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CATALYTIC HYDROGENATION OF AMINO ACIDS AND POLYHYDROXYALKANOATES

presented by

Frank Thomas Jere

has been accepted towards fulfillment
of the requirements for the

Ph.D. degree in Chemical Engineering

Dennis J Miller
Major Professor's Signature

8/21/03
Date

CATALYTIC HYDROGENATION OF AMINO ACIDS AND POLYHYDROXYALKANOATES

By

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ABSTRACT

CATALYTIC HYDROGENATION OF AMINO ACIDS AND POLYHYDROXYALKANOATES

By

Frank Thomas Jere

Aqueous phase hydrogenation of L-alanine (L-(+)-2-amino-propanoic acid) to L-alaninol (L-(+)-2-amino-propanol) was performed in a three-phase, stirred batch reactor. Under optimal conditions selectivities over 97% with 93% alanine conversion and > 99 ee% was achieved. Observed side products included ammonia, ethylamine, and isopropylamine. The catalyst used for this hydrogenation was 5 wt% ruthenium on carbon.

Calculations using standard engineering correlations showed that mass transfer through the gas-liquid and liquid-solid films and intra-particle mass transfer did not limit the rate of conversion. The absence of mass transfer limitations allowed for the derivation of a kinetic model. Conditions within the following experimental matrix were used for kinetic model parameter estimation: alanine feed concentration from 0.22 to 0.46 M, phosphoric acid feed concentration from 0 to 1.2 M, temperatures from 90 to 150°C, hydrogen pressures from 5 to 13 MPa H_2, and 1 to 2 grams catalyst per 100 grams feed. A complete kinetic model was developed that predicts reaction trajectories to an 8% error between predicted and experimental data. Modeling results showed

showed that the activation energy for the surface reaction step was 81.5 kJ/mol. The model predicted the observed dependences on hydrogen pressure, temperature, and ionic solution structure.

Hydrogenations have also been performed on biobased polymers PHB (poly-3-hydroxybutanoic acid) and PLA (polylactic acid; 2-hydroxypropanoic acid). These reactions occurred through a two step process of hydrolysis of polymer chains to monomer and soluble short chained oligomers followed by hydrogenation to alcohol product. PHB was found to be only slightly reactive toward hydrogenation. PLA, on the other hand, was easily converted to propylene glycol (PG) at 150°C and 1000 psi H_2 over a 5% Ru/C catalyst.

Dedicated to my love, my life, my wife.

ACKNOWLEDGEMENTS

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Special thanks to fellow group members Mike Shafer, Atul Dhale, Dushyant Shekawat, Shubbam Chopade, Zhizang Zhang, Dalila Kovacs, Lars Peerboom, Prashant Srivastava, Brian Hogle, Abe Schuitman, and Brad Rokosz for their suggestions and help during this project.

I also want to offer my heartfelt thanks to my parents for their support throughout my education.

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A^- = deprotonated alanine (M)
a = mass transfer area per unit volume of reactor (m^2/m^3)
a = ratio of catalyst surface area to volume of fluid (m^2/m^3)
A = zwitterionic alanine (M)
A^+ = protonated alanine (M)
a_B = gas-liquid interfacial area per unit volume of reactor (m^2/m^3), (cm^2/cm^3)
Al = alanine (M)
A_L = alanine concentration in bulk solution (M)
Alol = alaninol (M)
$Alol^+$ = protonated alaninol (M)
Am = Ammonia (M)
Am^+ = protonated ammonia (M)
A_s = concentraction of alanine at catalyst surface (M)
A_T = total alanine concentration (M)
$C_{Aexperimental}$ = experimental alanine concentration (M)
$C_{Apredicted}$ = predicted alanine concentration (M)
C_{COOH} = concentration of alanine protonated (M)
C_s = species surface concentration (mol/L)
C_{TOTAL} = total concentration of alanine (M)
D_a = diffusion rate of species a (m^2/s)
D_e = effective diffusivity (m^2/s), $D_e = \varepsilon D_a$
d_I = impeller diameter (m), (cm)
d_p = particle diameter (m)
d_T = reactor diameter (m)
Ea = Ethylamine (M)
EA^+ = protonated ethylamine (M)
g = gravitation constant (m/s^2)
g = gravitational constant (m/s^2)
H = atomic hydrogen
H^+ = the hydronium cation (M)
H_2 = molecular hydrogen (M)
$H_{2,L}$ = concentration of hydrogen in the liquid phase (M)
$H_{2,s}$ = concentration of hydrogen at the catalyst surface (M)
H_2 = concentration of hydrogen in the gas phase (M)
IPA^+ = protonated isopropyl amine (M)
K_{A1} = first acidity constant of alanine
K_{A2} = second acidity constants of alanine
k_L = liquid film mass transfer coefficient (m/s), (cm/s)
k_La = the gas-liquid mass transfer coefficient (1/s)
K_{P1} = first acidity constant of phosphoric acid
K_{P2} = second acidity constant of phosphoric acid
K_{P3} = third acidity constant of phosphoric acid

k_s = the liquid solid mass transfer coefficient (m/s)
L = characteristic length of the catalyst (m), (d_p/6)
L = ratio of catalyst surface area per unit volume fluid (m^2/m^3)
N = stirring speed (rotations/s)
N_{min} = minimum stirring speed (rotations/sec)
OH^- = anionic hydronium ion (M)
P = H_3PO_4 (M)
P^- = $H_2PO_4^-$ (M)
P^{2-} = HPO_4^{2-} (M)
P^{3-} is PO_4^{3-} (M)
P_T = the total phosphoric acid concentration
r = reaction rate (mol/L-s)
$-R_G$ = observed reaction rate of the species ($kmol/m^3$-s)
S_1 = a site occupied by alanine (-COOH form) or phosphoric acid (H_3PO_4 form) (M)
S_2 = a site occupied by hydrogen (M)
Sh = Sherwood number (dimensionless)
ST = fluid surface tension (N/m)
u_g = gas velocity (cm/s)
u_g = gas velocity (m/s)
V_L = liquid volume (m^3)
V_L = volume of the solution (cm^3)
w' = catalyst loading (g cat/100 g feed)
w' = catalyst loading (kg/100 kg solution)
w` = catalyst loading (g/100 g solution)

Greek

$\eta\phi^2$ = observable modulus
β = impeller geometry constant
ε = support porosity (0.6 for the catalyst used)
ρ_L = fluid density (kg/m^3), (g/cm^3)
μ_L = liquid viscosity (kg/m-s)
ρ_P = catalyst density (kg/m^3)

Chapter 1. Introduction

1.1 Background

Currently the primary feedstock for organic chemical production is petroleum. Petroleum, while plentiful in 2003, is a finite resource, and as such it is prudent to seek chemical production routes that use renewable resources as feedstocks to replace traditional synthesis techniques as they become more costly.

As the U.S. government and manufacturers have sought to increase chemical production from renewables, considerable effort has been made to improve fermentation technologies which use corn-derived glucose, and other renewables, as feedstocks for organic chemical production. Several organic acids including citric acid,[1,2] gluconic acid,[3] and itaconic acid[3] have been traditionally produced via fermentation at the commercial scale. Today new technologies are targeting propanoic acid,[4,5,6] butyric acid,[7,8] and fumaric acid[9] for industrial scale production via fermentation as well. Two fermentation-derived organic acids have received considerable attention for use as platforms to produce multiple products. Lactic acid is a versatile feedstock that can be used to make acetaldehyde, propylene glycol, acrylic acid, 2,3-pentanedione, and

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[1] Grewal, H.; Kalra, K. *Biotechnol. Adv.* **1995**, *13*, 209.
[2] Pazouki, M.; Panda, T. *Bioprocess Eng.* **1998**, *19*, 435.
[3] Milson, P. E.; Meers, J. L. Gluconic and Itaconic Acids. *Comprehensive Biotechnology*; Moo-Young, M.; Blanch, H. W., Drew, H. W., Wang, D. I. C., Eds.; Pergamon Press: New York, 1985; Vol. 3, Chapter 35.
[4] Boyaval, P.; Corre, C. *Lait* **1995**, *75*, 453.
[5] Jin, Z. W.; Yang, S. T. *Biotechnol. Prog.* **1998**, *14*, 457.
[6] Rehberger, J. L.; Glatz, B. A. *J. Food Prot.* **1998**, *61*, 211.
[7] Vandak, D.; Zigova, J.; Sturdik, E.; Schlosser, S. *Process Biochem.* **1997**, *32*, 245.
[8] Hwang, S.; Hansen, C. L. *Biotechnol. Bioeng.* **1997**, *54*, 451.
[9] Du, J. X.; Cao, N. J.; Gong, C. S.; Tsao, G. T.; Yuan, N. J. *Appl. Biochem. Biotechnol.* **1997**, *54*, 451.

polylactic acid.[10] Succinic acid has also received considerable interest and high efficiency fermentations are under development.[11,12]

Another class of organic acids that are part of the "renewables" category are amino acids because they are primarily synthesized via fermentation with glucose or sucrose as feed materials. Their multiple functional groups and chirality make amino acids an attractive feedstock for chemical synthesis.

Hydrogenation of amino acids to amino alcohols is one route to utilize these materials. Addition of small scale, high-value chemical products to a biorefinery's product slate, such as amino alcohols from amino acids, could improve the overall economic viability of these plants.

In addition to economic incentives, the method for amino acid hydrogenation described here meets several of "The Twelve Green Chemistry Principles" outlined by Dr. Paul Anastas[13] and criteria outlined by the U.S. Department of Energy in their Chemical Vision 2020 technical roadmap series:[14] high atom economy, benign co-product (water), environmentally friendly solvent (water), high selectivities, and use of heterogeneous catalysts.

The focus of this study was to examine the stereoretentive hydrogenation of amino acids to amino alcohols, with focusing on L-alanine ((S)-2-aminopropanoic acid) to L-alaninol ((S)-2-aminopropanol). In this work we determined the best catalyst and operating conditions for amino acid

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[10] Datta, R.; Tsai, S. P. *ACS. Symp. Ser. #666*, **1997**, 224.
[11] Gorkarn, R. R.; Eitemann, M. A., Sridhar, J. *ACS Symposium Ser. #666* **1997**, 237.
[12] Nghiem, N. P.; Davison, B. H.; Richardson, G. R. *Appl. Biochem. Biotechnol.* **1997**, *63-65*, 565.
[13] Anastas, P. T.; Warner, J. C. *Green chemistry: theory and practice*; Oxford University Press: New York, NY, 1998.
[14] http://www.chemicalvision2020.org/techroadmaps.html

hydrogenation and derived a mechanism-based, kinetic model to describe reaction trajectories over a wide range of conditions. Deuterium exchange experiments were used to gain understanding of reactant and product interaction with the catalyst. Work in this area has also prompted the development of a simple method for deuterium labeling of amine bearing compounds.

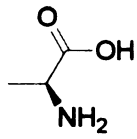
In addition to the focus on amino acid hydrogenation, preliminary studies were devoted to polylactic acid (PLA) and poly-3-hydroxybutanoic acid (PHB) hydrogenation. One of the major advantages of biobased polymers is biodegradability. The preferred method of disposal is composting, where PLA polymer hydrolyzes to lactic acid and is then consumed by bacteria which release carbon dioxide. Alternatively, PLA could be converted to propylene glycol (PG) through hydrogenation. Hydrogenation could also be used in manufacturing facilities as an alternative to disposal of batches that do not meet product specifications.

1.2 Literature Review

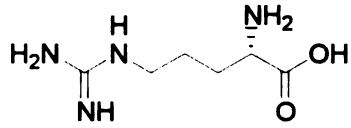
1.2.1 Amino acid background

Amino acids are carboxylic acids which bear an amine group. In nature amino acids are most commonly found as 2-amino acids, or α-amino acids. The general formula of amino acids is $RCH(NH_2)COOH$, where R is an alkyl or aryl side chain, and may contain hydroxyl, amino, mercapto, sulfide, and carboxy groups, as shown in Figure 1. Amino acids contain at least two functional groups and 19 of the 20 naturally occurring α-amino acids are chiral compounds, which make them attractive synthetic building blocks.

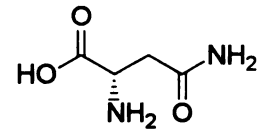
Figure 1. Naturally occurring α-amino acids



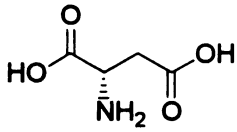
Alanine



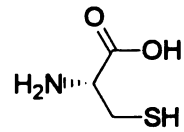
Arginine



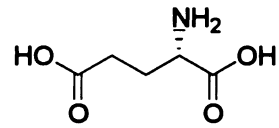
Asparagine



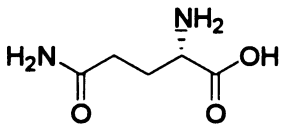
Aspartic acid



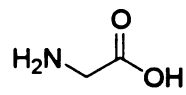
Cysteine



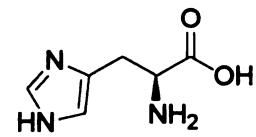
Glutamic acid



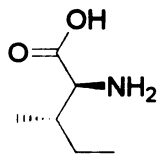
Glutamine



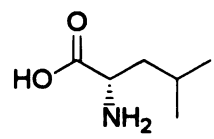
Glycine



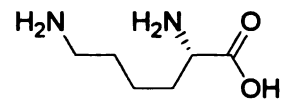
Histidine



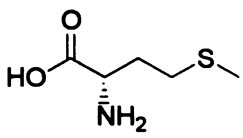
Isoleucine



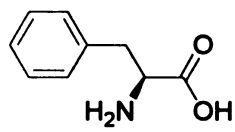
Leucine



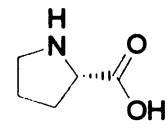
Lysine



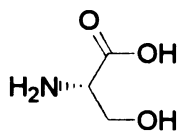
Methionine



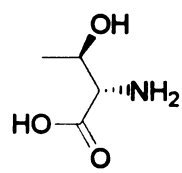
Phenylalanine



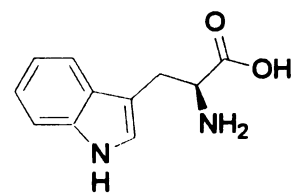
Proline



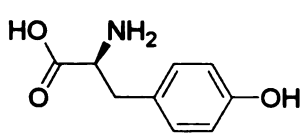
Serine



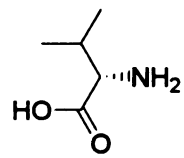
Threonine



Tryptophan



Tyrosine



Valine

Amino acids are unique chemically in that they are both acidic and basic because of their carboxylic acid and amine functionalities. In aqueous solution, the structure is determined by pH: under acidic conditions amino acids exist primarily as the cationic ammonium carboxylic acid **1**, under neutral conditions as the zwitterionic form **2**, and under basic conditions as the deprotonated 2-aminocarboxylate ion **3**, as shown in Figure 2.

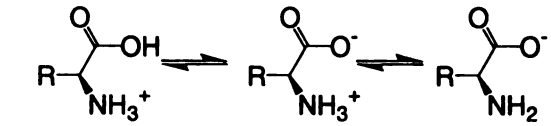


Figure 2: Amino acids in solution

Solution behavior, as discussed in Section 3.1, is a very important variable in amino acid hydrogenation.

1.2.2 Amino acid production

Amino acids are produced through four different processes: fermentation, extraction, chemical synthesis, and enzymatic routes. The most economical means of producing bulk amino acids is via fermentation of sucrose or glucose via overproducing microbial strains.

In 1999, the estimated worldwide production of amino acids was 1.6×10^6 tons/year. Amino acids are used primarily for human and animal nutrition with only 0.6% of the annual production utilized for pharmaceuticals, cosmetics,

agrochemicals, and industrial uses. Table 1 summarizes the production rate, preferred synthesis method, and price of several amino acids.[15]

In this study, L-alanine was the feed material in most reactions. Industrially, L-alanine is produced from L-aspartic acid in a pressurized bioreactor by immobilized *Pseudomonas dacunhae* cells.[16] However, there are reports of L-alanine production via fermentation with *Arthrobacter oxydans* from glucose with a yield of 52% and 95% ee.[17] Alanine is also still produced by isolation from protein hydrolysates.

Amino Acid	World Production in 1999, tons/yr	Preferred Production Method	Price, $/kg
L-Alanine	1,200	Enzymatic catalysis, fermentation	12-29
L-Arginine	1,500	Fermentation, extraction	44-51
L-Asparagine	150	Extraction	
L-Aspartic acid	12,000		10-12
L-Cysteine	3,500	Reduction of L-cystine (extraction), enzymatic synthesis	59-88
L-Glutamic acid	700,000	Fermentation	3
L-Glutamine	1,000	Fermentation, extraction	44-52
Glycine	15,000	Chemical synthsis	7-13
L-Histidine	300	Fermentation, extraction	110-147
L-Hydroxyproline	100	Fermentation, extraction	
L-Isoleucine	550	Fermentation, extraction	294-331
L-Leucine	800	Fermentation, extraction	74-147
L-Lysine	430,000	fermentation	5-6
D,L-Methionine	450,000	Chemical synthesis and enzymatic resolution	5-6
L-Methionine	400	Enzymatic resolution	74-88
L-Phenylalanine	11,000	Fermentation	59-88
L-Proline	800	Fermentation, extraction	147-294
L-Serine	300	Fermentation, extraction	74-132
L-Threonine	30,000	Fermentation	125-147
L-Tryptophan	1,200	Fermentation	74-147
L-Tyrosine	150	Extraction	74-110
L-Valine	1,100	Enzymatic catalysis, fermentation	110-147

Table 1. World production, preferred production method, and price of selected amino acids

[15] Amino Acids. *Ulmann's Encylopedia of Industrial Chemistry* , Karlheinz, D.; Berd, H.; Kleeman, A.; Krimmer, H.; Leuchtenberger, W.; Weckbecker, C., 7th. ed.; Wiley: New York, 2002.
[16] Furui, M.; Yamashita, K. *J. Ferment. Technol.* **1983**, *61*, 587.
[17] Hashimoto, S.; Katsumata, R. *Proc. Ann. Meet. (Agric. Chem. Soc. Jpn.)*, **1994**, 341.

1.2.3 Amino alcohols

Amino alcohols are important intermediates in pharmaceutical and peptide chemistry,[18,19,20,21] as insecticidal intermediates,[22] and chiral auxiliaries.[23] Because of the growing emphasis on chiral molecules in these applications,[24] the worldwide market for fine chemicals and pharmaceuticals sold as single enantiomers in 2002 was $7 billion and $159 billion, respectively.[25] Economical formation of enantiomerically pure amino alcohols may provide a route to lower raw material costs for many therapeutics.

1.2.3.1 Amino alcohol synthesis techniques

The earliest report of amino alcohol production was from Karrer in 1921 via the reduction of amino acid esters with sodium in ethanol.[26] Since then, many such reductive techniques have been performed using both amino acids and amino esters as starting materials. Reducing agents include sodium borohydride ($NaBH_4$)-sulfuric acid,[27] $NaBH_4$-iodine,[28] lithium aluminum hydride ($LiAlH_4$),[29,30,31,32,33,34] borane-methyl sulfide in the presence of boron trifluoride

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[18] TenBrink, R. E. *J. Org. Chem.* **1987**, *52*, 418.
[19] Nicollaides, E. D.; Tinney, F. J.; Kaltenbronn, J. S; Repine, J. T.; DeJohn, D. A.; Lunney, E.A.; Roark, W. H.; Marriot, J. G.; Davis, R. E.; Voigtmen, R. E. *J. Med. Chem.* **1986**, *29*, 959.
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etherate,[35,36,37,38,39] and lithium borohydride in the presence of trimethylsilyl chloride.[40] Amino ester hydrochlorides have also been reduced to the corresponding amino alcohols with $LiAlH_4$[41,42] or $NaBH_4$.[43]

The primary advantage of these reductive techniques is that they are, for the most part, stereo-retentive. However, they suffer from one or a combination of the following: high cost, flammable and toxic reagents, laborious product separation procedures, and large waste streams. Thus, production on the multi-kilogram scale of amino alcohols is costly. Despite this, there are many amino alcohols produced at commercial scale listed in the *Handbook of Chiral Chemicals,*[44] as shown in Table 2. These compounds may be produced using a technique related to those listed above (or bio-catalytically).

Another route that has been examined is catalytic hydrogenation of amino esters. In the 1940's, Adkins and co-workers produced amino alcohols from amino acid esters over Raney nickel and reported optical rotation close to that of pure samples; therefore enantiomeric excess was near 100%.[45] In addition to these studies performed more than half a century ago, in 2001 Studer, *et. al,*[46] studied hydrogenation of amino acid esters as well. In their study, Nishimura

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[44] Ager, D., ed., *Handbook of Chiral Chemicals*, Marcel Dekker, Inc., New York, N.Y.,**1999**.
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[46] Studer, M., Burkhardt, S., Blaser, H. U. *Adv. Synth. Catal.* **2001**, *343* (8), 802.

