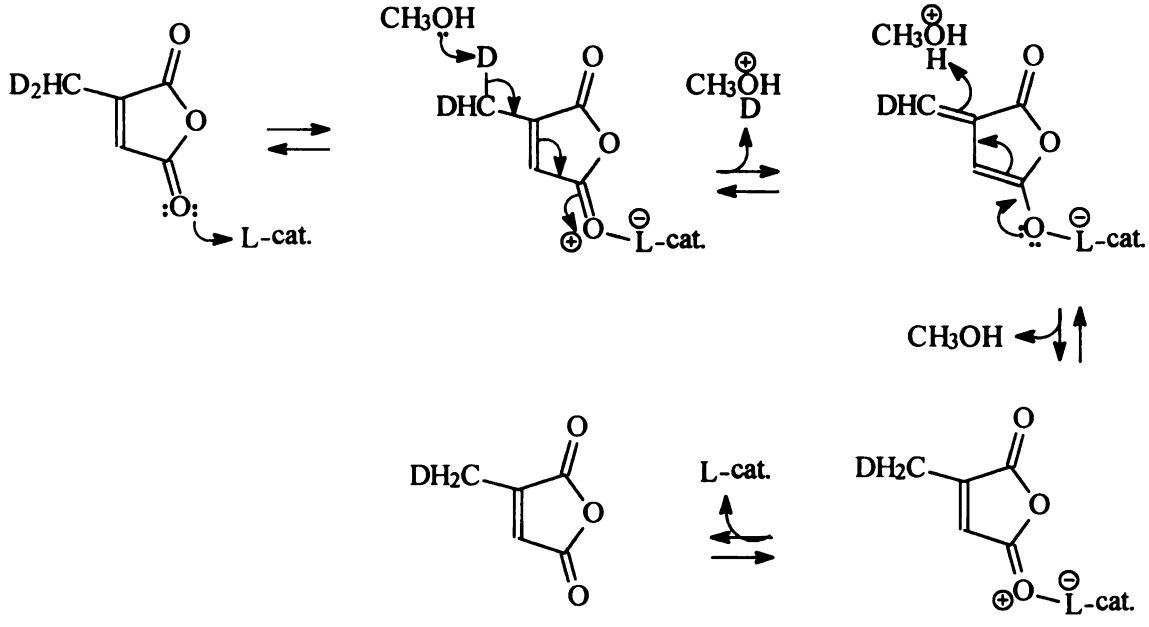


Figure 2.4.9. Mechanism for the loss of deuterium from D_2-CA

L-cat. represents the Lewis site, on the catalyst surface.

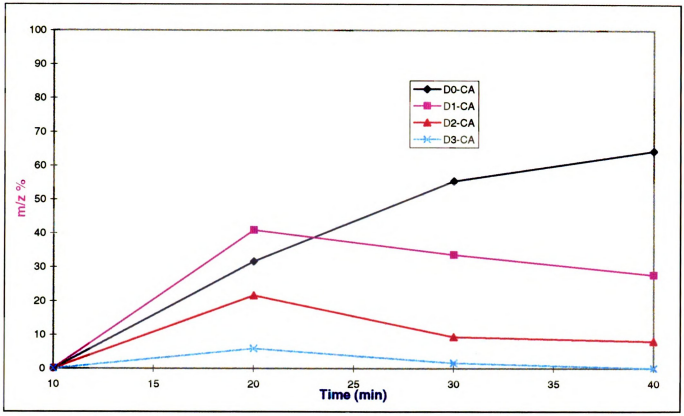


Figure 2.4.7. Extent of deuterium incorporation in CA
CD_2O/DMS Experiment 2

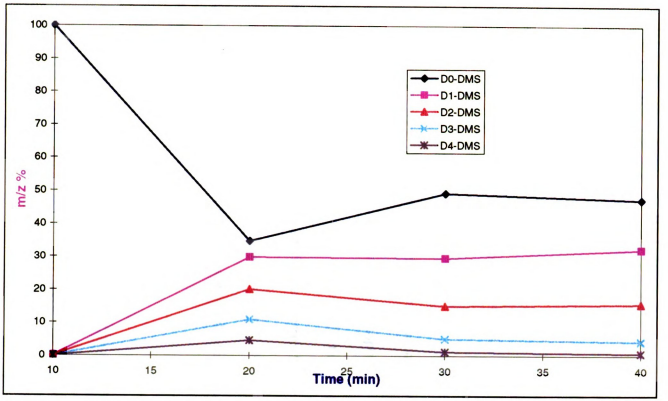


Figure 2.4.8. Extent of deuterium incorporation in DMS
CD_2O/DMS Experiment 2

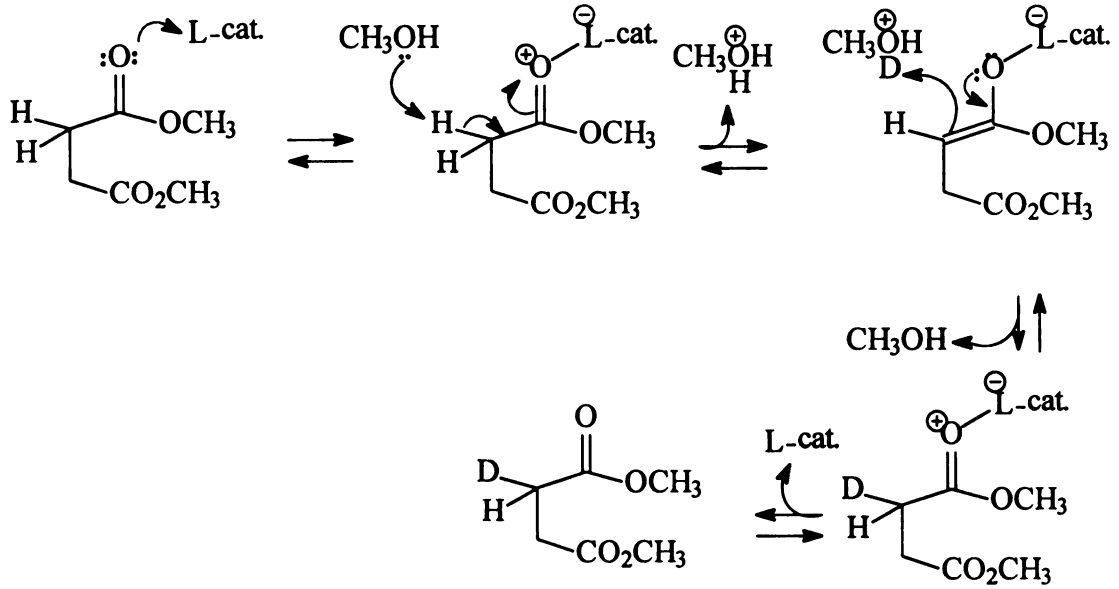


Figure 2.4.10. Mechanism for deuterium incorporation in DMS

The methanol obtained during the condensation is responsible for the H/D exchange between D_2-CA and DMS. It abstracts a deuterium from D_2-CA and then donates this deuterium to a DMS molecule, thus serving as a carrier for the deuterium between D_2-CA and DMS. This proves that for the regular catalytic Stobbe condensation (no deuterated species involved) the hydrogens from citraconic anhydride are continuously exchanged with the ones from C_2 and C_3 in DMS.

2.5. Experiments involving CH_2O and $D_3COCOCH_2CH_2COOCD_3$

2.5.1. Introduction

In classic Stobbe condensations, in the first sequence of the mechanism, a methoxy group is liberated and in the second sequence it abstracts a proton from the intermediary paraconic acid. There is no report in the literature about hydrogen atoms

from this methoxy group being incorporated in the condensation product. In order to verify whether this is also true for Stobbe-like condensation under heterogeneous catalytic conditions, experiments using CH_2O and DMS deuterated at the ester groups, $D_3COCOCH_2CH_2COOCD_3$ (D_6-DMS), were performed. The reaction is expressed by the following scheme (Figure 2.5.1.) :