Compound	Supplier
(R)-(-)-2-aminobutanol	Themis
(S)-(+)-2-aminbutanol	Themis
(R)-(-)-2-amino-3-methyl-1-butanol, (D-Valinol)	Boehringer, Newport, Rexim/Degussa
(S)-(-)-2-amino-3-methyl-1-butanol, (L-Valinol)	Boehringer, Newport, Rexim/Degussa
(S)-(+)-2-Amino-3-methyl-1-pentanol , ((L)-(+)-Isoleucinol)	Boehringer, Rexim/Degussa
(R)-(+)-2-Amino-4-methyl-1-pentanol , ((D)-(-)-Leucinol)	Rexim/Degussa
(S)-(+)-2-Amino-4-methyl-1-pentanol, ((L)-(+)-Leucinol)	Boehringer, Rexim/Degussa
(R)-(-)-2-amino-1-propanol (D-Alaninol)	Boehringer, Newport
(S)-(-)-2-amino-1-propanol (L-Alaninol)	Boehringer, Newport, Synthetech
(S)-(+)-2,6-Diamino-1-hexanol , (L-(+)-Lysinol)	Boehringer
L-tert-Leucinol	Rexim/Degussa
(R)-(+)-Phenylalaninol	Boehringer, Newport, NSC Technologies, Rexim/Degussa, Urquima
(S)-(-)-Phenylalaninol	Boehringer, Newport, NSC Technologies, Rexim/Degussa, Synthetech, Tanabe
(S)-Prolinol	Boehringer, Newport, Rexim/Degussa
(L)-Threoninol	Rexim/Degussa

Table 2. Amino alcohols available at commercial scale

catalyst (mixed Rh/Pt oxide) was loaded to 10 wt% at room temperature with 10 MPa hydrogen and amino acid ester. Conversions and yields in excess of 90% were achieved without racemization of the amino alcohol product. In all of these studies, amino acid esters were used as a starting material, which requires an esterification step prior to hydrogenation.

Recently, two patents by Antons[47,48] reported production of optically active amino alcohols via aqueous phase hydrogenation of the free amino acid in aqueous solution over supported ruthenium catalysts. However, these patents do not discuss either mechanism or kinetics.

1.2.4 Organic acid hydrogenation

Hydrogenation of organic acids and esters over metal catalysts has been the subject of numerous studies over the last several decades. In the 1930's Adkins studied the hydrogenation of esters and ketones to alcohols over copper-chromium oxide[49] and nickel catalysts[45] under 2200-2900 psi H_2 at 250°C. In the 1950's, Carnahan and Ford[50] used ruthenium catalysts to hydrogenate organic acids such as acetic acid, oxalic, adipic, succinic, and hydroxyacetic acid in a temperature range of 94 to 192°C under pressures in excess of 7000 psi H_2 with yields ranging from 47 to 88%. Later, Broadbent[51] studied hydrogenations of organic acids catalyzed by rhenium that was prepared *in situ* in a temperature range of 137-286°C and pressures ranging from 2200 to 4800 psi H_2. In their

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[47] Antons, S.; Beitzke, B. U.S. Patent 5,536,879, 1996.
[48] Antons, S., Tilling, A., Wolters, E. U.S. Patent 6,310,254, 2001.
[49] Bowden, E., Adkins, H. *J. Am. Chem. Soc.* **1934**, *56*, 689.
[50] Carhnahan, J. E.; Ford, T. A.; Gresham, W. F.; Grigsby, W. E.; Hager, G. F. *J. Am. Chem. Soc.* **1955**, *77*, 3766.
[51] Broadbent, H. S.; Campbell, G. C.; Bartley, W. J.; Johnson, J. H. *J. Am. Chem. Soc.* **1959**, *24*, 1847.

study, formic, acetic, propionic, butyric, capric, lauric, stearic, lactic, maleic, succinic, and glutaric acid were all reduced to their corresponding alcohol.

In this research group, lactic acid has been reduced to propylene glycol (1,2-propanediol)[52,53] under mild conditions with ruthenium on carbon as the preferred catalyst. Reactions were performed in batch and trickle bed reactors at temperatures ranging from 100 to 170°C and pressures ranging from 1000 to 2000 psi. At 95% conversion of lactic acid, selectivities in excess of 90% were reported.

Antons[54] also studied hydrogenation of lactic and malic acid over ruthenium catalysts and reported that the addition of a second metal, preferably rhenium, enhances reaction rates. At temperatures of 60-70°C and 1450 psi H_2, they produced alcohols with enantiomeric excess greater than 97%.

Recently, Dumesic[55] has performed vapor phase lactic acid hydrogenation over silica-supported copper. At 473 K and a hydrogen partial pressure of 100 psi H_2, they achieved propylene glycol yields of 88% with high selectivities.

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[52] Zhang, Z. G., Jackson, J. E., Miller, D. J. *Appl. Catal. A-Gen.* **2001**, *219*, 89.
[53] Zhang, Z. G., Ph.D. Dissertation, Michigan State University, 2000.
[54] Antons, S.; Tilling, A. S.; Wolters, E. U.S. Patent 6,355,848, 2002.
[55] Cortright, R. D.; Sanchez-Castillo, M.; Dumesic J. A. *Applied Catal B: Env.* **2002**, *39*, 353.

Chapter 2. Experimental Methods

2.1 Amino acid hydrogenation studies

2.1.1 Materials

Feeds (L(+)-alanine, glycine, L(+)-serine, L(+)-phenylalanine) were purchased from Aldrich Chemical Co. in enantiomerically pure forms with optical purities exceeding 99 ee%. The acid used in the reaction was ACS grade 85% phosphoric acid (J. T. Baker). Water used was of HPLC grade purity (J.T. Baker, USA). Ultra high purity hydrogen (AGA Gas, 99.999%) was used for all runs. For deuterium labeling experiments D_2 gas (AGA Gas, 99.5%) and deuterium oxide (Sigma Aldrich, 99.9%) were used in place of hydrogen and water.

The catalyst used was a 5% ruthenium on carbon powder obtained from PMC, Inc. (Severville, TN). The particles had a mean diameter of 150 microns, BET surface area of 860 m^2/kg, porosity of 0.6, and bulk density of 800 kg/m^3.

2.1.2 Batch reactor system

Reactions were carried out in a 300 mL batch reactor (Parr Instrument Co, USA) equipped with a gas entraining impeller and a temperature controller that maintained temperature to ±1°C. The reactor was constructed of 316 stainless steel and rated to a maximum pressure of 3000 psi at 350°C. The reactor was equipped with a liquid sampling system and a gas sampling vent so that analyses could be performed during the course of an experiment. A Teflon liner was employed in the reactor to minimize corrosion from the acidic reaction media.

Reactions were typically conducted using the following procedure. Catalyst (usually 1 g dry basis per 100 g feed solution) was placed in the reactor.

The vessel was purged with nitrogen to flush out oxygen, heated to 150°C, and charged with hydrogen to 250 psi. The catalyst was reduced for 1 hr at these conditions with the gas valve slightly open to regulate pressure and allow impurities to escape. The reactor was then cooled to room temperature and the hydrogen vented.

The reactor vessel was next charged with 100 grams of a 2 wt% amino acid solution containing inorganic acid and again purged with hydrogen. Heating and stirring (1200 rpm) were then initiated. The reaction began when the reactor reached the desired temperature, and was pressurized with hydrogen. Reactions were performed at temperatures from 80 to 150°C and at pressures from 100 to 2000 psi H_2. Throughout the reaction liquid samples were taken and analyzed. Reaction times ranged from four to 16 hours with 6 hours being the preferred time. At the conclusion of the reaction the vessel was cooled and the pressure reduced.

2.1.3 Amino acid analysis

2.1.3.1 HPLC analysis

Liquid products were analyzed using high pressure liquid chromatography (HPLC). The system consisted of a computer-controlled pump (Waters 600), a UV detector (Waters 610), and differential refractometer (Waters 490). Waters 600 Maxima software was used to monitor both detectors. The separation was carried out on a Waters NovaPak C_{18} (3.9 X 150 mm) column operating at a flow rate of 1 mL/min at 40°C, with a 70:30 mobile phase of 0.2 M acetate buffer (pH 5) solution and methanol.

To separate enantiomers of amino acids and amino alcohols, the following derivatization procedure was modified from an existing method:[56] 1 mL of 1 wt% TAGIT (2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate) in acetonitrile was added to 1 mL of 1% (v/v) triethylamine in water solution. To the above, 40 μL of reaction sample were added, shaken vigorously, and allowed to derivatize for 1 hour. Internal standard, 40 μL 3 wt% citraconic acid in water, was then added and a 5 μL aliquot injected into the HPLC. Components were detected at a UV wavelength of 250 nm. This method separated both the enantiomers of alanine and alaninol and gave distinct peaks for ammonia, ethylamine, and isopropylamine.

2.1.3.2 Use of ^{1}H NMR for analysis of amino acids and amino alcohols

Proton NMR (^{1}H) was used for experiments performed in D_2O under deuterium or hydrogen pressure. Catalyst was removed from samples using a cellulose-based syringe filter. One mL of sample was added to a round bottom flask and dried by rotary evaporation to remove water. The sample was dissolved in 0.7 mL of deuterated water, which contained 1% acetic acid as an internal standard, before transfer to an NMR tube. NMR spectra were recorded on a 300 MHz Varian spectrometer. Extent of deuteration was determined by comparison of the integration value of the internal standard peak to relevant peaks of the product and reactant coupled with species concentration data from HPLC.

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[56] Gal, J. *J. Liquid Chromatography* **1986** *9, (2-3)*, 673.

2.1.4 Amino acid hydrogenation conditions matrix for kinetic parameter determination

Hydrogenation of amino acids was performed in a Parr 300 mL mini-reactor. Amino acids used as starting materials include glycine, alanine, serine, proline, and phenylalanine. However, only alanine was studied in detail and therefore, the kinetic analysis was limited to it. Reactions were performed within the following variable ranges:

1. Feed concentration: 0.22 to 1.10 M
2. Temperature: 80 to 150°C
3. Pressure: 0 to 2000 psi H_2
4. Phosphoric acid concentration: 0 to 1.16 M

Appendix A contains details of selected reactions (concentrations, conversion, etc. versus time data) used for the kinetic analysis in this study.

2.2 Experimental methods for PLA and PHB hydrogenation

2.2.1 Materials

Poly(3-hydroxybutyric acid) PHB was obtained from Sigma Aldrich with a weight-average molecular weight of ~437,000. Samples of PLA were obtained from Polysciences, Inc. with weight-average molecular weights of ~300,000 and ~16,000. Poly-L-lactic acid was supplied by the Composites Center at Michigan State University with a number average molecular weight of ~140,000. Lactic acid, 85% in aqueous solution, was obtained from J. T. Baker. Organic solvents methanol and THF were obtained from J.T Baker and Aldrich, respectively.

Hydrogen, Ru/C catalyst, and water were obtained from the same sources as described in Section 2.1.1.

2.2.2 Batch reactor system

Hydrogenation of PLA and PHB were carried out in the same system as described in Section 2.1.2 using the same catalyst preparation. Feed materials were introduced to the reactor directly by opening the reactor head, instead of transferring the feed from a pressurized vessel. Before experiments were initiated, the reactor was purged with helium or hydrogen if a hydrolysis or hydrogenation experiment were run, respectively.

2.2.3 Analysis for PLA and PHB reaction products

2.2.3.1 HPLC analysis of monomeric materials

Analysis of lactic acid, 3-hydroxybutanoic acid, propylene glycol, and 1,3-butanediol were performed by HPLC using a HPX-87H Aminex carbohydrates column (Biorad) at 50°C with 5 mM sulfuric acid flowing at 0.45 mL/min. Samples were diluted to 5% by volume in water and a 10 μL aliquot was injected. Samples were detected using a RI detector.

2.2.3.2 HPLC analysis of oligomeric materials

Acetylated oligomers of lactic acid were detected using High Pressure Liquid Chromatography. The system consisted of a computer-controlled pump (Waters), a UV detector (Waters 610), and differential refractometer (Waters 490). Waters 600 Maxima software was used to monitor both detectors. A Waters NovaPak C_{18} (3.9 X 150 mm) column operating at a flowrate of 1 mL/min at 40°C was used for the separation. The mobile phase was delivered at a flow

rate of 1 mL/min and operated along a 40 minute gradient from 95:5 (v/v) water:acetonitrile with 0.1% volume trifluoroacetic acid to 95:5 (v/v) acetonitrile:water with 0.1% volume trifluoroacetic acid. This method separated oligomers of lactic acid up to degree of polymerization 14.

The samples of lactic acid oligomers were derivatized according to the following procedure. The sample (5 g) was dried by rotary evaporation to remove water or solvent. To this, 5 mL of acetic anhydride was added and heated at 80°C for 4 hours. The contents were dried using a rotary evaporator to remove excess acetic acid, water, and acetic anhydride. To the dried sample one ml of acetonitrile and 1 mL of water was added and a 20 µl aliquot was injected.

2.2.3.3 NMR analysis of oligomeric lactic acid

In principle, proton NMR can be used to estimate the average degree of polymerization of PLA in reaction samples by comparison to the methyl peak in the acetyl group with the methyl groups in PLA. To prepare samples for this, 1 mL of the sample left over from HPLC analysis, Section 2.2.3.2, was dried to remove acetonitrile and water. Deuterated chloroform was added to the solution to dilute the solution to 1 wt% and transferred to an NMR tube. NMR spectra were recorded on a 300 MHz Varian spectrometer. This method did not prove to be reliable and was not used extensively for analysis purposes.

Chapter 3. Amino acid hydrogenation results

3.1 Exploratory studies

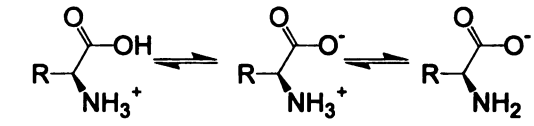
To determine the feasibility of amino acid hydrogenation, several sets of reaction conditions were investigated with a variety of amino acids and catalysts at different reaction conditions. The results presented in this section are meant to provide a qualitative description of observations from these studies. These reactions were performed before the development of an analytical method by HPLC, and thus ^{1}H-NMR spectra were used to identify product and reactant.

Glycine, as the simplest amino acid, was the first material examined to explore the feasibility of aqueous phase hydrogenation. Initial studies were carried out using nickel, palladium, and ruthenium catalysts. Ruthenium was the only catalyst to yield glycinol (ethanolamine) in the temperature range of 100 to 150°C under 1000 psi H_2.

A ramping experiment with glycine was carried out under hydrogenation conditions from 100 to 210°C under 1000 psi H_2 with 100 grams of a 2 wt% glycine solution and 1 g 5% Ru/C catalyst. A glycinol yield of less than 10% was observed at temperatures less than 150°C. Samples collected after reaction temperatures exceeded 150°C were pink and not suitable for NMR analysis.

Comparatively, lactic acid hydrogenates to propylene glycol rapidly under similar experimental conditions. Although they are similar compounds, there is at least one important difference that sets amino acids apart from α-hydroxy carboxylic acids with respect to aqueous phase hydrogenation.

As discussed in Section 1.2.1, and shown in Figure 3, the ionic state of amino acids is dependent on pH. From prior work with lactic acid and its salts,[53] it is known that for hydrogenation to occur, the carboxylic acid functionality may not be deprotonated form [**2**, **3**]. In dilute solutions, amino acids exist in the zwitterionic form **2** where the carboxylic moiety is deprotonated and hydrogenation is not thermodynamically favorable. Amino acids, because of the amino group at the alpha position, have a lower pK_a (1.8-2.6) than do normal alkanoic acids ($pK_a \approx 4.8$) and lactic acid ($pK_a = 3.8$).



Predominates pH<2	Predominates pH~5-9	Predominates pH>10
1	**2**	**3**

Figure 3. Amino acids in solution

To ensure that a high fraction of amino acid in solution was in the protonated state **1** (Figure 3) acid was added to the feed until an initial pH of ~1-2 was reached. To verify that the protonated form was present, the measured pH was entered into a rearranged form of the Hendersen-Hasselbach equation to estimate the fraction of amino acid that was protonated.

$$pH = pK_a + \log\left(\frac{[base]}{[acid]}\right) \rightarrow \frac{C_{COOH}}{C_{total}} = \frac{10^{-pH}}{10^{-pK_a} + 10^{-pH}} \qquad (1)$$

An experiment was carried out at 150°C with 100 grams of 2 wt% aqueous glycine under 1000 psi H_2 with 1 g 5% Ru/C. To acidify the feed solution, 0.3 M HCl was added to the feed mixture, which brought the solution pH

to ~1. At this temperature, a yield of roughly 40% was observed after 2 hours; this was an improvement over the previous case.

Phenylalanine, proline, alanine, and serine were also included in the initial investigation for hydrogenation feasibility. They were reacted under hydrogenation conditions of 150°C in 100 grams of 2 wt% amino acid solutions under 1000 psi H_2 with 1 g 5% Ru/C catalyst and 0.3 M HCl added. In each case, some product alcohol was formed, 20-40% as indicated by NMR analysis. In the case of phenylalanine, the ring was rapidly hydrogenated also to give cyclohexylalanine and cyclohexylalaninol.

The use of hydrochloric acid as an acidulant was not an appropriate choice for this reaction system because the reactor was constructed from stainless steel which was corroded by HCl. Frequently samples were colored pink, indicating metal leaching. The resulting dissolved metal ions made the NMR sample spectra collected very noisy.

The completion of these studies coincided with two very important developments in this work. First, the HPLC method described in Section 2.1.3.1 was developed and, secondly, phosphoric acid became the acidulant of choice.

The studies that pertain to amino acid kinetics were performed exclusively with alanine as the reactant and all cases, unless otherwise specified, contained phosphoric acid.

3.2 Experimental results with alanine

3.2.1 Control experiments with alanine

To determine the stability of alanine in solution, two experiments were performed. In the first experiment, 100 grams of 0.22 M alanine and 0.29 M phosphoric acid were fed to reactor with no catalyst present under 1000 psi H_2. The reactor operated sequentially at 100, 125, and 150°C for 2 hours at each temperature. Throughout this experiment a 1% yield of alaninol ((S)-2-aminopropanol) was observed and 5% yield of ammonia was observed after the 150°C interval. The presence of alaninol was probably due to a small amount of catalyst present in the reactor. In the second experiment, 100 grams of 0.22 M alanine and 0.29 M phosphoric acid were fed to reactor with 1 g of 5% Ru/C catalyst present under 1000 psi He. The reactor operated sequentially at 100, 125, and 150°C for 2 hours at each temperature. In this case, no side products were observed until after the 150°C interval. In this case, a 2% yield of ammonia and 5% yield D-alanine was observed. Amino acids are well known to racemize, particularly at elevated temperatures, a property that can be used for determining the relative or absolute age of biological materials.[57]

3.2.2 Effect of acid addition

The amount of phosphoric acid relative to alanine in the reaction mixture determines the maximum achievable yield. This ratio is important because the product formed is basic which causes the solution pH to increase as alanine is converted. With sub-stochiometric amounts of phosphoric acid added to the feed, alanine conversion ceased when the molar concentration of alaninol

[57] Bada, J. L. *Annu. Rev. Earth Planet Sci.* **1985**, *13*, 241.

approximately equaled the molar concentration of phosphoric acid added. Therefore, the effect of acid fed to the reactor was studied extensively, both with sub-stoichiometric and excess phosphoric acid relative to alanine.

3.2.2.1 Sub-stoichiometic phosphoric acid addition

In the studies presented in this section, 100 grams of a 0.22 M alanine solution was hydrogenated with varying phosphoric acid concentrations as specified in the text. In all cases 1000 psi H_2, 100°C, and 1 g of 5% Ru/C catalyst were used.

	0 M			0.07 M			0.15 M			0.29 M		
t(hr)	pH	X	C_{COOH}/C_t	pH	X	C_{COOH}/C_t	pH	X	C_{COOH}/C_t	pH	X	C_{COOH}/C_t
0	6.9	0.00	0.00	2.8	0.00	0.26	2.4	0.00	0.46	2.0	0.00	0.69
1	7.0	0.12	0.00	3.2	0.28	0.13	2.5	0.14	0.40	2.1	0.31	0.64
2	7.9	0.12	0.00	3.8	0.36	0.04	2.5	0.21	0.39	2.1	0.40	0.62
3	8.3	0.11	0.00	5.5	0.40	0.00	2.7	0.39	0.28	2.2	0.58	0.59
4	8.5	0.10	0.00	6.1	0.45	0.00	3.0	0.50	0.18	2.3	0.72	0.53
5	8.6	0.14	0.00	6.1	0.45	0.00	3.6	0.62	0.05	2.4	0.85	0.48
6	8.7	0.13	0.00	6.2	0.46	0.00	4.8	0.69	0.00	2.5	0.93	0.43

Table 3. Measured pH and calculated fraction of protonated alanine for data points in Figure 4. Reactions performed with 100 grams 0.22 M alanine feed solution, under 1000 psi H_2 with 1 g 5% Ru/C powder catalyst at 100°C.