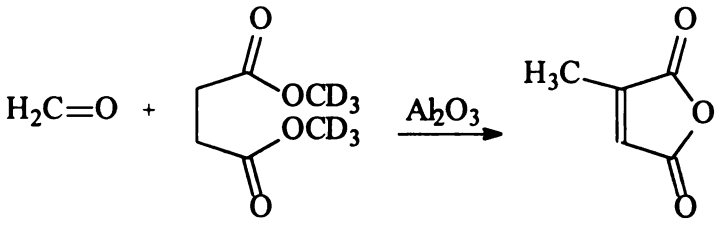
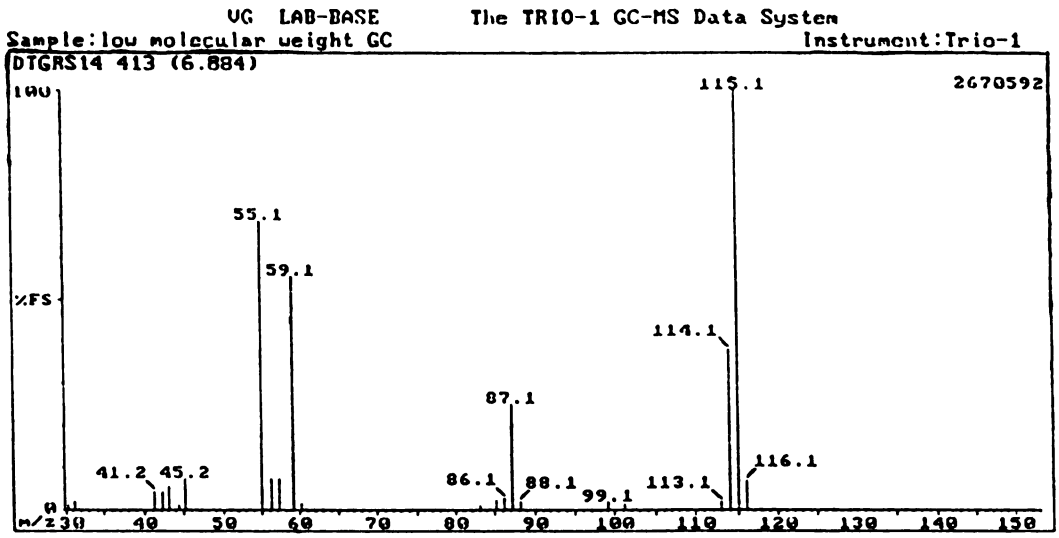


Figure 2.5.1. Reaction between CH_2O and $D_3COCOCH_2CH_2COOCD_3$

The results showed unexpected deuterium incorporation in citraconic anhydride. Also, the analysis of the recovered DMS revealed the incorporation of deuterium in positions other than the ester groups.

2.5.2. Experimental methods and results

Since $D_3COCOCH_2CH_2COOCD_3$ is not commercially available, it was synthesized[10] from CH_3OD and succinic acid. The $D_3COCOCH_2CH_2COOCD_3$ product was analyzed by GC-Mass spectrometry using a Hewlett Packard 5890 Series II gas cromatograph (SPB-1 non-polar column) connected with a VG Trio-1 mass spectrometer. A comparison between the mass spectra of standard DMS and of the synthesized $D_3COCOCH_2CH_2COOCD_3$ is presented in Figure 2.5.2. The deuterium incorporation is proved by the peak corresponding to the m/z = 118 fragment (obtained by loss of a