As shown in Table 3 and Figure 4, when a moderate excess of phosphoric acid (0.29 M) was present, the reaction proceeded unconstrained to near completion in 6 hours. The fraction of alanine protonated estimated by the Henderson-Hasselbach equation shows that during the entire course of the run there was in excess of 40% of the total alanine in solution protonated. In comparison, for cases where a sub-stoichiometric amount of phosphoric acid was fed reactions did not run to completion. As the amount of acid fed was reduced, as in the cases with 0.15 M and 0.07 M phosphoric acid, the initial rate of alanine conversion was nearly identical to the base case (0.22 M alanine, 0.29

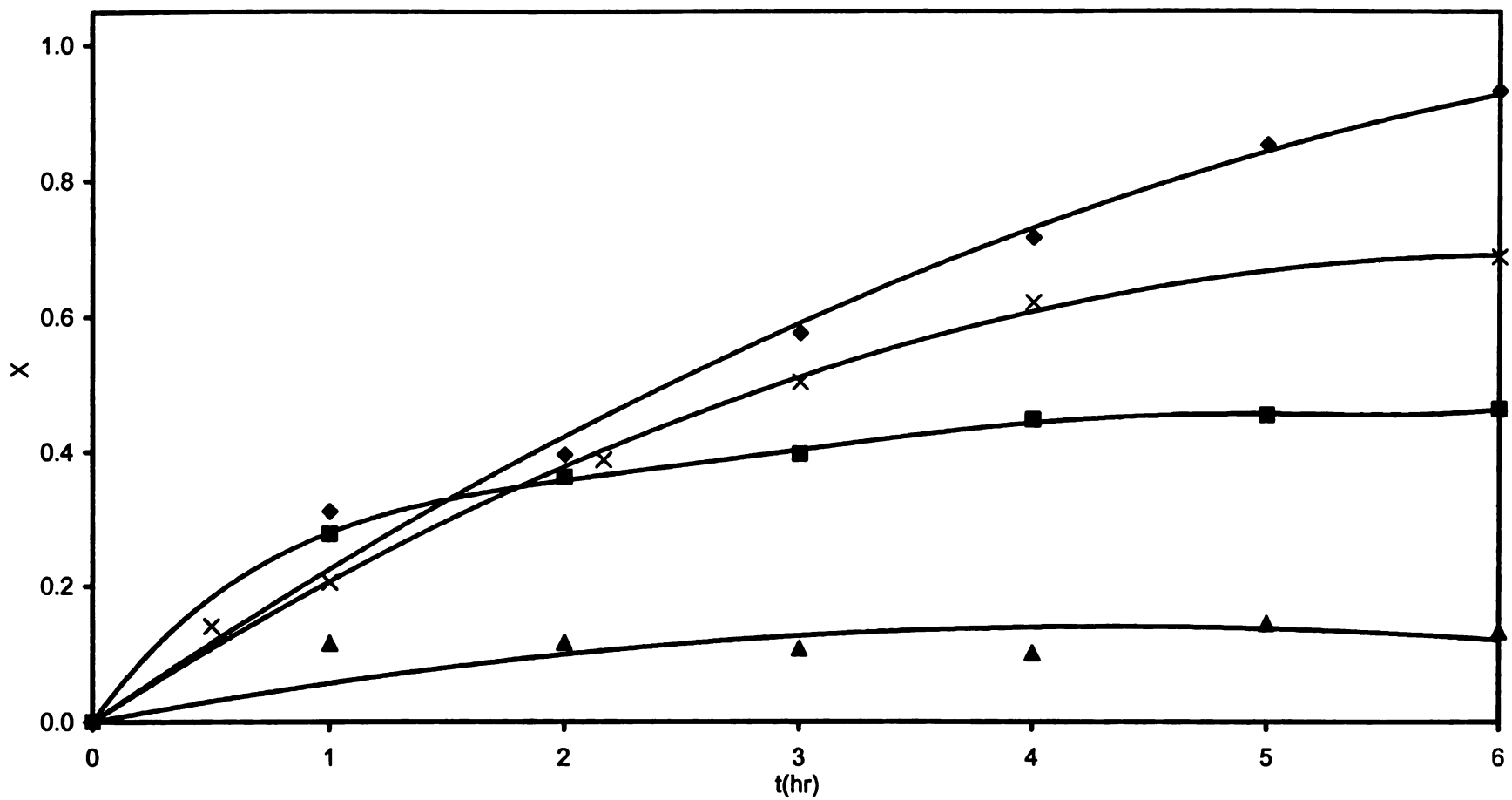


Figure 4. Effect of a deficiency of phosphoric acid on alanine conversion: (—♦—) 0.29 M, (--×--) 0.15 M, (–■–) 0.07 M, and (--▲--) 0.0 M phosphoric acid. Reaction performed with 100 grams of 0.22 M alanine solution, under hydrogen pressure of 1000 psi with 1 g 5% Ru/C powder catalyst in a 300 mL stirred reactor at 100°C.

M phosphoric acid) until the phosphoric acid was consumed by basic product, the fraction of alanine protonated approached zero, and the reaction stopped.

In the case where no phosphoric acid was present in solution, the calculated fraction of protonated alanine in the feed was zero. Strangely, conversion of 12% and yield of 8% was observed after the first hour. Considering the protonation requirement for hydrogenation, no yield or conversion was expected. However, acidic sites on the catalyst may donate a sufficient number of protons to facilitate this limited conversion.

To support the idea that the catalyst imparts a specific "acidity" or enables a specific molar conversion, two experiments were performed where no phosphoric acid was added to the feed. In one case the amount of alanine was doubled to 0.44 M and the other the catalyst loading was doubled. Both experiments were run at 100°C under 1000 psi H_2. In both cases the absolute molar amount of alanine converted and alaninol formed was nearly the same as when 0.22 M alanine was hydrogenated with 1 g of catalyst at the same temperature and pressure. Considering the assumption that the catalyst imparted a specific acidity, the same molar conversion in the case of 0.44 M alanine fed was expected. Similarly, with a doubling of catalyst, it was expected that the conversion of alanine and formation of alaninol would double the molar conversion and yield values observed in the base case, which was not the case. Therefore, these experiments together do not prove the idea that the catalyst had a specific acidity. However, an experiment where 0.28 M sodium hydroxide was added to the solution completely stopped the formation of alaninol. This

suggests that the catalyst did impart some acidity, although it is not clear how this was specifically related to conversion.

3.2.2.2 Effect of molar excess of phosphoric acid on conversion

In the studies presented in this section, 100 grams of a 0.22 M alanine solution was hydrogenated under varying phosphoric acid concentrations as specified in the text. In all cases 1000 psi, 100°C, and 1 g of 5% Ru/C catalyst were used.

In considering the base case of 0.22 M alanine and 0.29 M phosphoric acid, where the maximum conversion occurs in this set of studies, the fraction of alanine protonated in the feed was calculated to be roughly 70% and declined as alaninol was formed. This begs the question of what the effect would be of increasing the acid concentration above 0.29 M, thus increasing the fraction of protonated alanine. As shown in Figure 5, increasing acid concentrations to 0.59 and 1.16 M phosphoric acid decreased the conversion rate compared to the case with 0.29 M phosphoric acid concentration despite increasing the fraction of alanine protonated, as shown in Table 4. This effect was due to a combination of the following factors: hydrogen solubility decreased with increased acid concentration and phosphoric acid occupied active sites on the catalyst.

While both of these factors contributed to the observed reduction in rate, occupation of reactive sites by phosphoric acid was probably more significant. This was clear by comparing the final conversion of the three cases. The difference between the final conversion in the 0.29 M and 0.59 M cases was 25%, whereas the difference in the final conversion between the 0.59 and 1.16 M

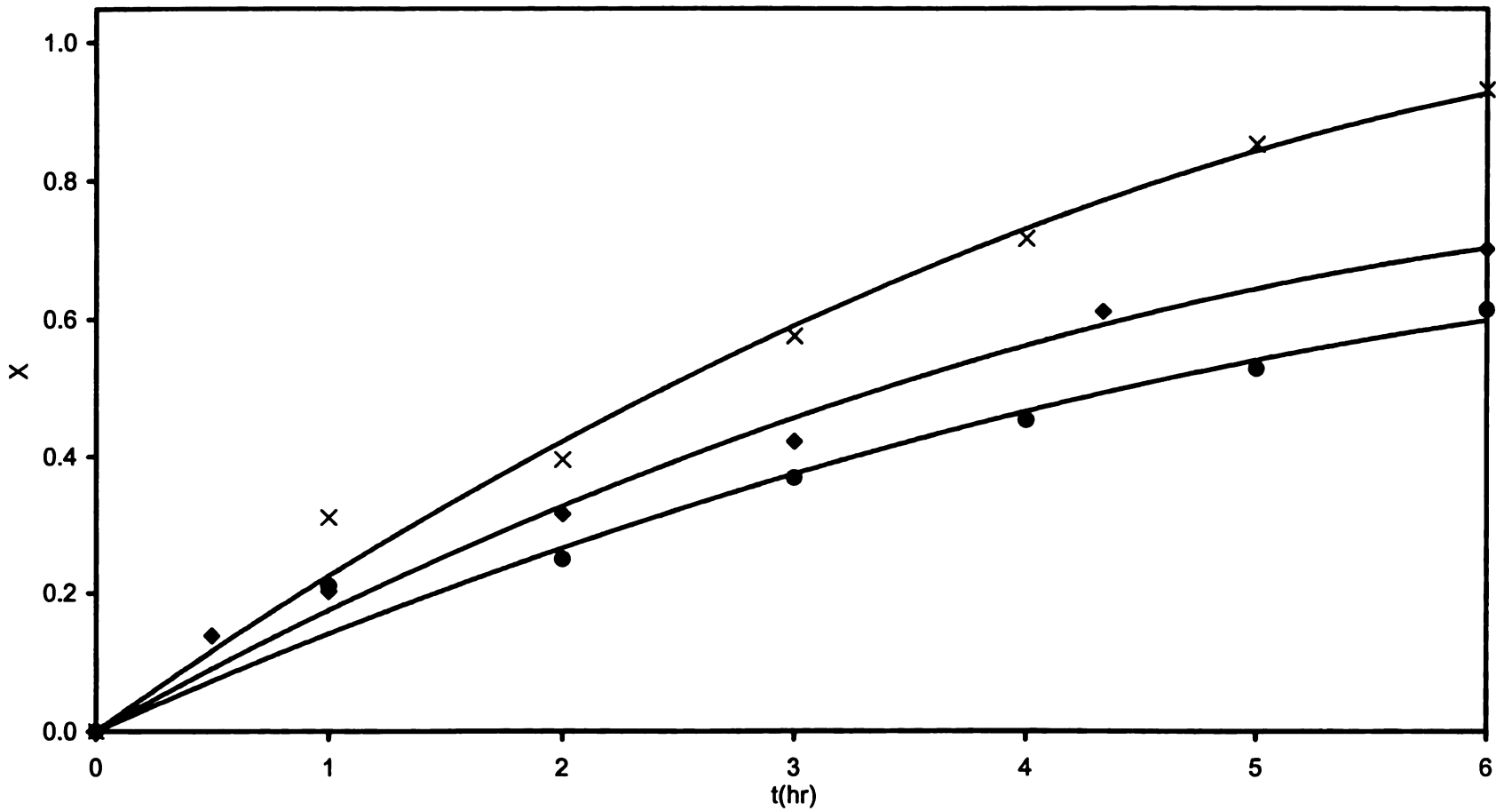


Figure 5. Effect of excess phosphoric acid on alanine conversion: (—×—) 0.29 M, (—♦—) 0.58 M, and (—●—) 1.12 M phosphoric acid. Reactions performed with 100 grams of 0.22 M alanine solution, under hydrogen pressure of 1000 psi with 1 g 5% Ru/C powder catalyst in a 300 mL stirred reactor at 100°C.

cases was only 13%. If the reduction in rate were due to a decrease in H_2 solubility the observed reduction in conversion should be relatively linear with respect to acid concentration. This observed reduction in rate appears mathematically to be better explained by an absorption model where phosphoric acid occupies active sites but does not bind as strongly as alanine. This was shown to be the case when the kinetic model was constructed in Section 4.2.

	0.29 M			0.59 M			1.2 M		
t(hr)	pH	X	C_{COOH}/C_t	pH	X	C_{COOH}/C_t	pH	X	C_{COOH}/C_t
0	2.0	0.00	0.69	1.5	0.00	0.87	1.0	0.00	0.96
1	2.1	0.31	0.64	1.5	0.20	0.86	1.1	0.21	0.95
2	2.1	0.40	0.62	1.6	0.32	0.86	1.1	0.25	0.95
3	2.2	0.58	0.59	1.6	0.42	0.85	1.1	0.37	0.95
4	2.3	0.72	0.53	1.6	0.61	0.84	1.1	0.45	0.95
5	2.4	0.85	0.48				1.1	0.53	0.95
6	2.5	0.93	0.43	1.7	0.70	0.82	1.1	0.61	0.95

Table 4. Measured pH and calculated fraction of protonated alanine for reactions with 0.15 M, 0.29 M, and 0.58 M phosphoric acid. Reactions performed with 100 grams 0.22 M alanine solution, under 1000 psi H_2 with 1 g 5% Ru/C powder catalyst.

A further discussion of acid-base equilibria calculations is presented in Section 4.2 and Appendix B, which compares the use of the Henderson-Hasselbach equation to a solution charge balance calculation that predicts the ionic state of alanine in solution.

3.2.3 Other acid solutions

In the experiments presented in this section sulfuric acid and triflic acid were studied as acidulants. In these experiments, 100 grams of a 0.22 M alanine solution was hydrogenated under 1000 psi H_2, at 100°C, with 1 g of 5% Ru/C.

To complement the experiments performed with phosphoric acid added, two experiments were performed with 0.29 M sulfuric acid and 0.29 M triflic acid (triflouromethanesulfonic acid) to determine if the use of strong acids would

enhance the conversion rate. The strong acidity of sulfuric acid (pK_{A1}=-2, pK_{A2}=1.9) and triflic acid (pK_A≈-13) shifts the solution equilibrium of alanine further to the protonated state and thus a higher conversion rate was expected.

With 0.29 M triflic acid added, the initial pH of the solution was 1.1 and increased to 1.4 by the end of the experiment (6 hours). At the end of the experiment the fraction of alanine protonated was greater than 90% and the yield was 46%. Similarly, with 0.29 M sulfuric acid added, the pH of the solution remained ~1 during the entire experiment, corresponding to greater than 95% of alanine in solution protonated. A yield of 45% was observed after 6 hours. Despite the high fraction of protonated alanine the conversion rate in both cases was roughly two-thirds of when phosphoric acid was used as the acidulant, as shown in Figure 6. In the kinetic model, Section, 4.2, phosphoric acid is an adsorbed species in the rate expression to account for the reduction in rate observed where an excess of phosphoric acid was present in solution (Section 3.2.2.2). Here a similar phenomena was likely observed, where these acids occupied active sites. However, these acids apparently bind much more strongly than phosphoric acid which caused the reduction in reaction rate to be much larger. This reduction in rate could also be attributed to catalyst poisoning from these sulfur containing acids.

3.2.4 Effect of pressure

In the studies presented in this section the effect of hydrogen pressure on reaction rate is presented. In these experiments, 100 grams of a 0.22 M alanine solution was hydrogenated under 1000 psi H_2, at 125°C, with 1 g of 5% Ru/C.

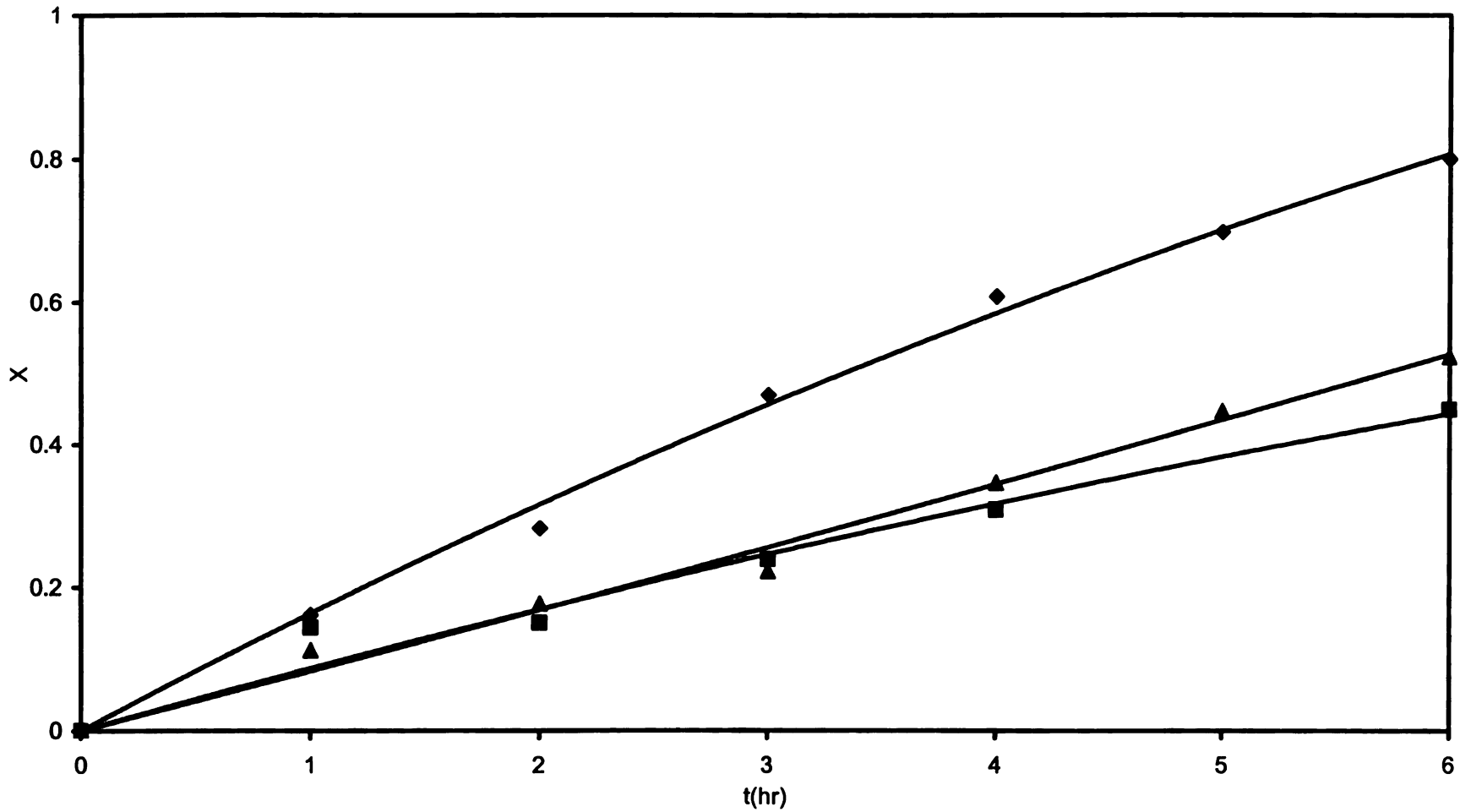


Figure 6. Dependence of conversion rate on acid type. Reactions performed at 100°C with 100 grams solution of 0.22 M L-alanine, 1 g of 5% Ru/C catalyst, 1000 psi hydrogen pressure. (♦) 0.29 M Phosphoric acid, (▲) 0.29 M triflic acid, (■) 0.29 M sulfuric acid.

Hydrogenation rate was only mildly dependent on hydrogen partial pressure above 1000 psi H_2. Because hydrogen solubility follows Henry's law, H_2 concentration in water varies nearly linearly with pressure. Figure 7 shows that the conversion rate declines when hydrogen pressure was reduced to 250 psi; however, above 1000 psi rate was independent of hydrogen concentration indicating the surface was saturated with hydrogen.

3.2.5 Temperature effect on amino acid hydrogenation

Temperature directly affects the rate at which alanine hydrogenates and alaninol degrades and was studied over range of 90 to 150°C. In these experiments 100 grams of a 0.22 M alanine solution with 0.29 M phosphoric acid was hydrogenated under 1000 psi H_2, with 1 g of 5% Ru/C.

Figures 8 and 9 detail hydrogenation reactions performed at 150 and 100°C, respectively. The upper set of curves in each figure show the concentrations of L-alanine, L-alaninol, and D-alaninol versus time. The lower curve in each figure shows alaninol enantiomeric excess versus time as a measure of the rate of racemization observed.

As shown in the upper graph of Figure 8, at 150°C conversion was complete in roughly 45 minutes, which equates to a rate roughly eight times greater than at 100°C. This point corresponds to a maximum yield in L-alaninol followed by a decrease in L-alaninol with an increase in D-alaninol. Mechanistically a very important observation was made; *the reduction of the carboxylic functionality and racemization of alaninol are separate processes.* Simply by performing experiments with temperatures at or below 100°C, as

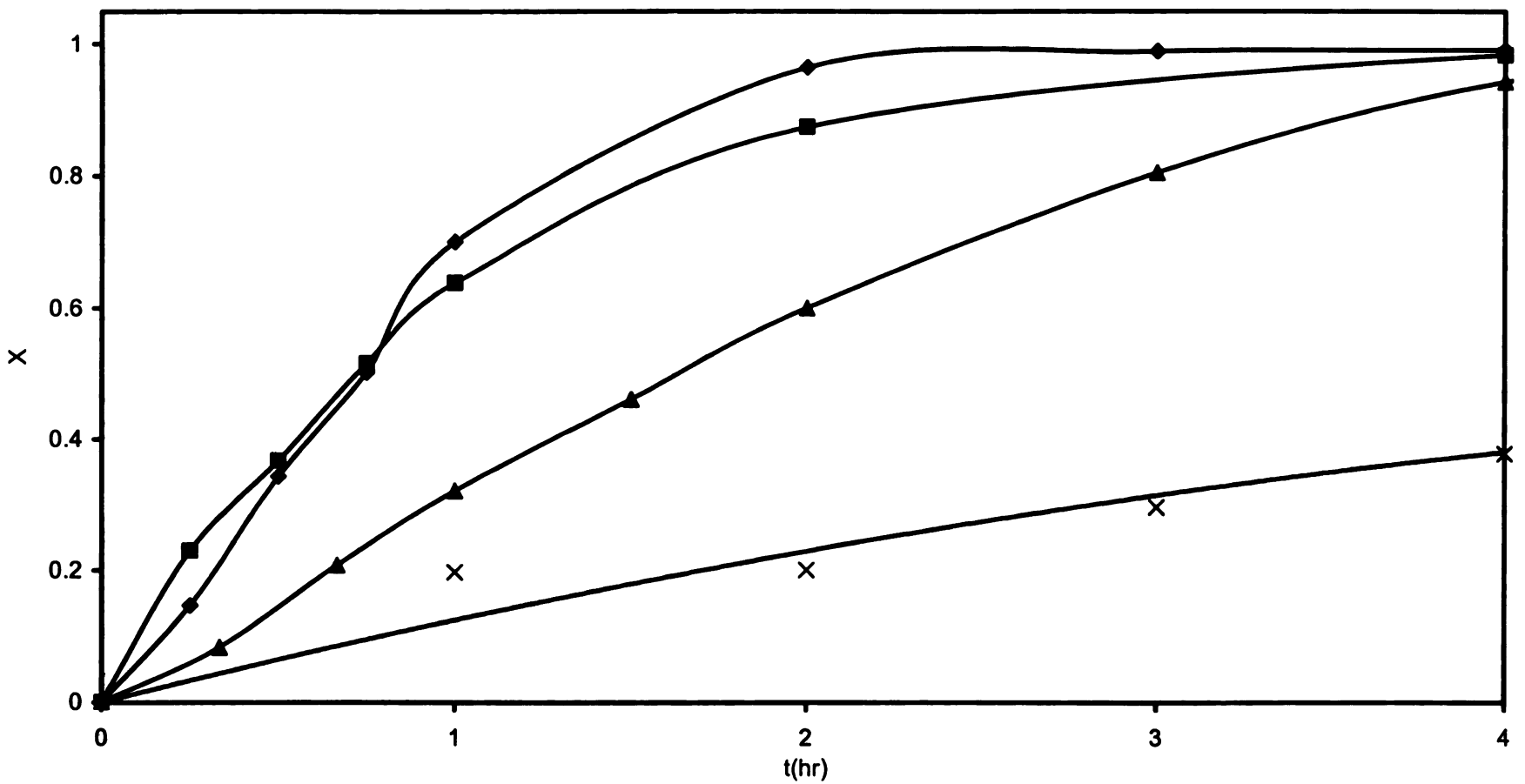


Figure 7. Dependence of alanine conversion rate on H_2 pressure. Reactions performed at 125°C with 100 grams solution of 0.22 M L-alanine, 0.29 M phosphoric acid, and 1 g of 5% Ru/C catalyst. Absolute bomb pressure: (—♦—) 1800 psi, (–■–) 1000 psi, (--▲--) 250 psi, (--×--) 100 psi.

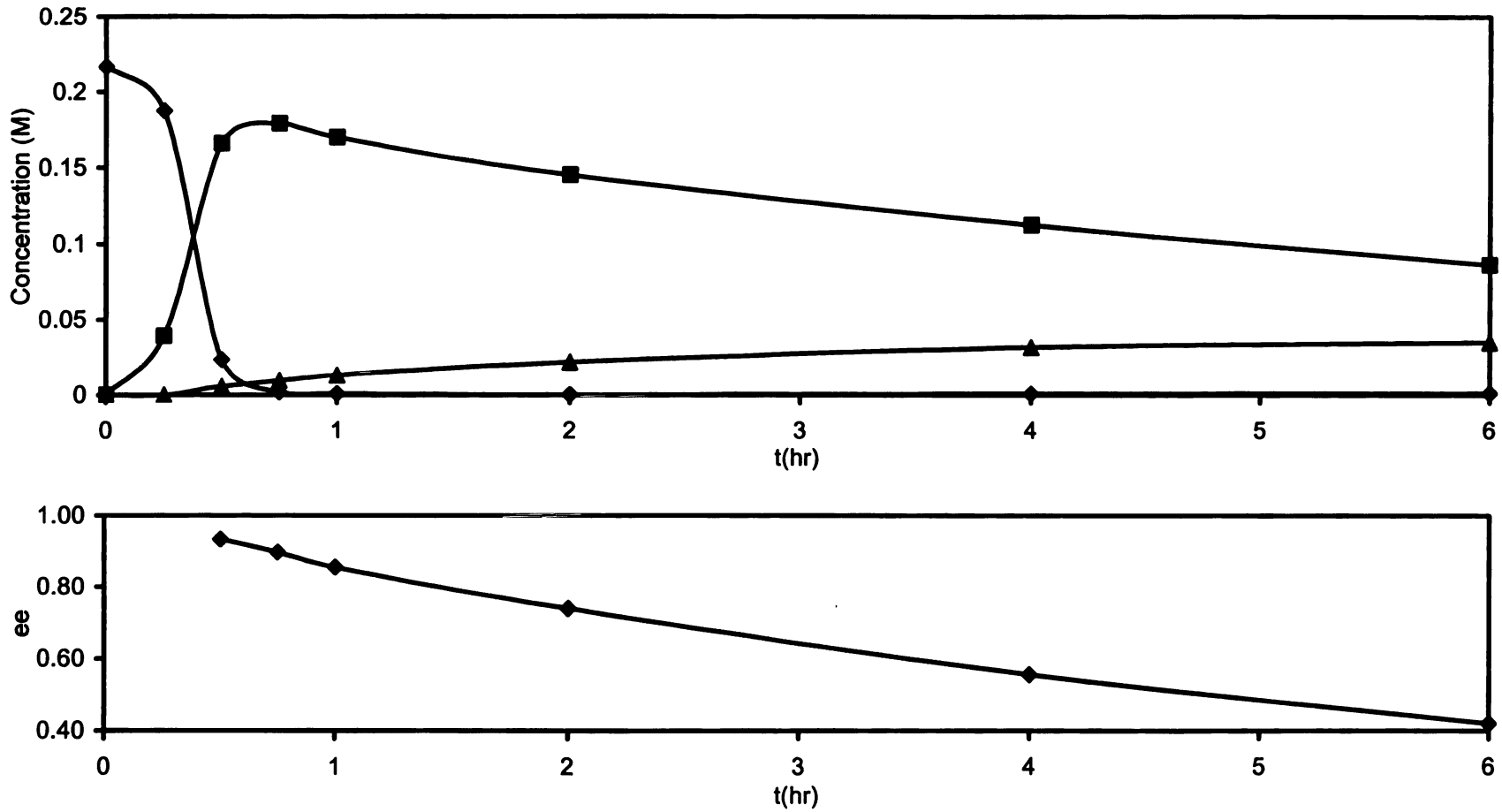


Figure 8. Secondary racemization of L-alaninol. Upper graph: (--◆--),L-alanine concentration; (--■--), L-alaninol concentration, (--▲--), D-alanine. Lower graph shows enantiomeric excess of alaninol in solution. Reaction performed with 100 grams of a 0.22 M L-alanine solution, under H_2 pressure of 1000 psi at 150°C with 1 g of 5% Ru/C powder catalyst. Phosphoric acid in solution was 0.29 M.

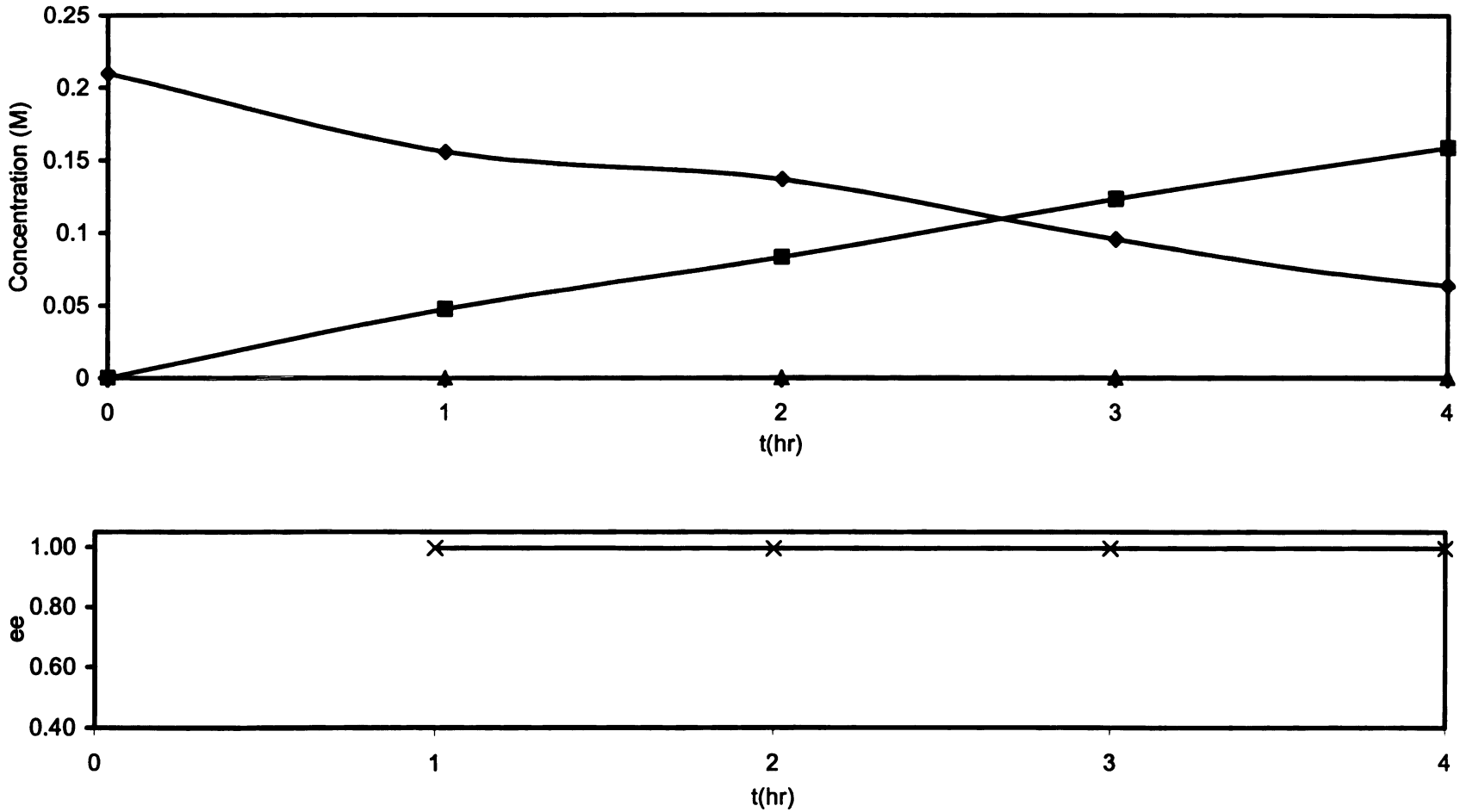


Figure 9. Formation of enatiomerically pure L-alaninol. Upper graph: (—♦—),L-alanine concentration; (–■–), L-alaninol concentration, (–▲–), D-alanine. Lower graph shows enantiomeric excess of alaninol in solution. Reaction performed with 100 grams of a 0.22 M L-alanine solution, under H_2 pressure of 1000 psi at 100°C with 1 g of 5% Ru/C powder catalyst. Phosphoric acid in solution was 0.29 M.

shown in Figure 9, the stereocenter of alaninol was maintained. Another important observation made here was that the main side product formed in alaninol racemization at 150°C was ethylamine. The co-product formed with ethylamine has not been positively identified because the HPLC method only detects amine-bearing compounds. However, the co-product was likely methanol or carbon dioxide.

3.2.6 Effect of increasing alanine concentration on molar conversion rate

In this section three experiments are presented that show the effect of alanine feed concentration on hydrogenation rate. In each experiment 100 grams of alanine solution was hydrogenated in a phosphoric acid-water solution. Feed concentrations of 0.22 M and 0.29 M, 0.44 M and 0.59 M, and 1.2 M and 1.5 M of alanine and phosphoric acid, respectively, were used. In all cases the reaction conditions were 1000 psi H_2, 100°C, and 1 g of 5% Ru/C catalyst.

Figure 10 shows alanine conversion versus time for each of the reactions based on the feed concentration. On a molar basis, the initial rate of conversion in each case was approximately the same. After 2 hours the rate of conversion diverged. This result was expected because the rate expression is a function of alanine concentration. As conversion proceeds, the rate must decrease.

3.3 Alaninol degradation

3.3.1 Control experiment with alaninol

As a control experiment, 100 grams of 0.22 M alaninol and 0.29 M phosphoric acid were fed to the reactor with 1 g of 5% Ru/C catalyst present under 1000 psi helium. The reactor operated sequentially at 100, 125, and

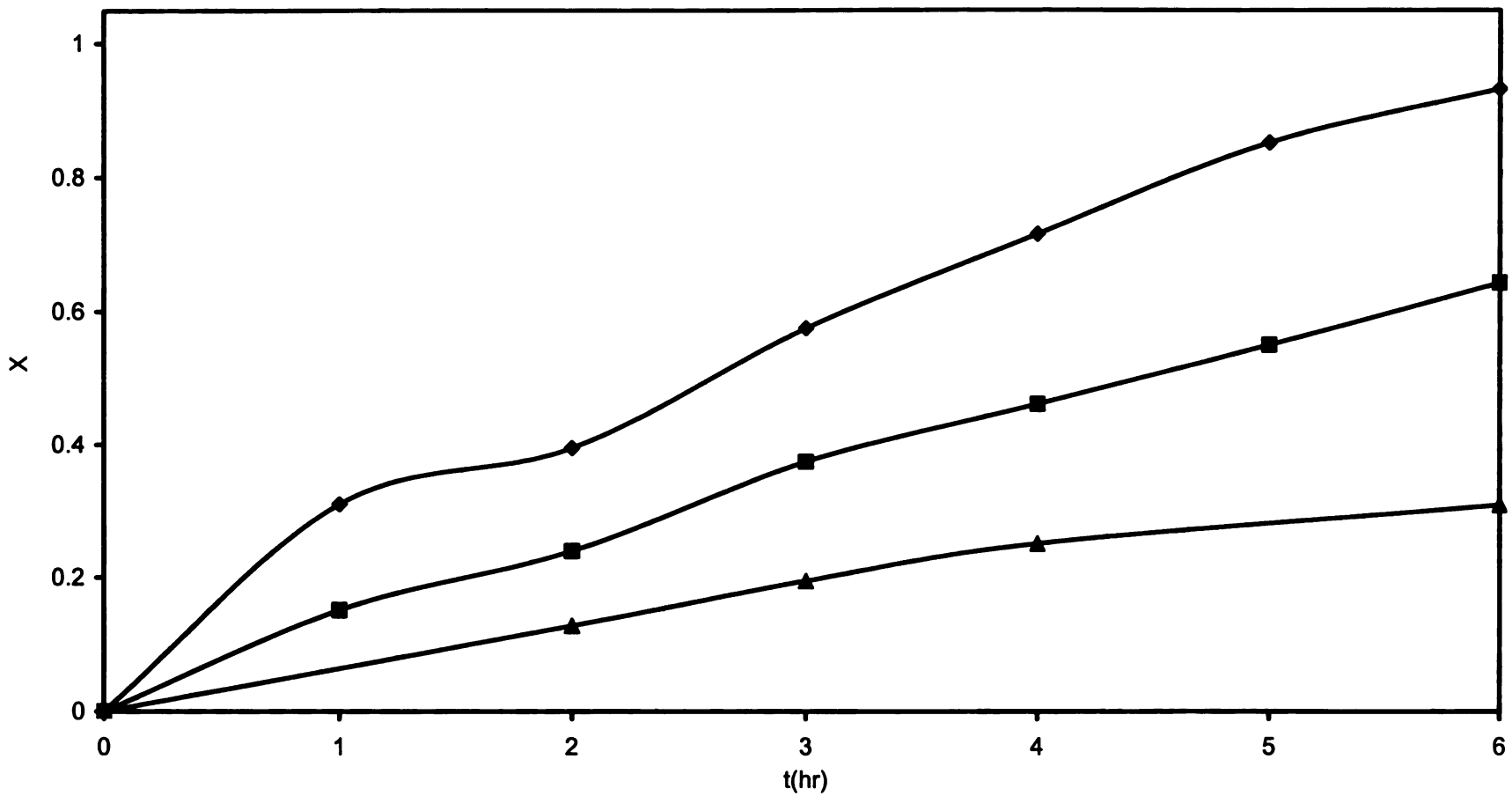


Figure 10. Effect of alanine concentration on molar conversion rate. Reactions performed at 100°C with 100 grams L-alanine solution, 1 g of 5% Ru/C catalyst, 1000 psi H_2 pressure. Feed concentrations: (♦) 0.22 M alanine and 0.29 M phosphoric acid, (■) 0.46 M alanine and 0.59 M phosphoric acid, (▲) 1.2 M alanine and 1.5 M phosphoric acid.

150°C for two hours at each temperature. In this study, no racemization of alaninol was observed. However, the last sample taken, at 150°C, showed a 5% yield of ammonia.

3.3.2 Temperature effect on alaninol degradation

An experiment was performed with 100 grams of 0.22 M alaninol fed to the reactor with 0.29 M phosphoric acid. The experiment was carried out under hydrogenation conditions of 1000 psi H_2 and 150°C with 1 g of 5% Ru/C catalyst. At 150°C, the rate of alaninol racemization, 41% ee after 6 hours, was nearly the same as when formed from alanine, 42% ee of alaninol after 6 hours, as presented in Section 3.2.4.

In the collection of experiments performed in this work, 100°C was the lower boundary where racemization of alaninol becomes activated by the catalyst.

Racemization of amino alcohols induced by catalysts at high temperature has been also been observed by Antons[47] (Ru/C), Harsey[58] (Raney Cobalt), and by Studer[46] (Rh/Pt oxide). Interestingly, despite using different catalysts, all share 100°C as a starting point for product racemization.

3.3.3 Effect of phosphoric acid on alaninol degradation rate

Two experiments were performed with 100 grams of 0.22 M alaninol at 125°C under 1000 psi H_2 with 1 g of 5% Ru/C catalyst. One experiment contained 0.29 M phosphoric acid and no acid was added to the other. At the end of a six hour run, the measured enantiomeric excess of alaninol remaining

[58] Harsey, S. G., U. S. Patent 4,990,666, 1991.

was nearly identical in both cases (89% and 91%, for 0.29 M phosphoric and no phosphoric acid, respectively). However, without phosphoric acid added roughly 24% of the alaninol fed was lost in six hours versus 11% loss of alaninol over six hours with 0.29 M phosphoric acid added. This was likely due, in part, to phosphoric acid occupying sites. In both cases the side products are ammonia, ethylamine, and isopropylamine.

3.4 Hydrogenation of β-Alanine

As a complement to our studies of alanine, two hydrogenation experiments with β-alanine (3-aminopropanoic acid) were performed. Experiments were performed with 100 grams of 0.22 M β-alanine solution fed to the reactor with 0.29 M phosphoric acid. The experiments were carried out under hydrogenation conditions of 1000 psi H_2 with 1 g of 5% Ru/C catalyst at 100 and 150°C, respectively. At 100°C, a 16% yield of 3-aminopropanol product was observed at 6 hours. L-alanine under identical conditions reached a yield of 91% in 6 hours. At 150°C, β-alanine was completely consumed in six hours. However, a maximum 3-aminopropanol yield of 49% was observed after 4 hours followed by degradation of 50% of the product. L-alanine under these conditions rapidly hydrogenates with high selectivity in the first hour of the reaction followed by subsequent degradation of the product.

As noted in the Section 1.2.4, α-substituted carboxylic acids are more easily hydrogenated than normal alkanoic acids and non-α-substituted carboxylic acids, and thus the observed results are unsurprising.

Chapter 4. Kinetics and mass transfer

4.1 Mass transfer calculations

For each reaction performed in the parametric series, a complete set of mass transfer calculations was performed. To ensure that reactions were run optimally, there were many conditions within the reactor that were considered in regards to the catalyst, as well as mass transfer.

4.1.1 Catalyst suspension

Before considering calculation of various mass transfer coefficients, complete suspension of the catalyst must be ensured. Any calculation in batch reactors assumes that the contents of the reactor are well mixed. If the catalyst is suspended, the entire surface of the catalyst is available for reaction. If some catalyst remains on the bottom of the reactor, reactants must diffuse into those masses of catalyst which would slow the reaction. In 1958, Zwietering[59] studied the conditions necessary to completely suspend particles in a baffled vessel. For particles to be considered suspended, no single particle should remain on the bottom of the reactor for more than 1 or 2 seconds. He proposed the following correlation for predicting the minimum stirring speed to ensure complete suspension.

$$N_{min} = \frac{\beta \cdot d_p^{0.2} \cdot \mu_L^{0.1} \cdot g^{0.45} \cdot (\rho_p - \rho_L)^{0.45} \cdot w'^{0.13}}{\rho_L^{0.55} d_i^{0.85}} \qquad (2)$$

where N_{min} = minimum stirring speed (rotations/sec)

β = constant determined by the impeller geometry

w' = catalyst loading (grams catalyst /100 grams solution)

[59] Zwietering, T. H. *Chem Eng. Sci.* **1958**, *8*, 244.

d_p = particle diameter (m)

μ_L = liquid viscosity (kg/m-s)

g = gravitation constant (m/s^2)

ρ_p = particle density (kg/m^3)

ρ_L = liquid density (kg/m^3)

d_I = impeller diameter (m)

In our system, 1 g of catalyst in 100 grams of water required a minimum stirring speed of approximately 475 rpm. Complete suspension was ensured by stirring at 1200 rpm.