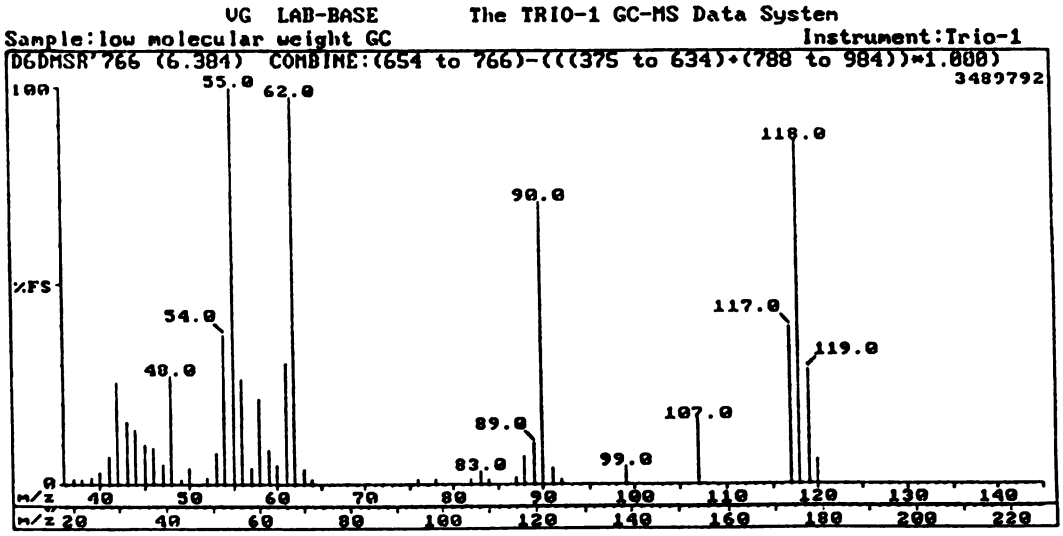


Figure 2.5.2. Comparison between the mass spectra of standard DMS (top) and of $D_3COCOCH_2CH_2COOCD_3$ synthesized (bottom)

methoxy group from $D_3COCOCH_2CH_2COOCD_3$), which replaces the peak corresponding to the m/z=115 fragment.

The experiments were performed at 380°C in the set-up presented in Figure 2.1.1. The molar ratio of the reagents was CH_2O : $D_3COCOCH_2CH_2COOCD_3$ = 2 : 1. The flow rate of the reagent mixture was 0.3 mL/min. Nitrogen was used as the carrier gas at a flow rate of 20 mL/min., controlled by a Cole-Parmer rotameter. The catalyst, alumina SA 3177, 30-60 mesh in size, was heated in the reactor at 380-400°C for at least 3 hours to eliminate moisture before the reagent mixture was added. The product mixture was passed through an air condenser for cooling purposes and collected in glass vials every 7 minutes for 35 minutes.

The product mixture was analyzed by GC-Mass spectrometry using a Hewlett Packard 5890 Series II gas cromatograph (SPB-1 non-polar column) connected with a VG Trio-1 mass spectrometer.

The monitored compounds were: citraconic anhydride and recovered DMS . Using their mass spectra obtained for each sample, the change in the content of various deuterated species was obtained and is presented in Figure 2.5.3. for citraconic anhydride and in Figure 2.5.4. for DMS.

In the citraconic anhydride case, the non-deuterated species, which should have been the only CA species present, has the highest concentration all the time, except for the first sample, where is overtaken by the D_1-CA species. The D_1-CA species has a considerable concentration all the time, between 45% and 25%. The D_2-CA species has a

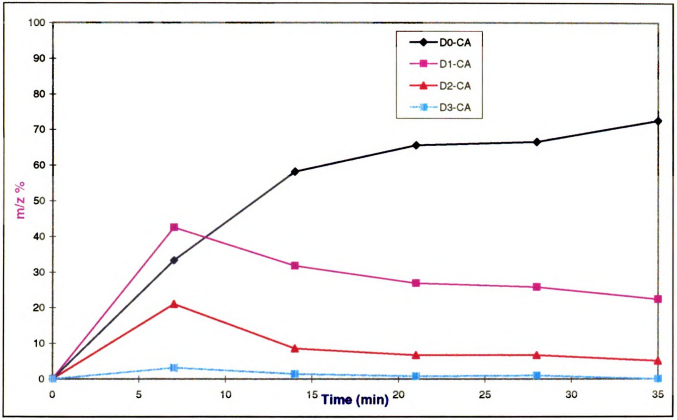


Figure 2.5.3. Extent of deuterium incorporation in CA
D_6-DMS/TO Experiment

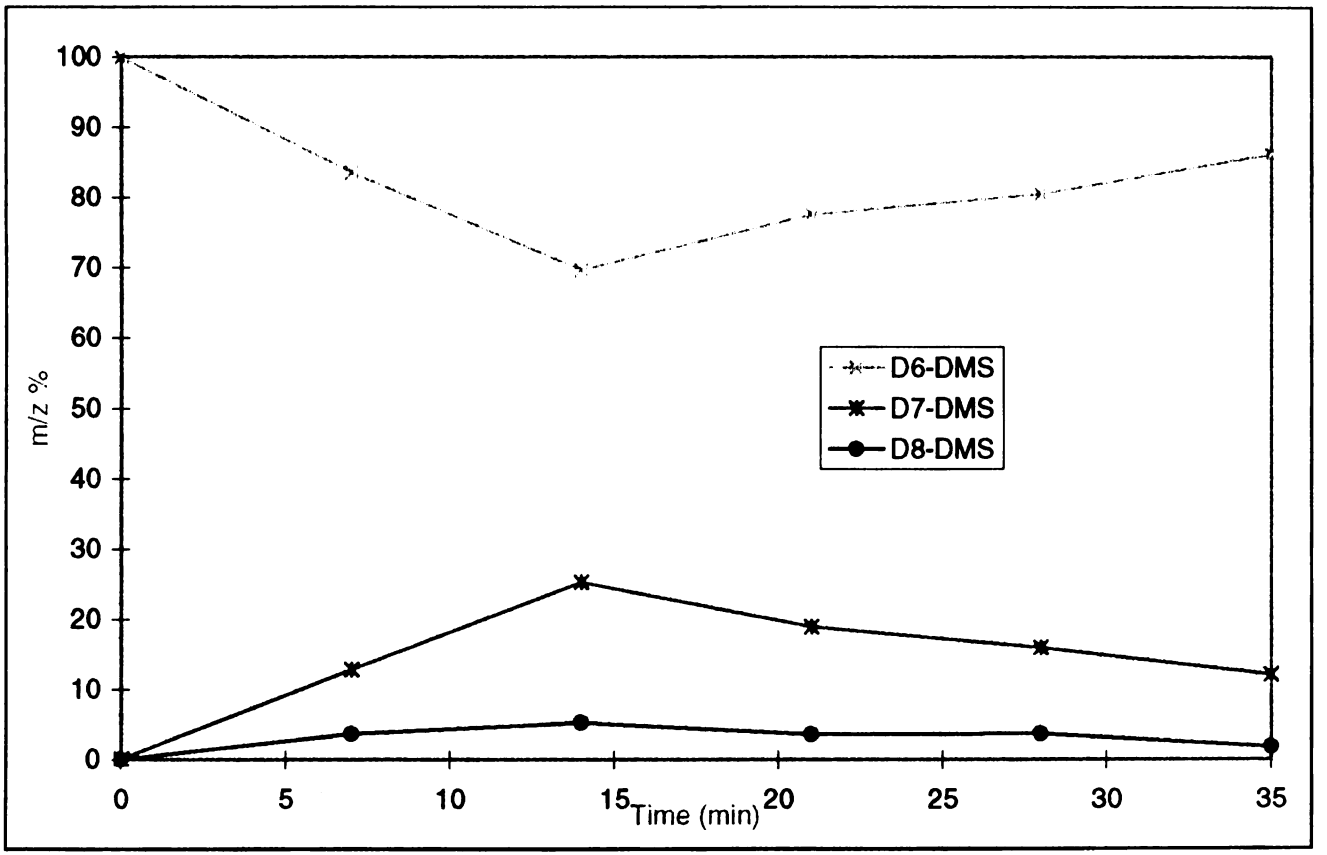


Figure 2.5.4. Extent of deuterium incorporation in DMS
D_6-DMS/TO Experiment

significant concentration (20%) only for the first sample, then its concentration becomes low (about 10%). The D_3-CA species has a very low concentration all the time.

In the deuterated DMS case, the D_6-DMS has the highest concentration all the time. The D_7-DMS and D_8-DMS species have a low concentration.

The deuterium incorporation in citraconic anhydride and D_6-DMS is surprising. A possible explanation comes from the fact that a small amount of DMS is usually hydrolyzed to monomethyl succinate, thus liberating methanol, in this case CD_3OH. The oxidation of CD_3OH allows the formation of CD_2O, which is then incorporated in citraconic anhydride, which in turn can be involved in a H/D exchange with DMS, as shown previously.

For a better understanding, the experiment was repeated in the same conditions, but using only $D_3COCOCH_2CH_2COOCD_3$ as a reagent.