4.1.2. Mass transfer coefficients

In this three-phase system, the following steps occur in the process of making the alcohol product:

a. Transport of hydrogen from the bulk gas phase to the gas-liquid interface.
b. Transport of hydrogen from the gas-liquid interface to the bulk liquid.
c. Transport of the alanine and hydrogen from the bulk liquid to the catalyst surface.
d. Intraparticle diffusion of the reactants in the pores of the catalyst.
e. Adsorption of the reactants on the active sites of the catalyst.
f. Reaction on the surface of hydrogen and alanine to produce alaninol.
g. Desorption of products.

The three phases of this system; gas, liquid, and solid, are shown in Figure 11 along with the film layers that separate them. This figure describes the

concentration of the sparingly soluble gaseous hydrogen and dissolved alanine in the different regions.

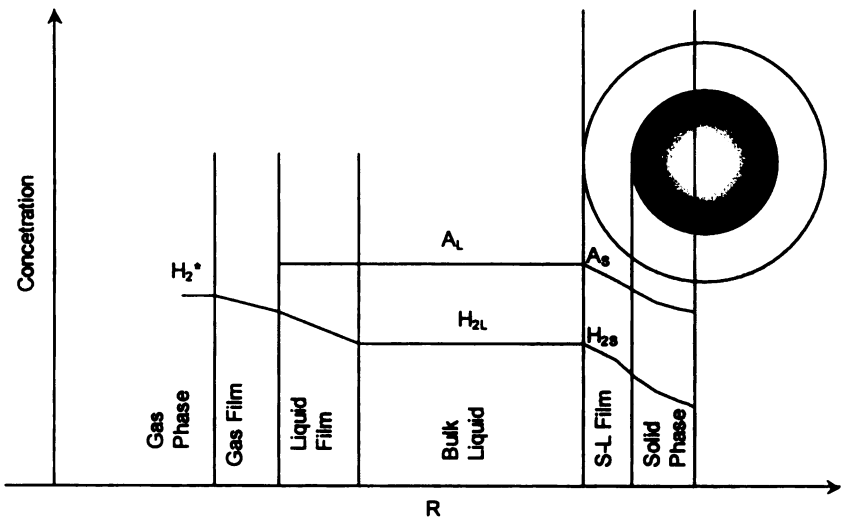


Figure 11. Three phase mass transfer in catalytic system

4.1.3 Reaction rate and mass transfer

In this three phase system, hydrogen must pass through both the gas-liquid and liquid-solid films while alanine must pass through the liquid-solid film to reach the catalyst surface. The rate at which these diffusion processes occur is equal to the observed reaction rate, or the rate at which they are consumed by reaction. The observed reaction rate is related to these transfer rates by the following equations:

Gas-liquid transfer:

$$-R_{G,H_2} \cdot L = k_L a\left(C_{H_2,G} - C_{H_2,L}\right) \tag{3}$$

liquid-solid transfer

$$-R_{G,H_2} \cdot L = k_{s,H_2} a\left(C_{H_2,L} - C_{H_2,S}\right) \tag{4}$$

$$-R_{G,A} \cdot L = k_{s,A} a (C_{A,L} - C_{A,S}) \quad (5)$$

Where $-R_G$ = observed reaction rate of the species (kmol/m^3-s)

L = ratio of catalyst surface area per unit volume fluid (m^2/m^3)

a = mass transfer area per unit volume of reactor (m^2/m^3)

$k_L a$ = the gas-liquid mass transfer coefficient (1/s)

k_s = the liquid solid mass transfer coefficient (m/s)

In these expressions, the mass transfer is driven by the concentration differences between the two phases. The mass transfer coefficients are also related to the observed reaction rate by the expressions above. They can be calculated via correlations in the literature or observed experimentally. The correlations used in this study will be discussed in Sections 4.1.4 and 4.1.5.

Once the mass transfer coefficients are obtained the maximum mass transfer rate may be calculated. This is achieved by setting the driving force equal to the value of the higher concentration.

$$\text{Maximum gas - liquid mass transfer rate} = k_{L H_2} a \cdot C_{H_2,G} \quad (6)$$

$$\text{Maximum liquid - solid mass transfer rate} = k_{s,H_2} a \cdot C_{H_2,L} \quad (7)$$

$$= k_{s,A} a \cdot C_{A,L} \quad (8)$$

The maximum mass transfer rates calculated from these expressions are compared to the observed reaction rate. If the maximum rate of mass transfer is greater than the observed reaction rate in each case, the reaction is not mass transport limited.

4.1.4 Gas-liquid mass transfer coefficient

The gas phase in these studies was composed primarily of hydrogen, represented as H_2^*. Water vapor was also present in this phase, however, in the temperature range studied, 90 -150°C, the volume of water present in the gas phase was small and assumed to be zero for calculation purposes.

To enter the bulk liquid phase, hydrogen must pass through the gas and liquid films, which are also commonly referred to as the gas-liquid film. As shown in the Figure 11, as hydrogen passes through this layer, its concentration decreases. In this set of studies centered around 100°C and 1000 psi H_2, the solubility of hydrogen was on the order of 0.05 M. The rate at which hydrogen passes through this film is called the gas-liquid mass transfer coefficient and is usually represented as $k_L a_B$. To estimate this rate, two well known correlations have been used.

In 1975 Yagi and Yoshida[60] proposed the following correlation for gas liquid mass transfer, $k_L a_B$.

$$Sh = \frac{k_L a_B d_I^2}{D_a} = 0.06 \cdot \left(\frac{d_I^2 N \rho_L}{\mu_L}\right)^{1.5} \left(\frac{d_I N^2}{g}\right)^{0.19} \left(\frac{u_L}{\rho_L D_a}\right)^{0.5} \left(\frac{\mu_L u_g}{S_T}\right)^{0.60} \left(\frac{N d_I}{u_g}\right)^{0.32} \quad (9)$$

Where Sh = Sherwood number (dimensionless)

k_L = liquid film mass transfer coefficient (m/s)

a_B = gas-liquid interfacial area per unit volume of reactor (m^2/m^3)

d_I = impeller diameter (m)

[60] Yagi, H., Yoshida, F. *Ind. Eng. Chem. Proc. Des. Dev.* **14**, *488*, 1975.

D_a = diffusion rate of species a (m/s^2)

N = stirring speed (rotations/s)

ρ_L = liquid density (kg/m^3)

μ_L = liquid viscosity (kg/m-s)

g = gravitational constant (m/s^2)

u_g = gas velocity (m/s)

S_T = fluid surface tension (N/m)

This equation was shown to adequately predict CO_2 absorption at 30°C for a glycerol-water system.

In 1976 Bern[61] proposed the following equation for a slurry reactor used to hydrogenate oil in gas-liquid mass transfer controlled regime.

$$k_L a_B = \frac{0.011 \cdot N^{1.16} \cdot d_I^{1.979} \cdot u_g^{0.32}}{V_L^{0.0521}} \qquad (10)$$

Where k_L = liquid film mass transfer coefficient (cm/s)

a_B = gas-liquid interfacial area per unit volume of reactor (cm^2/cm^3)

d_I = impeller diameter (cm)

N = stirring speed (rotations/s)

ρ_L = liquid density (g/cm^3)

u_g = gas velocity (cm/s)

V_L = volume of the solution (cm^3)

[61] Bern, L., Lidefelt, J. O., and Schoon, N. H. *J. Am. Chem. Soc.* **53**, 463, 1976.

This correlation satisfied their data obtained for both 30 and 500-liter reactors. It also compared well with experimental data obtained from 11 and 14 m^3 reactors.

4.1.5 Liquid-solid mass transfer coefficient

From the bulk liquid phase, alanine and hydrogen must pass through the liquid-solid film (L-S) to reach the catalyst surface. As shown in Figure 11, the concentrations of both species decrease as they pass though this film and are defined as A_S and H_{2S} at the catalyst surface. The rate of transport through this film is generally referred to as the liquid-solid mass transfer coefficient, k_s. In this study, the L-S mass transfer rate for both alanine and hydrogen was estimated by the Boon-Long[62] equation.

$$\frac{k_S d_p}{D_a} = 0.046 \cdot \left(\frac{2\pi^2 d_p d_T N}{\mu_L}\right)^{0.283} \left(\frac{\rho_L^2 g d_p^3}{\mu_L^2}\right)^{0.173} \left(\frac{w' V_L}{d_p^3}\right)^{-0.011} \left(\frac{d_T}{d_p}\right)^{0.019} \left(\frac{\mu_L}{\rho_L D_a}\right)^{0.461} \quad (11)$$

Where k_s = liquid-solid mass transfer coefficient (m/s)

d_p = particle diameter (m)

D_a = diffusion rate of species a (m^2/s)

d_T = reactor diameter (m)

N = stirring speed (rotations/s)

μ_L = liquid viscosity (kg/m-s)

ρ_L = liquid density (kg/m^3)

g = gravitational constant (m/s^2)

w' = catalyst loading (kg/100 kg solution)

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[62] Boon-Long, S., Laguerie, C., and Couderc, J. P. *Chem. Eng. Sci.* **1978,** *33,* 813,

V_L = liquid volume (m^3)

In liquid-solid mass transfer, the mass transfer area of catalyst per unit volume is calculated from the catalyst properties and experimental conditions as:

$$a = \frac{6w'\rho_L}{d_p\rho_p} \tag{12}$$

Where a = ratio of catalyst surface area to volume of fluid (m^2/m^3)

w' = catalyst loading (grams catalyst/100 grams feed)

ρ_L = fluid density (kg/m^3)

d_p = particle diameter (m)

ρ_P = catalyst density (kg/m^3)

These correlations for the gas-liquid and liquid-solid mass transfer have been used to characterize mass transport for all experiments in this study.

4.1.6 Intraparticle mass transfer

Finally, for reaction to occur the reactants must diffuse through the interstices of the catalyst to the active sites. The Weiss-Prater[63] criterion was used to determine whether the reactions were mass transport or reaction limited within the catalyst particles by calculation of the observable modulus, $\eta\phi^2$.

$$\eta\phi^2 = \frac{-r \cdot L^2}{C_s \cdot D_e} \tag{13}$$

Where $\eta\phi^2$ = observable modulus

r = reaction rate (mol/L-s)

L = characteristic length of the catalyst (m), ($d_p/6$)

[63] Weiss, P. B.; Prater, C. D. *Adv. Catal.* **1954**, *6*, 143.

C_s = species surface concentration (mol/L)

D_e = effective diffusivity (m^2/s), $D_e = \varepsilon^2 D_a$

ε = support porosity (0.6 for the catalyst used)

The observable modulus is the ratio of the observed reaction rate to the effective rate of diffusion in the catalyst particle. If the observable modulus is much less than 1, mass transport rate within the catalyst is greater than the reaction rate, and conversion rate is not mass transport limited.

4.1.7 Results from mass transfer calculations

Table 5 summarizes calculated values for the calculated maximum mass transfer rates, observed reaction rates, and maximum observed modulus for three different experiments. The mass transfer rate of each experiment was compared to the observed maximum reaction rate to determine if the rate of conversion was limited by mass transport. It was found that in no case in the study was the rate of conversion limited by mass transport through the film layers.

In all reactions performed using alanine, the observable modulus for both alanine and hydrogen was less than 1, and thus the conversion rates were not reaction rate limited. In this study, the observable modulus was usually on the order of 10^{-5}, and thus not diffusion limited within the catalyst.

Equation	Rate (fluid basis)	90°C	100°C	150°C
Bern, maximum g-l mass transfer rate of hydrogen	$k_L a_B C_{H2}$, (kmol/m^{3}s)	1.03×10^{-2}	1.03×10^{-2}	1.03×10^{-2}
Yagi and Yoshida, maximum g-l mass transfer rate hydrogen	$k_L a_B C_{H2}$, (kmol/m^{3}s)	1.77×10^{-2}	2.01×10^{-2}	3.5×10^{-2}
Boon-Long, maximum s-l mass transfer rate of hydrogen	$k_L a_B C_{H2S}$ (kmol/m^{3}s)	6.23×10^{-3}	7.05×10^{-3}	1.36×10^{-2}
Boon-Long, maximum s-l mass transfer rate of alanine	$k_L a_B C_{AS}$ (kmol/m^{3}s)	3.32×10^{-3}	3.63×10^{-3}	5.22×10^{-3}
Observed maximum reaction rate of alanine	R_A max (kmol/m^{3}s)	1.32×10^{-5}	3.01×10^{-5}	1.81×10^{-4}
Observed maximum reaction rate of hydrogen	R_H max (kmol/m^{3}s)	6.6×10^{-6}	1.5×10^{-5}	9.05×10^{-5}
$\eta\phi^2$, observed modulus for hydrogen		1.82×10^{-6}	3.54×10^{-6}	9.59×10^{-6}
$\eta\phi^2$, observed modulus for alanine		1.05×10^{-5}	2.09×10^{-5}	7.30×10^{-5}

Table 5. Summary of mass transfer calculations. Reactions performed with 0.22 M alanine in 100 grams 0.29 M phosphoric acid solution with 1 g 5% Ru/C catalyst under 1000 psi H_2.

4.1.8 Limiting reactant

In any reaction system, either of the reactants may limit the reaction rate, either by stoichiometry, if no mass transfer limitations occur, or by mass transfer limitations.

The ratio of the observable moduli for hydrogen and alanine identifies the limiting reactant as shown in equation 14.

$$\gamma = \frac{\left(\eta\varphi^2\right)_{H_2}}{\left(\eta\varphi^2\right)_A} = \frac{-R_{G,H_2} L^2 / C_{s,H_2} D_{e,a}}{-b \cdot R_{G,A} L^2 / C_{s,A} D_{e,a}} = \frac{C_{s,A} D_{e,A}}{b C_{s,H_2} D_{e,H_2}} \qquad (14)$$

In this case b is the stoichiometric coefficient of hydrogen, two in this case. The calculated ratio in every experiment was greater than 1, so hydrogen was the limiting reactant. This finding does not mean the reaction was mass transfer limited in hydrogen; it only serves to give a relative importance to the rates of transport within the catalyst particles.

4.2 Langmuir—Hinshelwood Model Development

Catalytic reactions proceed through a series of steps at the catalyst surface called the reaction mechanism. This series of steps serves as the basis for development of the mathematical description of the reaction kinetics, called the rate expression. Development of a kinetic model and rate expression is important because it sheds insight into the mechanism of the reaction and allows for the planning and development of industrial reactors.

In this section the proposed reaction mechanism, rate expression, and kinetic parameters that describe alanine hydrogenation are presented.

A Langmuir-Hinshelwood model was employed which includes protonated alanine (—COOH) and phosphoric acid (H_3PO_4 form) competing for one type of site and hydrogen dissociatively adsorbing on another type of site on the catalyst surface. This proposed model was supported by the following experimental evidence and literature references.

Experiments with less than a stoichiometric amount of phosphoric acid halt before alanine was completely consumed, as shown in Figure 4 and Table 3.

This effect was explained by the solution behavior of alanine, as discussed in Section 3.1. In developing this model, therefore, only protonated alanine was included in the surface reaction step, which makes the rate expression a function of protonated alanine.

The proposal that alanine and phosphoric acid compete for sites was supported by the observation that reaction rate decreased as phosphoric acid concentration was increased above a stoichiometric amount, as shown in Figure 5. Without phosphoric acid competing with alanine for sites, the reaction rate should increase due to a higher concentration of protonated alanine by further shifting the acid-base equilibria toward the protonated carboxylic acid form. Alternatively, this reduction in rate could be an effect of decreased hydrogen solubility. However, the observed decrease in conversion rate at higher acid concentration is only partially accounted for by reduced hydrogen solubility.

Finally, modeling hydrogen as dissociated on metal surfaces is widely accepted in the literature[64] and recently the Neurock group[65] published computational results on the hydrogenation of acetic acid over palladium which suggests that hydrogen and acetic acid adsorb on different sites. Therefore, hydrogen was modeled as dissociatively adsorbed and occupying different sites than alanine.

With this evidence, the following reaction mechanism was proposed.

1. $A^+ + S_1 = A^+ \cdot S_1$ (fast)
2. $P + S_1 = P \cdot S_1$ (fast)

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[64] Singh, U. K.; Vannice, M.A. *Applied Catalysis A: General* **2001**, *213*, 1.
[65] Pallassana, V., Neurock, M. *J. Catal.* **2002**, *209*, 289.

3. $H_2 + 2\ S_2 = 2H{\cdot}S_2$ (fast)
4. $2H{\cdot}S_2 + A^{+}{\cdot}S_1 \rightarrow A_1^{+}{\cdot}S_1 + 2\ S_2$ (slow)
5. $2H{\cdot}S_2 + A_1^{+}{\cdot}S_1 \rightarrow AlOl^{+}{\cdot}S_1 + 2\ S_2$ (fast)
6. $AlOl^{+}{\cdot}S_1 = AlOl^{+} + S_1$ (fast)

Where A^{+} is protonated alanine, P is phosphoric acid in H_3PO_4 form, H_2 is molecular hydrogen, H is atomic hydrogen, S_1 is a site occupied by alanine (—COOH form) or phosphoric acid (H_3PO_4 form), S_2 is a site that is occupied by hydrogen, and $AlOl^{+}$ is protonated alaninol.

These fundamental steps yield the following rate expression.

$$-r_A = k_s \frac{K_{A+}C_{A+}C_{S1}}{\left(1 + K_{A+}C_{A+} + K_P C_P\right)} \frac{K_{H_2}C_{H_2}C_{S2}}{\left(1 + \sqrt{K_{H_2}C_{H_2}}\right)^2} \qquad (15)$$

Where r_A is the reaction rate of alanine, k_s is the surface reaction rate coefficient, C_{A+} is protonated alanine concentration, K_{A+} is the protonated alanine adsorption equilibrium constant (—COOH), C_P is non-dissociated phosphoric acid (H_3PO_4) concentration, K_P is the phosphoric acid adsorption equilibrium constant (H_3PO_4), C_{S1} is the concentration of sites on which both protonated alanine and phosphoric adsorb competitively, C_{H2} is hydrogen concentration in solution, K_{H2} is the hydrogen adsorption equilibrium constant, and C_{S2} is the site concentration on which hydrogen dissociatively adsorbs.

Several other variations of this model were tested including alternative species adsorption, such as alanine and phosphoric acid adsorbed in all forms.

In these cases, the kinetic parameters determined using the search method described in Section 4.4 did not describe the experimental data as well as the proposed expression.

4.3 Solution charge balance

The proposed rate expression is a function of ionic species concentrations. However, analytical methods measure the overall concentration of the material, not individual ionic species. The ionic concentrations are calculated values derived from the overall concentration of all the species in solution. These concentrations were determined by way of a solution of charge balance, where the net charge of the solution is zero. The system of equations used to determine the ionic species concentrations from overall species concentrations is described in this section.

To estimate the concentration of ionic species in solution for modeling purposes, the overall charge balance for this system is expressed as follows:

$$0 = H^+ + A^+ + AlolH^+ + OH^- - A^- - P^- - 2P^{2-} - 3P^{3-} \qquad (16)$$

where H^+ is the hydronium cation, A^+ is protonated alanine, $AlolH^+$ is protonated alaninol, OH^- is the hydroxide ion, A^- is deprotonated alanine, P^- is $H_2PO_4^-$, P^{2-} is HPO_4^{2-}, and P^{3-} is PO_4^{3-}.

In this equation there are eight unknowns, therefore seven additional equations must be defined for the system. For modeling purposes, side product species were dropped from the overall charge balance and all alanine converted was assumed to form alaninol. This assumption was made because the rate of

formation of these species cannot be predicted as functions of reactant and product concentrations or from reaction conditions. This assumption will not lead to appreciable error because of the high selectivities observed and the similar pK_a values of the side products with alaninol.

First in aqueous solution, the product of $[H^+][OH^-] = 10^{-14}$. Therefore, OH^- may be written as:

$$OH^- = \frac{10^{-14}}{H^+} \tag{17}$$

Alaninol accepts only one proton and rearrangement of the Henderson-Hasselbach equation yields the general equation:

$$C_{AlolT}^{+} = \frac{C_{AlolT} H^+}{K_{Alol} + H^+} \tag{18}$$

Where C_{Alol+} is the ionic concentration of alaninol, C_{AlolT} is the total concentration of alaninol, and K_{Alol} is the acidity constant of alaninol.

Alanine and phosphoric acid exist in three and four ionic states respectively. The three states of alanine are represented by the following system of equations:

$$A_T = A^+ + A + A^- \tag{19}$$

$$K_{A1} = \frac{[H^+][A]}{[A^+]} \tag{20}$$

$$K_{A2} = \frac{[H^+][A^-]}{[A]} \tag{21}$$

The first equation is an overall balance including each of the three ionic forms of alanine in solution where A_T is total alanine concentration, A^+ is protonated alanine, A is zwitterionic alanine, and A^- is deprotonated alanine. The second and third equations are equilibrium equations, where K_{A1} and K_{A2} are the first and second acidity constants of alanine. Solving for each of the three ionic species as functions of total concentration yields the following system of equations:

$$A^+ = \frac{A_T}{1 + \frac{K_{A1}}{H^+} + \frac{K_{A1}K_{A2}}{(H^+)^2}} \tag{22}$$

$$A = \frac{A_T}{1 + \frac{H^+}{K_{A1}} + \frac{K_{A2}}{H^+}} \tag{23}$$

$$A^- = \frac{A_T}{1 + \frac{(H^+)^2}{K_{A1}K_{A2}} + \frac{H^+}{K_{A2}}} \tag{24}$$

Similarly, the ionic states of phosphoric acid are represented by the following system of equations:

$$P = \frac{P_T}{1 + \frac{K_{P1}}{H^+} + \frac{K_{P1}K_{P2}}{(H^+)^2} + \frac{K_{P1}K_{P2}K_{P3}}{(H^+)^3}} \tag{25}$$

$$P^- = \frac{P_T}{1 + \frac{H^+}{K_{P1}} + \frac{K_{P2}}{H^+} + \frac{K_{P2}K_{P3}}{(H^+)^2}} \tag{26}$$

$$P^{2-} = \frac{P_T}{1 + \frac{K_{P3}}{H^+} + \frac{H^+}{K_{P2}} + \frac{(H^+)^2}{K_{P1}K_{P2}}} \quad (27)$$

$$P^{3-} = \frac{P_T}{1 + \frac{H^+}{K_{P3}} + \frac{(H^+)^2}{K_{P2}K_{P3}} + \frac{(H^+)^3}{K_{P1}K_{P2}K_{P3}}} \quad (28)$$

where P_T is the total phosphoric acid concentration, P is H_3PO_4, P^- is $H_2PO_4^-$, P^{2-} is HPO_4^{2-}, P^{3-} is PO_4^{3-}, and K_{P1}, K_{P2}, K_{P3}, are the three acidity constants of phosphoric acid.

There is now a system of eight equations and eight unknowns. Because of the highly non-linear nature of the charge balance, an analytical solution for H^+ is not possible. Therefore, H^+ concentration is calculated using Solver in Microsoft Excel 7.0 by varying H^+ until the charge balance equals zero. Since all other species concentrations are defined as functions of H^+ only, determining the value of H^+ simultaneously specifies all other ionic species concentrations.

4.4 Determination of Kinetic Parameters

The matrix of conditions used to determine kinetic model parameters was derived from 20 experiments for a total of 109 data points. The operating conditions of the experiments used in parameter determination are shown in Table 6.

Experiment	Alanine (M)	H_2 solubilty (M)	Phosphoric acid (M)	Temperature (K)	Pressure (psi)
1	0.226	0.053	0.289	373	1000
2	0.231	0.053	0.591	373	1000
3	0.236	0.053	1.198	373	1000
4	0.468	0.053	0.595	373	1000
5	0.226	0.062	0.289	398	1000
6	0.226	0.056	0.289	383	1000
7	0.226	0.051	0.288	363	1000
8	0.227	0.056	0.289	383	1000
9	0.226	0.122	0.292	398	1800
10	0.227	0.026	0.288	398	500
11	0.226	0.011	0.288	398	250
12	0.226	0.011	0.288	373	250
13	0.226	0.004	0.291	373	100
14	0.227	0.004	0.287	398	100
15	0.227	0.053	0.197	373	1000
16	0.228	0.053	0.147	373	1000
17	0.226	0.053	0.074	373	1000
18	0.227	0.026	0.288	373	500
19	0.226	0.139	0.289	373	2000
20	0.227	0.091	0.289	373	1500

Table 6. Conditions matrix used for parameter determination

The proposed kinetic model has eight parameters: four pre-exponential rate constant factors (k_s, K_{A+}, K_{H2}, and K_P) and four activation energies (E_a, ΔH_{A+}, ΔH_P, and ΔH_{H2}). The parameter values are selected to predict the concentration of alanine versus time such that the sum of the squared differences between experimental alanine concentration and predicted data was minimized, as described by equation 29.

$$SS = \sum \left(C_{A_{experimental}} - C_{A_{predicted}} \right)^2 \qquad (29)$$

Where $C_{A_{experimental}}$ are experimental alanine concentration data points and $C_{A_{predicted}}$ are predicted alanine concentrations.

The reaction trajectories are predicted by a modification to the 4th order Runge-Kutta numerical method which estimates conversion over a series of

small time steps (100 over 6 hours for these studies) using a macro created in Microsoft Visual Basic for Excel. A more detailed description of the program created for parameter determination may be found in Appendix B.

To initialize the calculation, the charge balance is satisfied at the initial conditions using the Excel Solver add-in. The first time step is taken which predicts the change in alanine concentration. Because of the change in alanine concentration and formation of alaninol, the charge balance must again be satisfied by using Solver before the next time step is taken. This sequence is followed over all time steps.

A random walk technique was used to determine the set of parameters that minimize the sum of square differences between experimental and predicted data. For each step in the minimization, one of the eight parameters was selected randomly, then randomly increased or decreased by a specified percent. The reaction trajectory for each of the 20 reactions was then predicted using this new set of parameters. If this parameter change results in a decrease in the sum of squares, the new value of the parameter was retained; if not, the initial value was restored. The random walk was continued until no decrease in error was observed over 83 cycles. Employing standard statistical methods, 83 cycles was determined to give 95% probability that each parameter has been both increased and decreased at least once.

The fitted constants are given in Table 7. The estimated heats of adsorption for protonated alanine, phosphoric acid, and hydrogen are 81, 111, and 69 kJ/mol, respectively, which are reasonable for adsorbed species. The

activation energy for the surface reaction rate constant, k_s, is determined from the composite L-H rate constant $k_1 = k_s C_{t1} C_{t2}$, and was equal to 82 kJ/mol, also a reasonable value.

Rate or equilibrium constant	Value at 373 K	Activation energy (kJ/mol)
k_1(kmol/kg of cat/s)	3.455×10^{-6}	81.54
K_{A+}(m^3/kmol)	190.62	80.93
K_P(m^3/kmol)	40.31	110.76
K_{H2}(m^3/kmol)	101.80	68.78

Table 7. Rate Constants for L–H Rate Expression

Comparisons of predicted and experimental conversion data versus time for several sets of conditions are found in Figures 12 to 15. Over the wide range of conditions from the 109 points used in 20 chosen experiments, the average error between the experimental data points and the model prediction was 8%.

Figure 12 compares experimental and predicted conversion versus time data for experiments that vary in temperature from 90°C to 125°C at 1000 psi H_2 with 0.29 M phosphoric acid. Figure 13 compares experimental versus predicted conversion versus time data for experiments that vary in pressure from 250 to 1800 psi H_2 at 125°C with 0.29 M phosphoric acid. Figures 14 and 15 compare the reactions performed with excess and deficiency of acid. In Figure 14, the data show conversion rate decreasing with an increase in phosphoric acid concentration; this trend was accounted for by including phosphate as an adsorbed species in the rate expression. Figure 15 shows the effect of acid deficiency on alanine conversion. The model predicts this near stoppage in

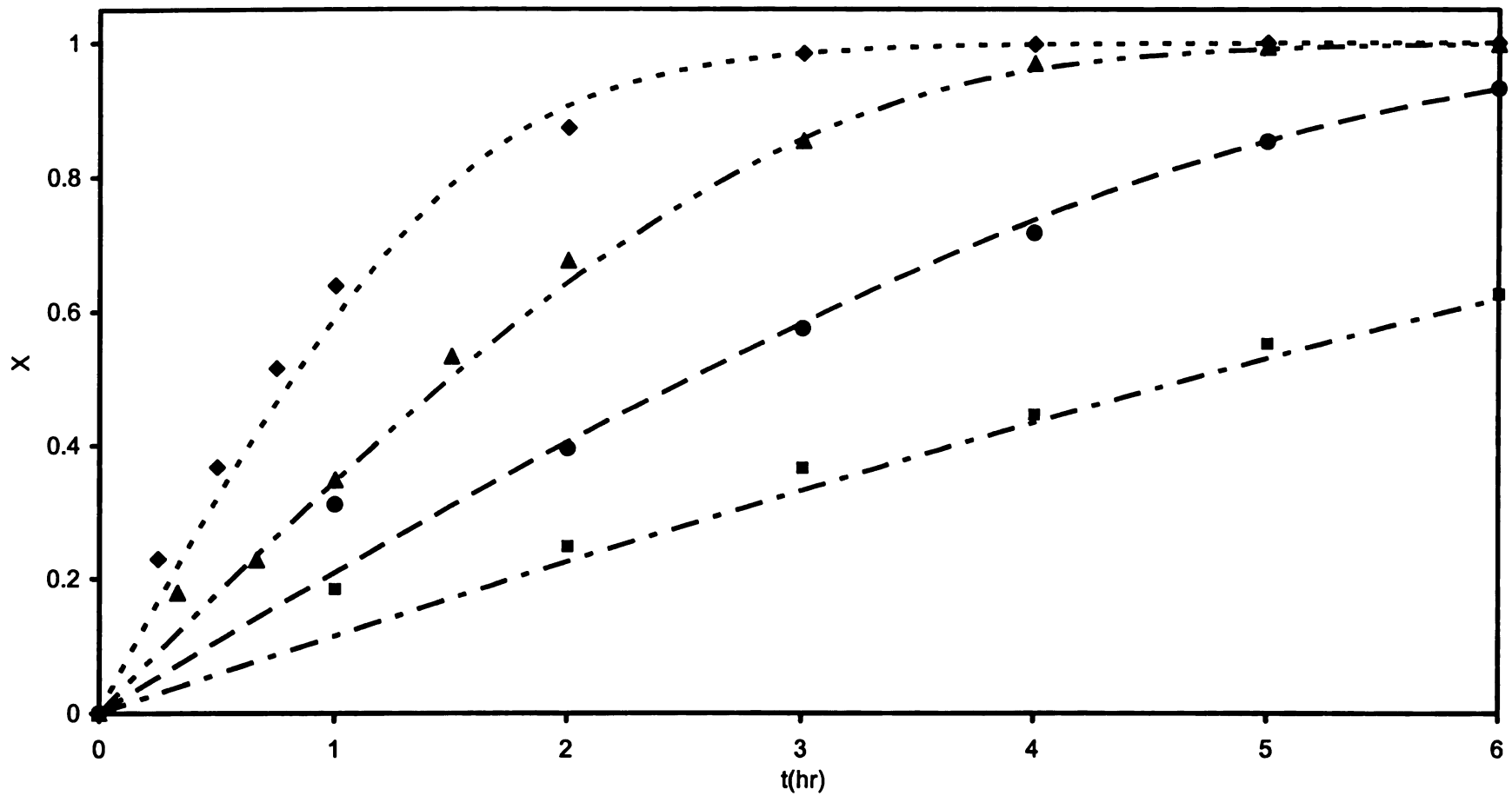

Figure 12. Experimental versus predicted alanine conversion rate at various temperatures. Reactions performed under 1000 psi H_2, with 0.29 M phosphoric acid and 0.22 M alanine. (♦)—Experimental Data, 125°C; (- - - -), Model Prediction, 125°C; (▲)—Experimental Data, 110°C; (- - — - -)—Model Prediction, 110°C; (●)—Experimental Data, 100°C; (— — —)—Model Prediction, 100°C; (■)—Experimental Data, 90°C; (— - — -), Model Prediction, 90°C.

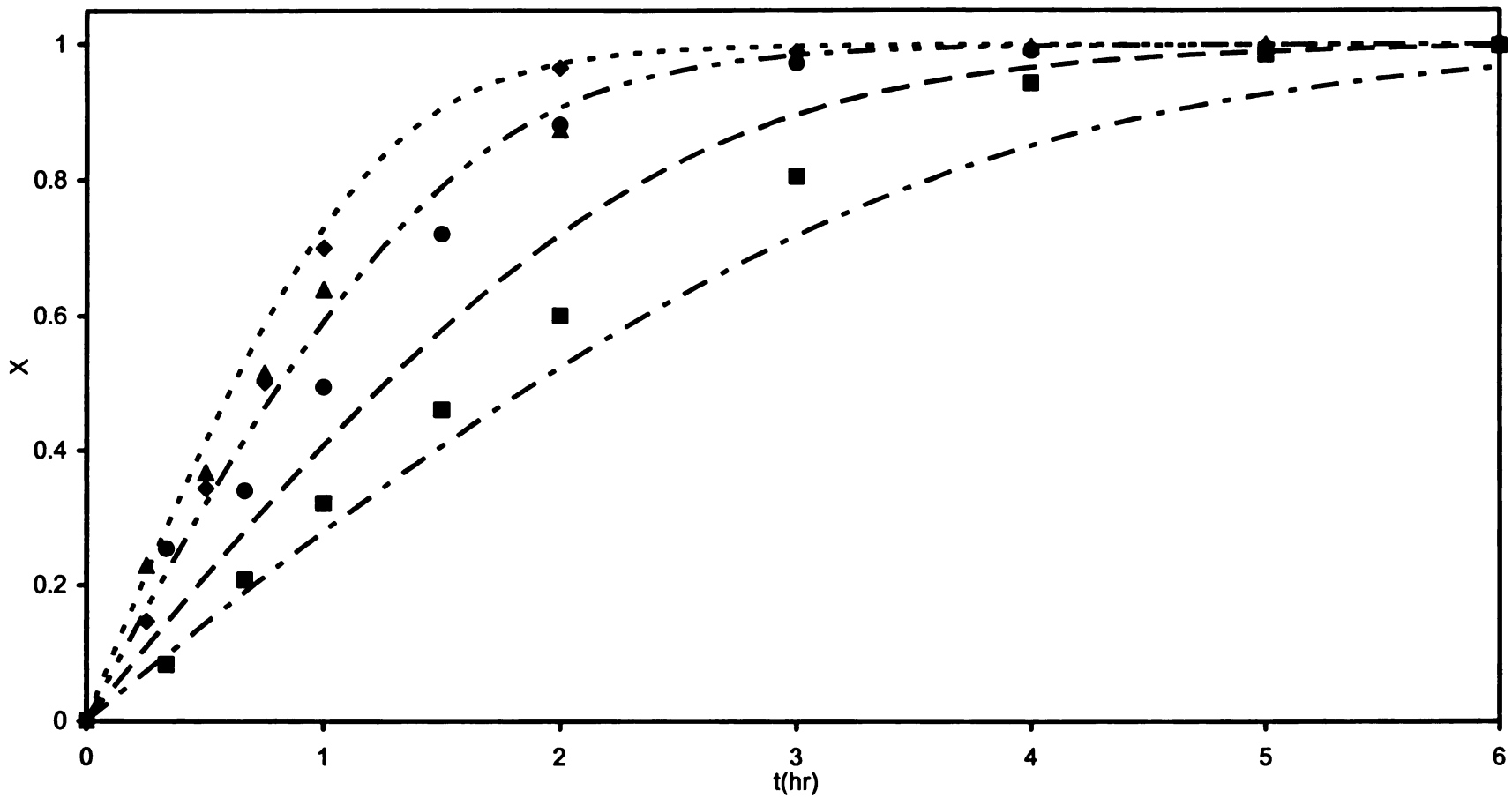

Figure 13. Predicted versus experimental alanine conversion rate with varying hydrogen pressure. Reactions performed at 125°C, with 0.29 M phosphoric acid and 0.22 M alanine. (♦)—Experimental Data, 1800 psi, (- - - -)—Model Prediction, 1800 psi; (▲)—Experimental Data, 1000 psi; (- - — - -)—Model Prediction, 1000 psi; (●)—Experimental Data, 500 psi, (— — —)—Model Prediction, 500 psi; (■)—Experimental Data, 250 psi; (— - — -)—Model Prediction 250 psi.

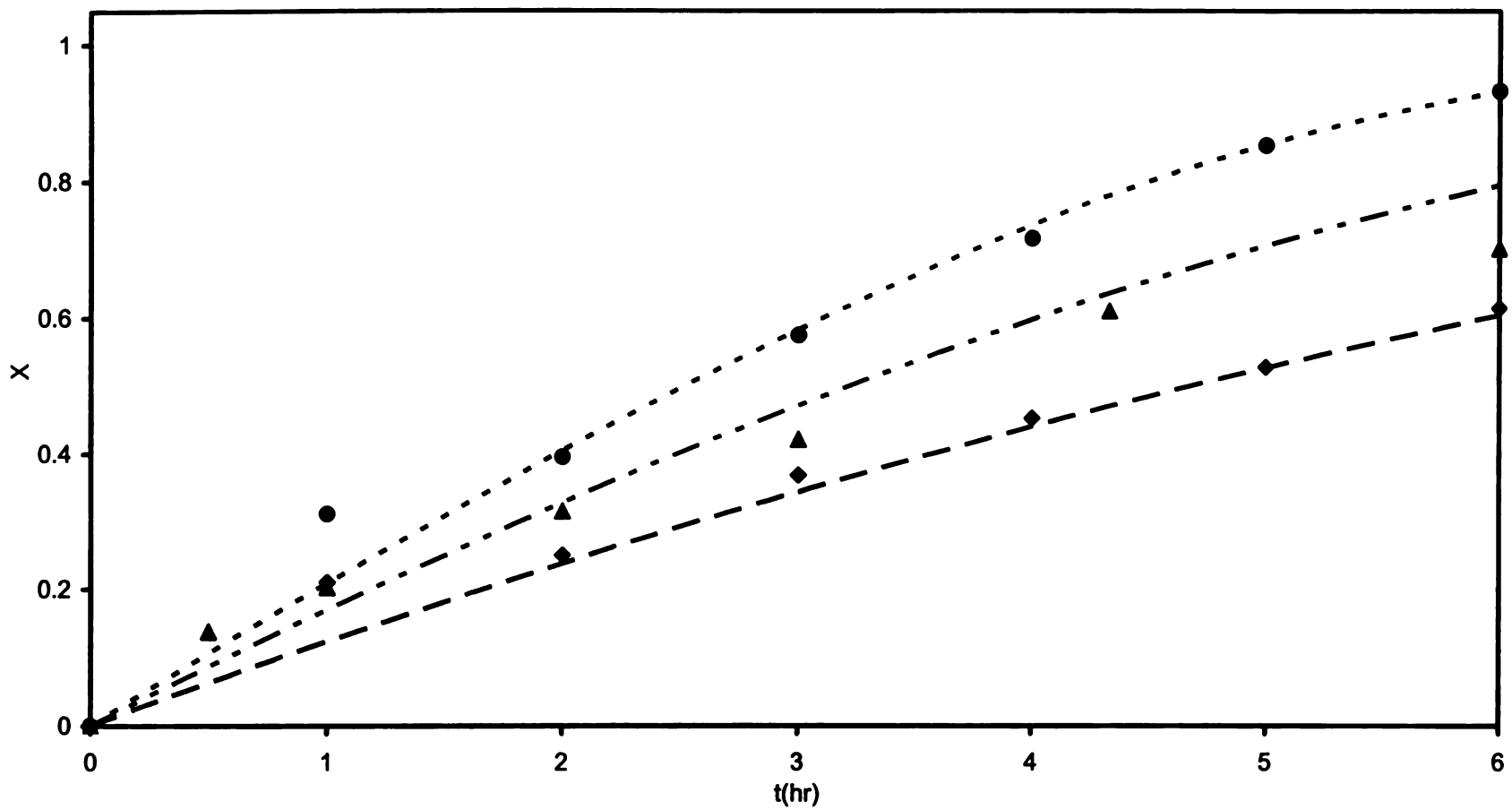

Figure 14. Experimental versus predicted alanine conversion rate with an excess of phosphoric acid. Reactions performed at 100°C, under 1000 psi H_2 and 0.22 M alanine. (♦)—Experimental Data, 0.29 M phosphoric acid; (- - - -)—Model Prediction, 0.29 M phosphoric acid; (▲)—Experimental Data, 0.6 M phosphoric acid; (- - — - -)—Model Prediction, 0.6 M phosphoric acid; (●)—Experimental Data, 1.2 M phosphoric acid; (— — —)—Model Prediction, 1.2 M phosphoric acid.