The product samples were analyzed by GC-Mass spectrometry using a Hewlett Packard 5890 Series II gas cromatograph (SPB-1 non-polar column) connected with a VG Trio-1 mass spectrometer. The results are presented in Figure 2.5.5.

The D_6-DMS species has the highest concentration all the time. The D_7-DMS and D_8-DMS have a low concentration, showing a low extent of H/D exchange.

Since only D_6-DMS was used, and still, the recovered DMS composition showed that H/D exchange took place, then somehow, deuterium from the methoxy group replaced the hydrogen from D_6-DMS. A possible explanation comes from the hydrolysis of a small amount of D_6-DMS to the corresponding monomethyl succinate, thus liberating methanol, in this case CD_3OH. As stated before, the oxidation of CD_3OH allows the

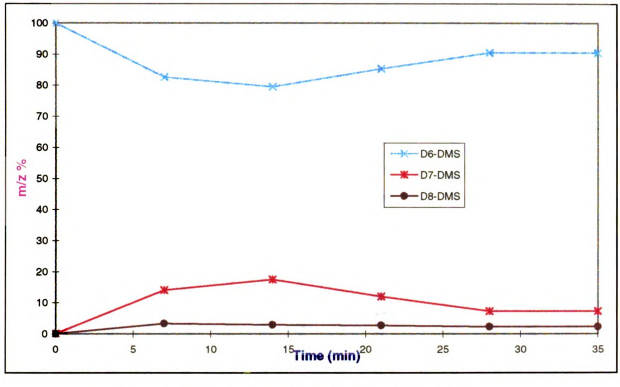


Figure 2.5.5. Extent of deuterium incorporation in DMS
D_6-DMS (plain) Experiment

formation of CD_2O, which is then incorporated in citraconic anhydride, which in turn can be involved in a H/D exchange with DMS.

Since the GC-Mass spectrometry analysis did not detect any citraconic anhydride, an HPLC analysis was tried. The HPLC column used was BIO-RAD 5, connected to a Waters 410 refractometer. The eluent used was 20% acetonitrile in 0.005 M H_2SO_4. Oxalic acid was used as internal standard. The HPLC results showed, indeed, the presence of citraconic anhydride in very small amount in the product mixtures: 0.2% in the third sample, 0.3% in the first and fifth samples and 0.5% in the second and fourth samples. This proves the proposed explanation stated previously.

2.6. Proposal of a mechanism for catalytic Stobbe condensation.

Based on the above experiments, a mechanism for the Stobbe condensation between formaldehyde and DMS, using γ-alumina as catalyst, is proposed.

The Lewis acid site catalyzes the loss of a proton from DMS (Figure 2.6.1.) to a methanol molecule, followed by the attack of the corresponding anion on the carbon of a formaldehyde molecule. A carbon-carbon bond is formed and the oxygen from formaldehyde abstracts the proton from the $CH_3O^+H_2$ species, to form a hydroxy diester.

The lone pair of electrons from the hydroxyl group attacks the carbonyl group (Figure 2.6.2.) and closes a ring, which is stabilized as a lactone derivative by the loss of a methoxy group and of a proton. The loss of a proton from the resonance form of the lactone derivative and detachment from the Lewis acid site allows the formation of monomethyl itaconate.