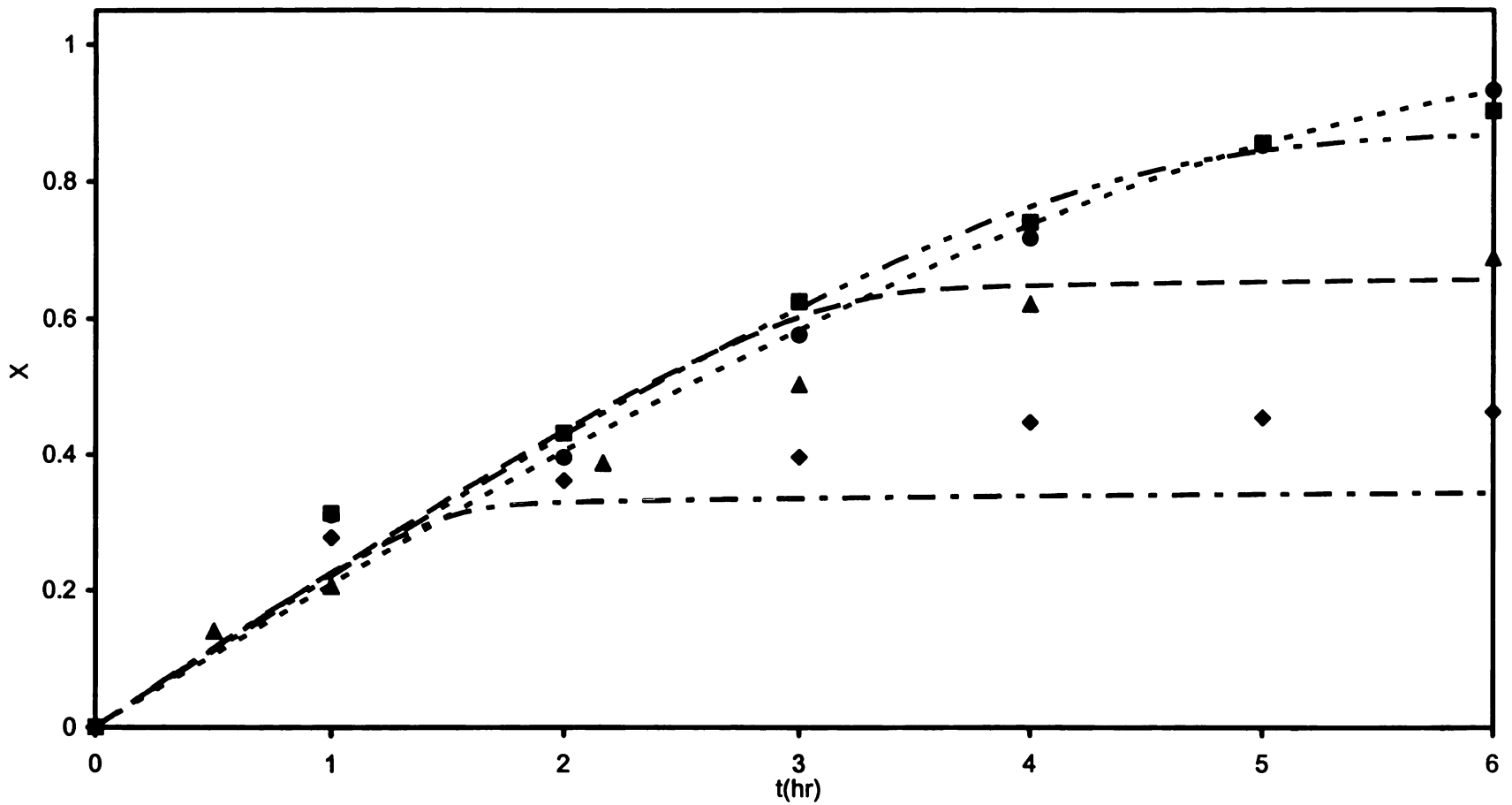

Figure 15. Experimental versus predicted alanine conversion rate with a deficiency of phosphoric acid. Reactions performed at 100°C, under 1000 psi H_2 and 0.22 M alanine. (●)—Experimental Data, 0.29 M phosphoric acid; (- - - -)—Model Prediction, 0.29 M phosphoric acid; (■)—Experimental Data, 0.19 M phosphoric acid; (- - — - -)—Model Prediction, 0.19 M phosphoric acid; (▲)—Experimental Data, 0.14 M phosphoric acid; (— — —)—Model Prediction, 0.14 M phosphoric acid; (♦)—Experimental Data, 0.07 M phosphoric acid; (— - — -)—Model Prediction, 0.07 M phosphoric acid.

alanine conversion at the point that phosphoric acid was consumed due to alaninol formation forcing the concentration of protonated alanine (—COOH form) to zero.

The model does not predict alanine conversion without phosphoric acid added. In experiments without phosphoric acid added to the solution an 8% yield of alaninol was observed in 6 hrs. As discussed in 3.2.2.1, this result was surprising because the pH of the 0.22 M alanine feed was 6.9. At this pH, nearly 100% of the alanine molecules in solution are in the zwitterionic form. Patents by Antons[46] also show limited conversion of alanine to alaninol in the presence of ruthenium oxides and Ru/C catalysts without the presence of acid.

4.5 Confidence intervals

Determining confidence intervals for highly non-linear models with large numbers of parameters, such as in this study, is difficult. Attempts were made to use the likelihood ratio and the approximate t-interval to determine confidence intervals for kinetic parameters. Preliminary investigation into confidence intervals for this model has yielded intervals greater than 100% of the optimal values. For this type of model, this is not to be unexpected as noted by the Belohlav group of Czechoslovakia,[66] who have worked extensively in parameter estimation for rate expression of catalytic hydrogenation systems. Since the calculated confidence intervals were so large, they are not meaningful and will not be presented.

[66] Belohlav, Z.; Zamostny, P.; Kluson, P.; Volf, J. *Can. J. Chem. Eng.* **1997**, *75*, 735.

Chapter 5. Deuterium incorporation

5.1 Deuterium incorporation in amino acid hydrogenation—mechanistic analysis

5.1.1 Methods

Deuterium incorporation studies were performed in the Parr batch reactor according to the procedures outlined in Section 2.1.2, with the exception that hydrogen and water were replaced with deuterium and deuterated water, respectively.

Proton (^1H) NMR spectra were recorded for each sample in the study. Since ^1H NMR is not active for deuterium, peaks in the spectra which correspond to specific sites on the molecule decrease as H is replaced with D, until the peak is completely absent when 100% replacement occurs. Acetic acid was added as an internal standard from which the concentration of H at each site of the molecules was calculated by evaluating the ratios of the acetic acid methyl peak with the other relevent peaks in the spectra. This was compared to the concentrations measured by HPLC to determine the extent of deuteration.

5.1.2 Results

Incorporation studies were performed with alanine and alaninol as feed materials in a range of temperatures from 100 to 150°C and 1000 psi D_2, with a general summary of results in Figure 16 and numerical details found in Table 8.

Hydrogenation of alanine at 100°C, as expected, added D at the C1 position of alaninol by hydrogenation. Complete incorporation of D was not observed at the C2 position of product alaninol indicating incorporation at C2 occurs separately from hydrogenation.

							% D Incorporation at each position				
Substrate	T (°C)	t (hr)	Acid (M)	Alanine Conv.	L-Alaninol Yield	Alaninol ee%	Alanine C2	Alanine C3	Alaninol C1	Alaninol C2	Alaninol C3
Alanine	100	1	0.27	18	18	>99.9	62	6	100	39	1
Alanine	100	6	0.27	84	78	99.7	100	2	100	89	0
Alanine	100	1	0	8	4	>99.9	92	0	100		0
Alanine	100	6	0	20	14	95.5	96	0	100	100	0
Alanine	150	1	0.26	98	84	95.3			100	100	25
Alanine	150	6	0.26	99.5	74	84.1			100	100	61
Alanine	150	1	0	34	14	79.3	80	31	100	100	23
Alanine	150	6	0	65	21	58.7	100	58	100	100	52
Alaninol	100	1	0.28			99.9			75	42	14
Alaninol	100	6	0.28			99.7			100	87	15
Alaninol	100	2	0			>99.9			100	100	0
Alaninol	100	6	0			99.8			100	100	0
Alaninol	150	1	0.29			95.7			100	100	30
Alaninol	150	6	0.29			80.7			100	100	65
Alaninol	150	1	0			91.5			100	100	7
Alaninol	150	6	0			60.5			100	100	32
[b]Alanine feeds 0.26 M; Alaninol feeds 0.22 M, under 1000 psi D_2; D-incorporation measured by ^1H NMR											

Table 8. Summary of Incorporation studies with alanine and alaninol

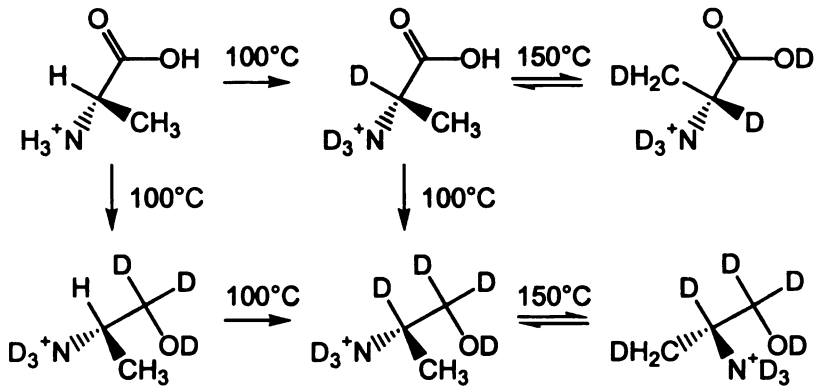

Figure 16. General incorporation scheme for amino acids

As temperature was increased, the rate of D incorporation into the C2 position of both alanine and alaninol increases. At 150°C, D incorporation also occurs at the C3 position of both alanine and alaninol. Simultaneously, racemization of product alaninol was observed. An attempt at making a mathematical or statistical correlation between the extent of racemization and D content at C3 has shown that racemization does not occur exclusively through the C2-C3 bond.

At 100°C D incorporation at C2 occurs without loss of optical purity for both alanine and alaninol. This result suggests that the catalyst facilitates deprotonation of the amino acid or alcohol to yield a surface-bound intermediate as shown in Figure 17. At 100°C, this species must uniformly undergo deuteration on the face from which the H loss occurred, thus retaining optical purity. Higher temperatures would then disrupt the surface binding, so that D incorporation can take place on the opposite face. At the same time, exchange at C3 becomes possible, presumably via tautomeric equilibration.

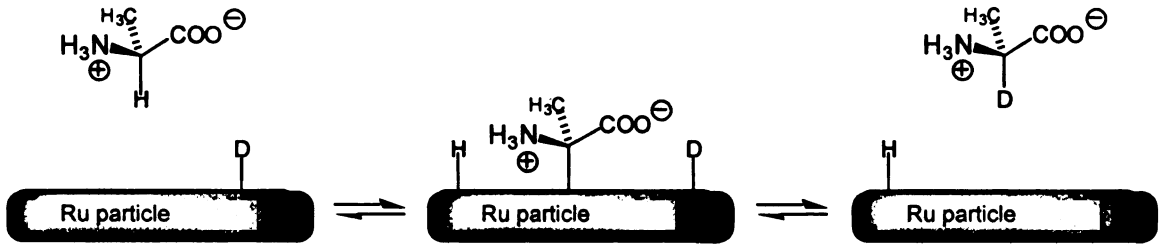

Figure 17. Alanine interaction with the catalyst in D_2/D_2O

5.2 Method for deuterium labeling

This discovery of stereoretentive C—H bond activation at amine bearing sp^3 C sites was the most unexpected finding in this work. Related catalytic H/D exchange processes have long been known, but they were typically run in organic solvents and typically there is little discussion of stereochemistry.[67] Such reactions are thought to form imine intermediates, enabling alkyl group transfers via transamination pathways.[68] Indeed, alkyl group exchanges via catalytic activation of amines has been explored as a process to convert primary to secondary and tertiary amines.[69] Only in recent years has the potential for functionalization via C—C bond formation at such sites begun to be exploited, enabling addition of alkyl or acyl groups at the C—H bond sites to amines.[70] In these reactions, however, the amines require attached 2-pyridyl groups, which serve as directing ligands for the transition metals effecting the C—H bond activation.[71,72,73]

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The chemical behavior that has emerged from our own studies of amino acid hydrogenation mirrors the above C—H bond reactivity, as evidenced by isotopic exchange, and with the added bonuses of complete retention of stereochemistry, simple aqueous-phase heterogeneous catalysis, and relatively mild, green conditions. This discovery has led us to actively pursue the possibility of stereo-controlled replacement of H with other functionalities under aqueous heterogeneous catalytic conditions.

5.2.1 Background on amino acid labeling

Deuterium labeled α-amino acids are widely used to probe biological structure and pathways.[74,75] Unfortunately, specific labeling by chemical synthesis typically leads to racemic materials. For biological studies, significant effort is then required to separate the enantiomeric forms or to differentiate their biological roles.

In 1977, Maeda, *et al.*,[76] described selective hydrogen-deuterium exchange of amino acids and aliphatic amines over platinum oxide. After 40 hours at 100°C, incorporation occurs throughout the molecule up to 40% of the maximum. The Zolorarev group in Russia has published several studies on the incorporation of deuterium into amino acids. In their US patent,[77] they describe a method in which a biologically active molecule, and a platinum group supported metal on an inorganic support may be used to deuterate the compound. Essentially, the compound of interest forms a complex with the metal-inorganic

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[75] Pearce, D. A., Hammershoi, A., Harrowfield, J. M., Sargeson, A. M. *Chem. Com.* **2000**, 2431.
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[77] Zolotarev, J. A.; Zaitsev, D. A.; Tatur, V. J.; Mysasoedov, N. F. U. S. Patent 5,026,909, **1991**.

carrier. The mixture is then exposed to low-pressure deuterium gas between 100-300°C. This process incorporates deuterium into several places in the molecule with yields of hydrogen replacement up to 90%. Killgore[78] studied labeling of amino acids by the hydrogenation of N=C double bonds. In this strategy, an α-(N-substituted azomethine)-substituted carboxylic acid equivalent is dissolved in a deuterated protic solvent and exposed to hydrogen and a metal catalyst, forming racemic labeled product. There are several examples using microorganisms[79,80,81] to make α-deuterated amino acids. While biological transformations maintain the stereochemistry, these processes are limited by which amino acid substrates may be used and their products are difficult to purify.

5.2.2 Deuteration method

Catalyst and reactor setup are the same as described in Section 2.1.2, with quantification methods specified in Section 5.1.1. Deuteration experiments were performed under H_2 (30-50 psi) or D_2 pressure (1000 psi) in a temperature range of 30 to 100°C. Deuterations were preferably carried out under 50 psi H_2 and 75°C in a 2 wt% amino acid D_2O solution with 1 g 5% Ru/C catalyst (dry basis). Deuterations were performed on alanine, cysteine (2-amino-mercaptopropanoic acid), proline (2-pyrrolindine carboxylic acid), lysine (2,6-diaminohexanoic acid), and phenylalanine (2-amino-3-phenylpropanoic acid). Samples were prepared by filtration followed by rotary evaporation.

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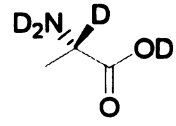
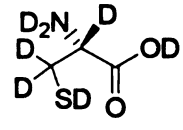
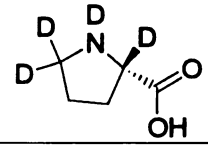
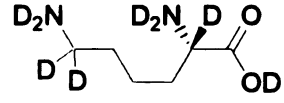
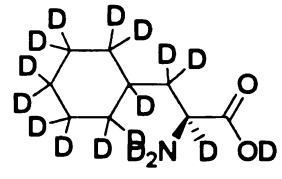
[78] Kilgore, J. L.; U.S. Patent 5,254,730, 1993.
[79] Lim, Young-Hee, Yoshimura, T., Soda, K., and Esaki, N. *J. Ferment. Bioeng.* **1998**, *86*(4), 400.
[80] Feeney, J., Birdsall, B., Ostler, G., Carr., M. D., and Kairi, M. *Febs. Letters* **1990**, *272*(1,2), 197.
[81] Mitulovi, G., Lammerhofer, M., Maier, N. M., Lindner, W., *J. Labelled Cpd. Radiopharm.*, **2000**, *43*, 449.

5.2.3 Deuteration results

Alanine undergoes stereorentive D incorporation at C2 at pressures as low as 30 psi H_2 and a temperature range of 50-100°C in deuterated water without acid added. The combination of low temperature and pressure, and absence of acid, ensured that no hydrogenation of the carboxylic acid functionality occured. The D_2O served as the deuterium source because H/D exchange takes place readily between H_2 and D_2O in the presence of catalyst and the ratio of H_2 to D_2O was small (less than 0.5%). Unfortunately this method was not specific to the C2 site. Deuteration also occurred at sites adjacent to electron withdrawing groups, as summarized in Table 9. In proline, incorporation occurred on both carbons adjacent to the nitrogen in the pyrroline ring. In cysteine, incorporation occurred at the C3 position, adjacent to the mercapto group. In lysine, deuteration occured at the C2 and C6 position, both adjacent to amine groups. Phenylalanine has proved to be especially reactive with ruthenium catalyst, with the ring undergoing rapid reduction and D-incorporation occuring at all available sites.

The low pressure conditions make this transformation easily performed in chemical laboratories equipped with standard equipment.

Table 9. Deuterium labeling summary

Amino acid	Observed structure	Comments
L-alanine		Complete incorporation at C2 in 6 hours at 75°C and 50 psi H_2
Cysteine		Greater than 80% incorporation at C2 and C3 in 6 hours at 75°C and 50 psi H_2
Proline		Complete incorporation at C's adjacent to N in 6 hours at 75°C and 50 psi H_2
Lysine		Greater than 75% incorporation at C2 and C6 at 6 hours at 75°C and 50 psi H_2
Phenylalanine		Incorporation at all positions at conditions and ring saturation at conditions as mild as 30°C and 30 psi H_2

Chapter 6. Amino acid hydrogenation economic analysis

6.1 Purpose of economic study

The purpose of this chapter is to compare the raw material costs of alaninol production from alanine via hydrogenation and borohydride reduction. This analysis is based on a particular production rate and estimates the cost of each raw material per pound of alaninol produced. A general process diagram and process description is included for each process.

6.2 Production rate

In each case, reactions are carried out in a batch reactor and will produce 1000 lbs of alaninol per batch from 1200 lbs of alanine assuming 100% conversion and selectivity. This process will operate 22 times per month. At this production rate, 158 tons of alanine will be consumed per year to produce 132 tons of alaninol. As shown in Table 1, the worldwide production alanine is 1,200 tons per year with a price that ranges from 12-29 $/kg (5.50-13.00 $/lb). Therefore, the cost of alanine per lb of alaninol produced is $5.50-13.00. At the lower end of the estimate, the purchase price of alanine per year would be ~$1.7 MM/yr. However, if alanine is produced on-site the actual cost would be much lower.

6.3 Alaninol production via hydrogenation

6.3.1 Hydrogenation process description

A general process diagram is shown in Figure 18. Alanine is produced on-site via fermentation and is sufficiently purified to be suitable for hydrogenation. The purified alanine is dissolved in a solution of water and

inorganic acid and fed to a reactor containing Ru/C catalyst. The reactor will operate under hydrogen pressure at 1000 psi H_2 and 100°C. At the conclusion of the reaction, the reactor is drained and the contents fed to a centrifuge to remove the catalyst. The inorganic acid is then neutralized using a strong base. Water is then removed from the product by evaporation.

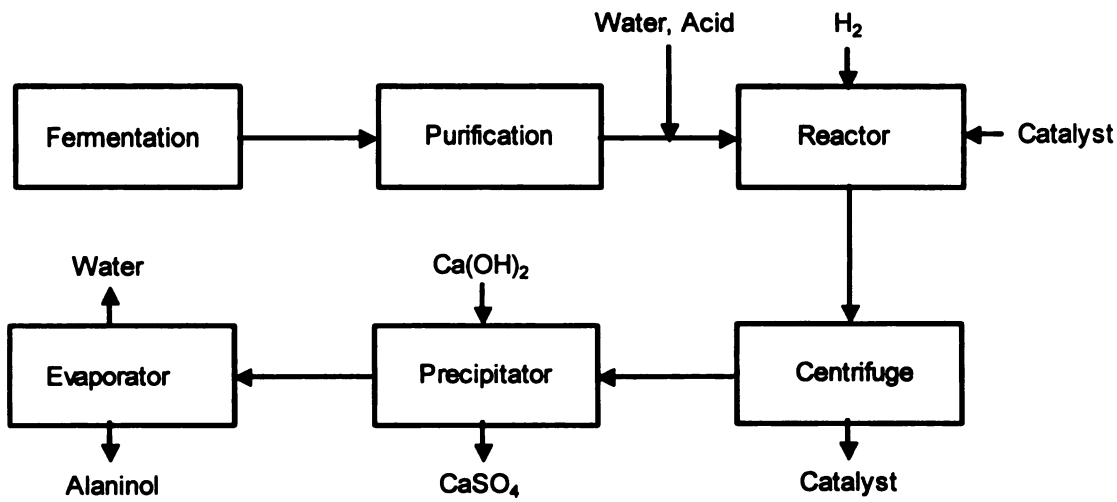


Figure 18. Hydrogenation process diagram

6.3.2 Materials costs for hydrogenation

For this process material costs include alanine, hydrogen, catalyst, sulfuric acid, and calcium hydroxide. The costs are calculated based on 1200 lbs of alanine per batch with 22 batches performed per month. This corresponds to a 1000 lbs and 132 tons of alaninol produced per batch and year respectively. Costs are presented as per pound of product formed.

Sulfuric acid: The most economical inorganic acid suitable for this process is sulfuric acid. Because of the strong acidity of both protons in sulfuric acid only a ½ molar equivalent is added to the reactor relative to alanine. This

corresponds to 660 lbs/batch of sulfuric acid. At $80/ton, the cost of sulfuric acid per pound alaninol product 2.6 ¢/lb and the plant would require 87 tons/yr of sulfuric acid. Another advantage is the ease with which sulfuric acid is neutralized with calcium hydroxide to form calcium sulfate. Calcium hydroxide is an inexpensive reagent and the cost incurred is less than 1 ¢/lb of alaninol produced.

Hydrogen: Alanine hydrogen requires 2 moles of hydrogen per mole of alanine reacted. A hydrogen price of $1.00/lb is used as a rule of thumb for engineering economic estimates. This corresponds to a cost of $27/batch and 5 ¢/lb alaninol formed.