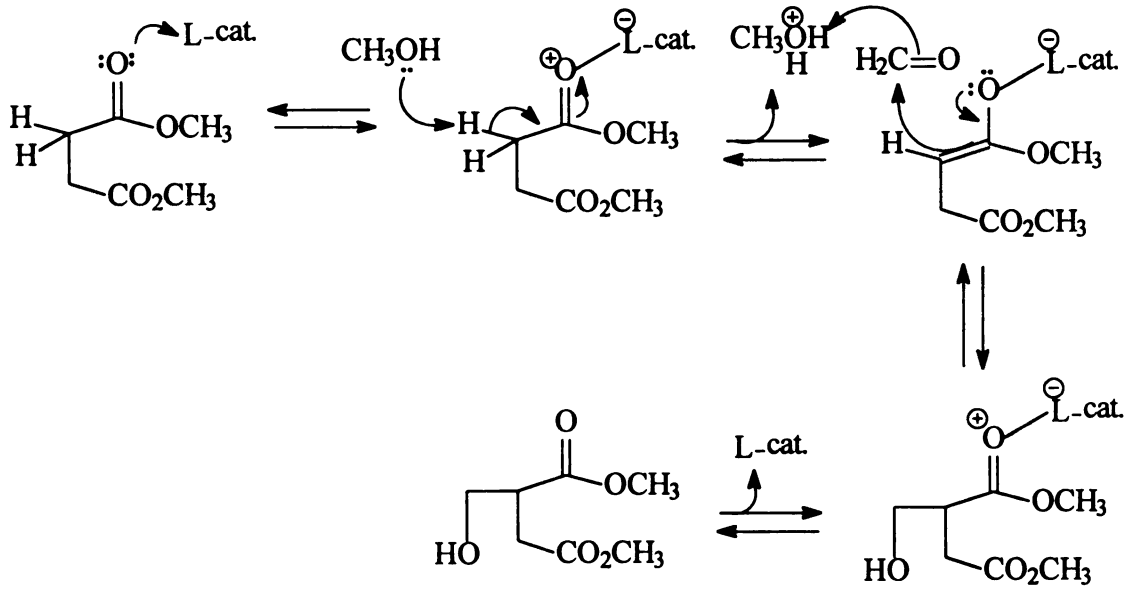


Figure 2.6.1. Proposed mechanism for catalytic Stobbe condensation. First step.

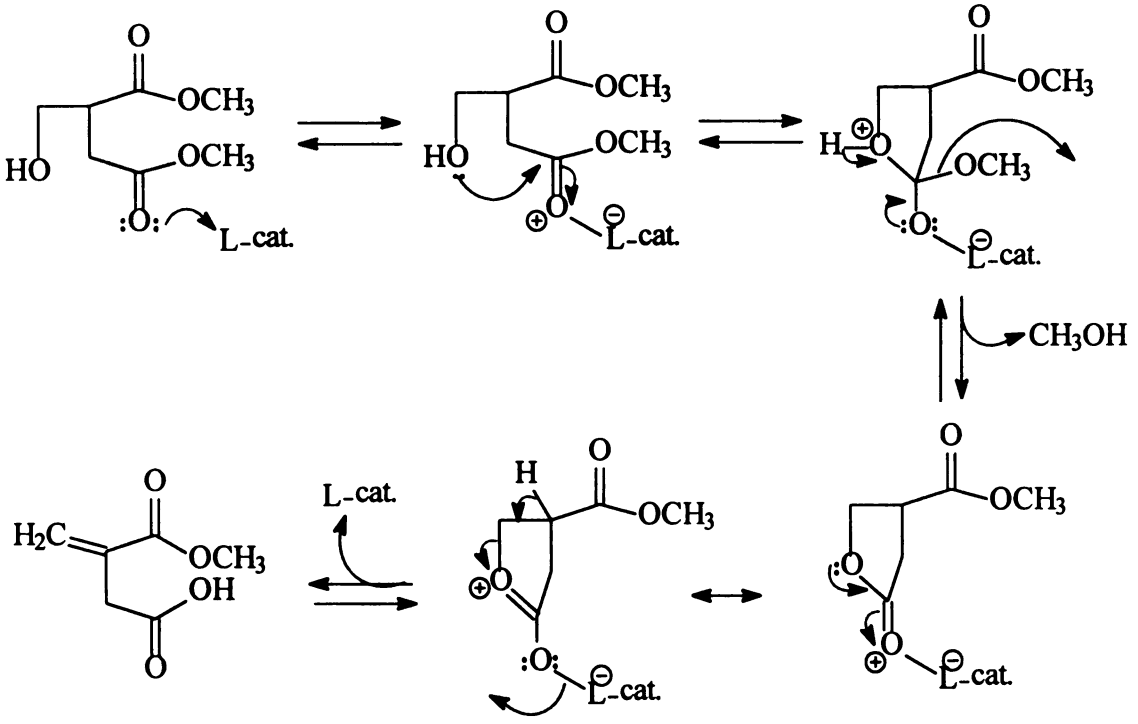


Figure 2.6.2. Proposed mechanism for catalytic Stobbe condensation. Second step.

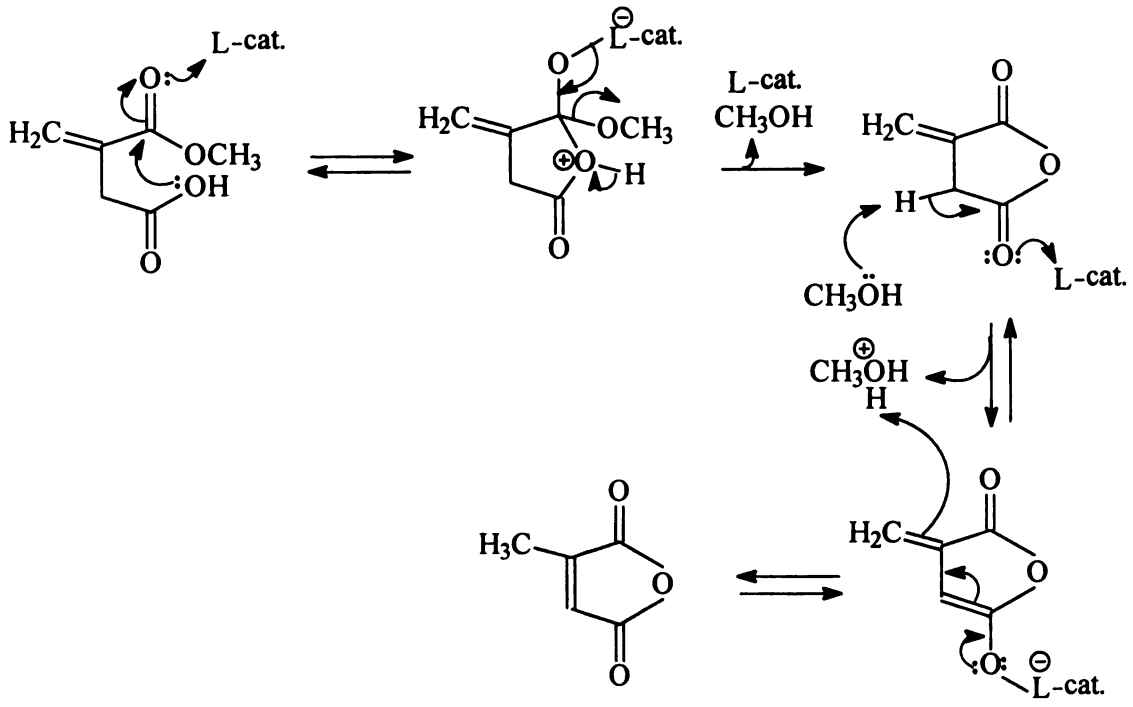


Figure 2.6.3. Proposed mechanism for catalytic Stobbe condensation. Third step.

The attack of the lone pair of electrons from the oxygen of the hydroxyl group, on the carbonyl group, followed by loss of the methoxy group and of a proton, allows the formation of itaconic anhydride which is then isomerized to citraconic anhydride, a molecule of methanol serving as carrier for the proton (Figure 2.6.3.).

2.7. Summary

Ever since it was first reported, the classic Stobbe condensation reaction proved to be special, because it was limited to succinate esters. Chemists struggled and succeeded in solving the mechanism of this condensation. The classic Stobbe condensation is a stoechiometric reaction, which uses a strong base as a condensing agent. It is used for the synthesis of many useful compounds.

Recently chemists became interested in performing this reaction in a catalytic fashion. Up to now, the only carbonyl compound that offered good results was formaldehyde. The condensation product, citraconic anhydride, can be easily converted into itaconic acid, a valuable monomer.

Since no information about the mechanism under catalytic conditions was available, we decided to investigate it. For this purpose, experiments involving deuterium-labeled compound were performed, using γ-alumina as the catalyst. The products were analyzed by GC-Mass spectrometry and the extent of deuterium incorporation was determined. The experiments proved the enolization of DMS and showed that the Lewis acid sites on the catalyst surface are responsible for the catalytic activity, in this case. Mechanisms were proposed to explain each H/D exchange process.

Finally, a mechanism for the condensation of formaldehyde with DMS, using γ-alumina as catalyst, was proposed.

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