Catalyst: Ruthenium on carbon catalyst is used for hydrogenation. Estimating the cost of catalyst is based on the following criteria: the reactant to catalyst ratio is 10:1, which corresponds to 120 lbs catalyst per batch, purchase price of fresh catalyst is $50/kg, and ruthenium metal is recovered making the effective price of the catalyst 1/3rd the fresh cost. The number of times that catalyst may be reused without significant loss in activity is unknown. However, estimates for catalyst use based on 1, 4, and 10 times use correspond to a cost of 91, 31, and 9 ¢/lb alaninol formed.

Using this simple economic analysis, the raw material costs are on the order of $0.17-0.99/lb of product produced excluding alanine cost.

6.4 Alaninol production via borohydride reduction

A process for reduction is shown in Figure 19. The process is derived from a borohydride reduction found in the literature.[27] This process was chosen

because of the use of relatively inexpensive reagents, no need for intermediate esterification, and safety considerations.

6.4.1 Reduction process description

Alanine is produced on-site via fermentation and is sufficiently purified to be suitable for hydrogenation. The purified alanine is dissolved in a solution of THF and sodium borohydride. Sulfuric acid is slowly added to the reaction mixture until the reaction reaches completion. The reactor is drained and the solvent removed by evaporation. Water is then removed from the product by evaporation.

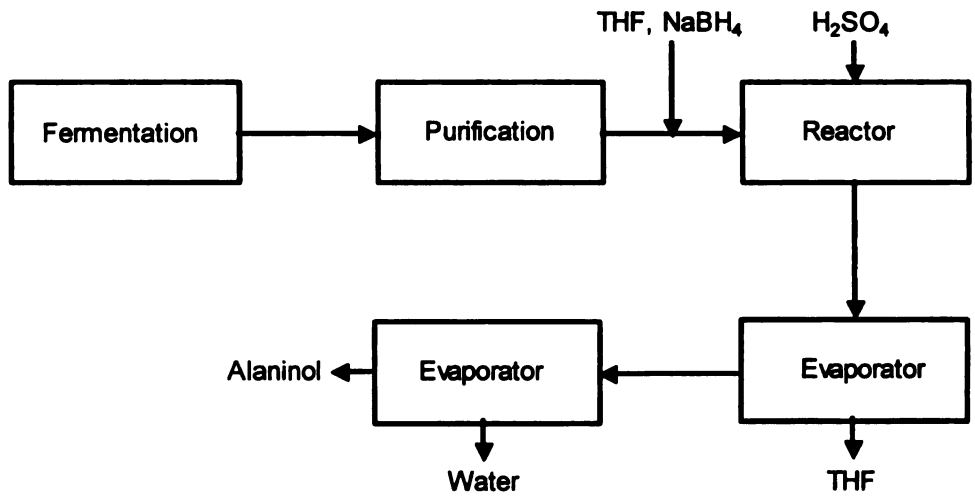


Figure 19. Reduction process diagram

6.4.2 Materials cost for reduction

Under reduction conditions raw material costs are derived from sodium borohydride, sulfuric acid, and solvents.

Sodium Borohydride: The ratio of sodium borohydride to alanine fed is 2.5:1, which corresponds to 1280 lbs/batch. At a cost of $846/ton, the cost of borohydride is $0.54/lb product.

Sulfuric acid: The ratio sulfuric acid to alanine is 1.25:1. This corresponds to 1652 lbs/batch. At a price of $80/ton, the cost per pound of product is $0.07.

THF: The other cost significant cost is solvent. THF is the preferred solvent for this reaction and has a selling price of $1.55/lb. For estimation purposes, 6000 lbs/batch of THF will be used to make a total batch mass of 10,000 lbs/batch. If an efficient recovery system is made for THF and 95% is recovered, a solvent cost of 39 ¢/lb product is incurred. If the percent of THF recycled per batch falls to 75 and 50%, the cost of solvent increases to 1.94 and 3.87 $/lb of product, respectively.

According to the estimates above the material costs for borohydride reduction is $1.00-4.48/lb alaninol product.

6.5 Economics conclusion

As shown above, on a raw materials cost basis, amino alcohol production via hydrogenation is competitive with the more often used reduction route. Hydrogenation offers a "greener" route by the use of heterogeneous catalysts and water as a solvent. The cost of raw materials for reduction is highly dependent on solvent recycle and thus the material costs may vary widely.

Table 10. Summary of economic evaluation

Alanine use and alaninol production

Alanine			Alaninol	
1200	lbs/batch	→	998	lbs/batch
316800	lbs/year		263407	lbs/year
158.4	tons/yr		132	tons/yr
12	$/kg-low end			
5.45	$/lb-low end			
29	$/kg-high end			
13.18	$/lb-high end			
1728000	$/yr-low end			
4176000	$/yr-high end			

Hydrogenation Raw Materials

Sulfuric Acid		Hydrogen		Ca(OH)2		Catalyst		
80	$/ton	1	$/lb	10	$/ton	7.58	$/lb	
660	lbs/batch	27	lbs/batch	498	lbs/batch	120	lb/batch	
174240	lbs/year	13052	lbs/yr	131569	lbs/yr	31680	lb/year	
6970	$/yr	13052	$/yr	658	$/yr	240000	$/year	
0.03	$/lb product	0.05	$/lb product	0.002	$/lb product	0.91	$/lb product	1 reaction
						0.23	$/lb product	4 reactions
						0.09	$/lb product	10 reactions

Total Raw Materials		
0.99	$/lb product	1 time catalyst use
0.31	$/lb product	4 time catalyst use
0.17	$/lb product	10 time catalyst use

Reduction Raw Materials

Sodium Borohydride		Sulfuric Acid		THF		
846	$/ton	80	$/ton	1.55	$/lb	
1281	lbs/batch	1652	lbs/batch	6000	lbs/batch	
338157	lbs/yr	436045	lbs/yr	0.39	$/lb product	95% recycle
143041	$/yr	17442	$/yr	1.94	$/lb product	75% recycle
0.54	$/lb product	0.07	$/lb product	3.88	$/lb product	50% recycle

Total Raw Materials		
1.00	$/lb product	95% recycle THF
2.55	$/lb product	75% recycle THF
4.48	$/lb product	50% recycle THF

Chapter 7. Amino acid hydrogenation conclusions and recommendations

Catalytic hydrogenation of amino acids to amino alcohols under hydrogenation conditions was studied with alanine as the primary reactant of the study. In acidified aqueous solution, alanine readily hydrogenates to alaninol under mild conditions with high conversion, selectivity and enantiomeric excess.

7.1 Hydrogenation of alanine

Experiments were performed in stirred batch reactor under hydrogen pressure. Ruthenium was the most effective catalyst for amino acid hydrogenation.

Alanine readily undergoes hydrogenation to alaninol in acidified aqueous solution. For hydrogenation of amino acids to occur, the carboxylic acid functionality must be in the undissociated state (-COOH). To shift the acid-base equilibrium toward this state, inorganic acid was added to the solution. In this study maximum hydrogenation rates were observed when phosphoric acid was used as the acidulant. When less than a stoichiometric amount of phosphoric acid is added to the solution, conversion ceases before conversion reaches completion. As phosphoric acid addition was increased above a stoichiometric amount, the rate decreased owing to phosphoric acid occupying active sites on the catalyst.

Reaction rate is a strong function of temperature. At temperatures at or below 100°C selectivities and enatiomeric excess near 100% were observed. At temperatures greater than 100°C racemization of alaninol, along with side product formation of ammonia, ethylamine, and isopropyl amine was observed.

Experiments at 150°C clearly showed that racemization and hydrogenation were separate steps.

Reaction rate was essentially independent of hydrogen pressure above 1000 psi H_2, indicating the surface was saturated.

7.2 Kinetic modeling

A Langmuir-Hinshelwood (L-H) kinetic model was presented in which protonated alanine and undissociated phosphoric acid compete for one set of surface sites and H_2 dissociatively adsorbs on a second type of site. Conversion rate was not limited by mass transport resistances over the range of temperature (353-398 K), hydrogen pressure (250-2000 psi), alanine feed concentration (0.22-0.46 M), and phosphoric acid concentration (0-1.2M) investigated. The average error between experimental and predicted conversion over all data collected was 8%.

7.3 Deuterium incorporation

Deuterium incorporation experiments were performed on alanine and alaninol under hydrogenation conditions. Alanine hydrogenation experiments show addition of D at C1 by reduction. Incorporation of D occurs at C2, the chiral center, in both alanine and alaninol product without racemization. At temperatures in excess of 100°C, incorporation occurs at C3. This occurs simultaneously with racemization, although no direct link is known.

Detuerium incorporation results led to the development of a simple D labeling method that is easily performed using standard laboratory equipment. Using this procedure, D_2O is used as the D source and H_2 gas is supplied at

pressures as low as 50 psi. At this pressure, less than 1% of the total pool of H and D is H and therefore, a high replacement is possible. At temperatures below 75°C and without adding phosphoric acid added, no reduction of the carboxylic acid occurs.

The observed incorporation at C2 without the occurrence of racemization suggests that C-C bond formation at the chiral center is possible.

7.4 Recommendations

To optimize this reaction further, it is suggested that investigation of different acidulants proceed. The greatest liability towards green processing is the use of inorganic acids. These require stoichiometric addition of base relative to inorganic acid added for post-reaction neutralization. This creates a significant amount of waste. A more attractive option would be the use of acetic acid which would be unreactive under the mild hydrogenation conditions used and is easily separated from solution.

Further study of amino acids with different side groups, and their effect on hydrogenation would add further insight to the feasibility of for use of hydrogenation of a wide variety of amino acids.

Chapter 8. PHA hydrogenation

As an extension of our work with amino acids and lactic acid, we have performed some preliminary hydrogenation studies with two types of PHA's, polylactic acid (PLA) and poly-3-hydroxybutyric acid (PHB).

8.1 Sustainable chemical processes

Currently, the most favorable means of handling waste PLA and PHB is by composting, where these PHAs degrade in active composts to carbon dioxide, water, and organic material. At the near-term projected yearly production of these renewables-based polymers, composting PHAs would require a significant effort in both collection and compost volume. Because PHAs are renewables-based, CO_2 released does not represent a net carbon increase in the atmosphere; however this fixed carbon could be recycled into another application before eventual return to the biosphere.

There will continue to be a large worldwide demand for PG, and the use of 1,3-BDO will grow over time. As the world chemical market increasingly demands biobased feedstocks, the use of cropland for chemical and food uses will have to be well planned to ensure that both needs are met. To reduce the acreage devoted to chemical needs, discarded bio-based products, such as PHAs, may be well suited to become feedstocks for other processes.

8.2 Background on feedstocks

8.2.1 PLA

PLA is now being produced at the commercial scale by Cargill-Dow LLC, a joint venture by Cargill and Dow, in Blair, Nebraska. The plant began operation

in November 2001, and at capacity will produce 300 MM lbs/yr. In the long term, the worldwide production for PLA could reach 10 billion lbs/yr.[82]

The current world demand for PG is on the order 1.25 B lbs/yr, with a selling price of $0.68/lb[83] via propylene oxide hydration. In the Miller/Jackson group, propylene glycol has been produced from fermentation-derived lactic acid via aqueous phase catalytic hydrogenation.

8.2.2 PHB

Poly((R)-3-hydroxybutyric acid) is currently produced via fermentation. Under optimum conditions, PHB accumulates inside microorganisms at up to 80% of their dry weight. The cells are then harvested and the PHB collected. Lemoigne first observed PHB in 1927[84] and it has since been the topic of numerous studies. Imperial Chemical Industries (ICI) began searching for an economically viable fermentation route to PHB in 1976. In 1993, the annual production was on the order of 800 tons per year. In 1996, Monsanto purchased BIOPOL® (the tradename for PHB) but stopped production in 2000 because of the high selling price (~$17/kg) of the product. In May 2001, Metabolix (Cambridge, MA) purchased the rights to Monsanto's BIOPOL business, and in September of that year was awarded $7.4 MM from the U.S. Department of Energy to continue their work in PHB production in plants. Metabolix plans to produce PHB in plants with full-scale production beginning in four to ten years.

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[82] Testimony before the United States Committee on Agriculture, Nutrition, and Forestry, March 29th, 2001 by Pat Gruber, Cargill Dow LLC.
[83] Chem. Market Reporter, Jan. 28th, 2002.
[84] Lemoigne, M, *Ann. Inst.*, **1927**, *14*, 148.

Commercial-scale uses of PHB polymers are on the horizon. Although PHB is expensive as a polymer, as a chiral intermediate feedstock it is relatively inexpensive. As an alternative to composting, both optically active and racemic 1,3-BDO (1,3-butanediol) could be produced from this otherwise discarded feed.

(R)-1,3-butanediol is used as the starting material to make azetidinone derivatives, which are important intermediates for penem and carbapenem antibiotics,[85,86] as well as pheromones,[87] fragrances,[88,89] and insecticides.[90] Racemic 1,3-butanediol is a FDA approved food additive and is used as solvent for natural and synthetic flavors. Chiral 1,3-BDO will find more widespread use if it can be synthesized via a more economic route.

8.3 Polylactic acid results

The purpose of this section is to provide preliminary results of polylactic acid hydrogenation. Reactions were performed with lactic acid, lactic acid oligomers, and three PLA samples with molecular weights of 16,000, 140,000 and 300,000. Experiments were performed in a temperature range of 100-175°C, under 1000 psi H_2, with 1 g of 5% Ru/C catalyst.

There are many challenges in conducting a study the hydrogenation of PLA because of its physical properties, reactivity, and ability to hydrolyze. PLA is not water soluble unless it is present as a low chain length oligomer, apparently $n<7$ from experimental observations. Therefore, when performing experiments

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[85] Nakayama, T.; Iwata, H.; Tanaka, R.; Imajo, S.; Ishiguro, M. *J. Chem. Soc., Chem. Com.* **1991**, *9*, 662.
[86] Tanaka, R.; Iwata, H.; Ishiguro, M. *J. Antibiot.***1990**, *43*, 1608.
[87] Mori, K.; Miyake, M. *Tetrahedron* **1987**, *43*, 2229.
[88] Ohloff, G.; Giersch, W.; Decorzant, R.; Buechi, G. *Helv. Chim. Acta* **1980**, *63*, 1589.
[89] Ferreira, J.; Ferreira, B.; Simonelli, F.; *Tetrahedron*, **1990**, *46*, 6311.
[90] Choi, V.; Elliot, J.; Johnson, W.; *Tetrahedron Lett.*, **1984**, *25*, 591.

with PLA, the contents of the reactor make up a 4 or 5 phase system including insoluble, solid PLA, insoluble amorphous-leathery PLA, and insoluble liquid oligomeric PLA depending on the temperature the reaction is carried out at and the time the material has been in the reactor.

The presence of insoluble, solid PLA in solution is particularly problematic. It was often observed when opening the reactor after the completion of an experiment that PLA was stuck in the headspace of the reactor above the level of liquid. Because of this, the actual yield and conversion could not be determined accurately for the experiment. The presence of solid masses also made sampling very difficult because chunks became lodged in the outlet tube, which limited the number of samples for many reaction conditions.

In the temperature region studied, 100-175°C, PLA goes through a transition from a hard solid to a "leathery" material, and finally to a liquid. At 150°C, PLA is leathery and sticky. Because of this, during the course of some reactions the PLA stuck together and formed a sphere. This agglomerate would get caught in the mechanical workings of the impeller and forced the experiment to be stopped before completion.

Despite the apparent physical barriers, PLA is rapidly converted to PG under mild conditions.

8.3.1 Initial results

In the first set of studies, two experiments were performed with PLA with average molecular weight of ~16,000, which corresponds to a chain length of ~220. In the first experiment, 100 grams of a 1 wt% PLA mixture was

hydrogenated with 1 g 5% Ru/C catalyst under 1000 psi H_2 at 130°C. For comparison, the same feed mixture was hydrolyzed at 130°C under 1000 psi helium. This feed concentration of PLA corresponds to a maximum molar concentration of monomeric lactic acid, or product PG, of 0.14 M.

As shown in Figure 20, formation of PG was rapid under the hydrogenation conditions described above and achieved greater than 50% yield in less than 1 hour before approaching the observed maximum of 77% in 5 hours. As shown in Figure 20, under the hydrolysis conditions described above, the lactic acid concentration versus time data was exponential in behavior with a 2.5% yield of lactic acid observed after 1 hour and reached 67% at 6 hours.

Under hydrogenation conditions the rate of formation of PG was much more rapid than the formation of lactic acid under hydrolysis conditions. This observation answers a fundamental question: will the ester linkages of polylactic acid hydrogenate? If the ester linkages of PLA do not hydrogenate, the formation of PG from hydrogenation would be at the same rate, or slower, than the formation of lactic acid from hydrolysis.

The rate of PG formation from PLA under hydrogenation was surprising when compared to the formation of PG from lactic acid at the same conditions. Zhang studied lactic acid hydrogenation extensively and developed a kinetic model that predicts lactic acid conversion at 130 and 150°C[91] using the same 5% Ru/C catalyst as in this study. Using this model, the formation of PG from lactic acid was predicted for 100 grams of 0.14 M lactic acid solution at 130°C, under 1000 psi H_2, with 1 g of catalyst as shown in Figure 21 (assuming 100%

[91] Zhang, Z.; Jackson, J. E.; Miller, D. J. *Ind. Eng. Chem. Res.* **2002**, *41*, 691.

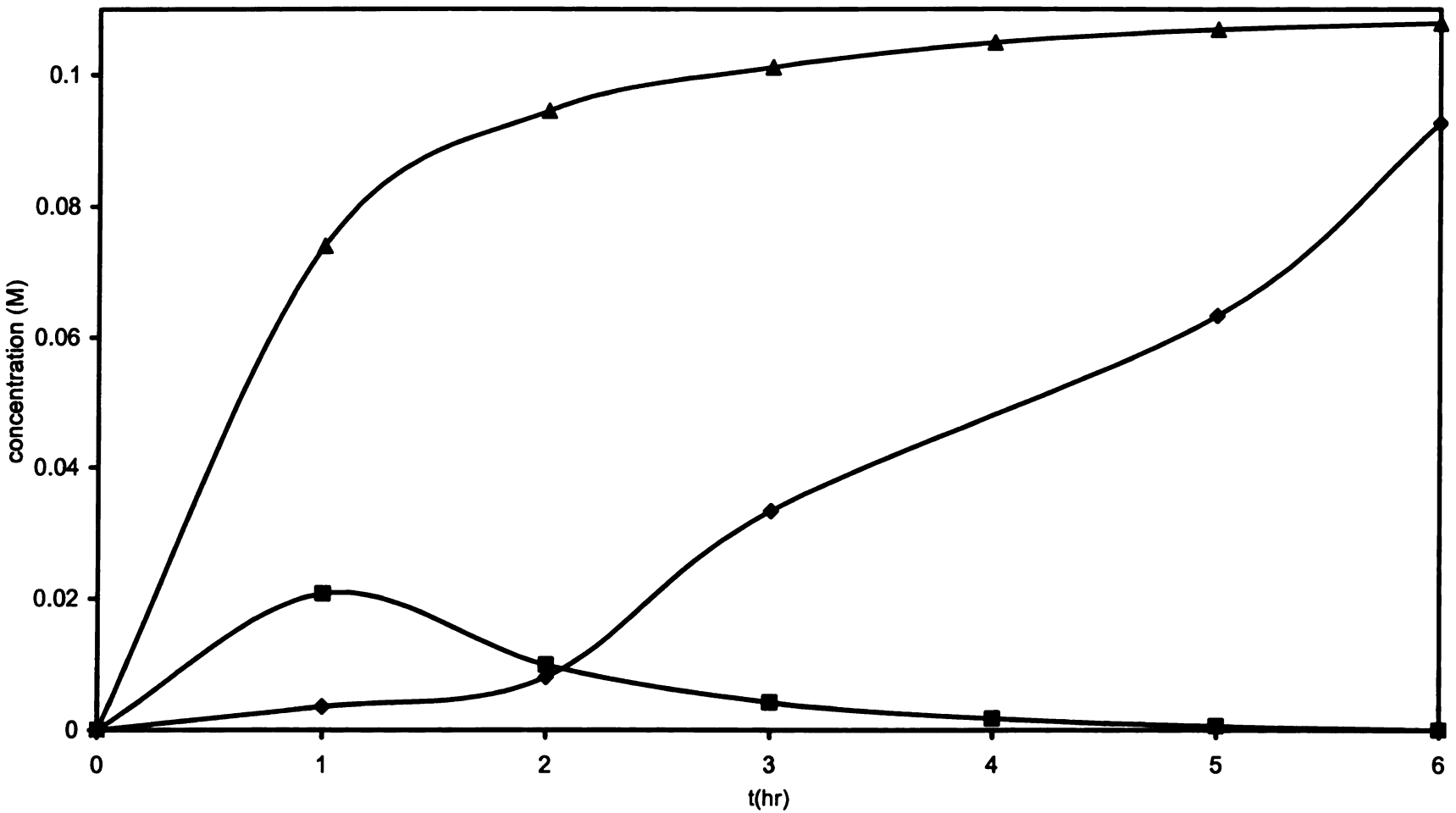

Figure 20. PLA hydrogenation versus hydrolysis. 100 grams 1 wt% PLA at 130°C. Hydrogenation carried out under 1000 psi H_2 with 1 g 5% Ru/C catalyst. Hydrolysis carried out under 1000 psi helium. Hydrogenation results—(▲)-PG (M), (■)—lactic acid. Hydrolysis results—(♦)-lactic acid (M).

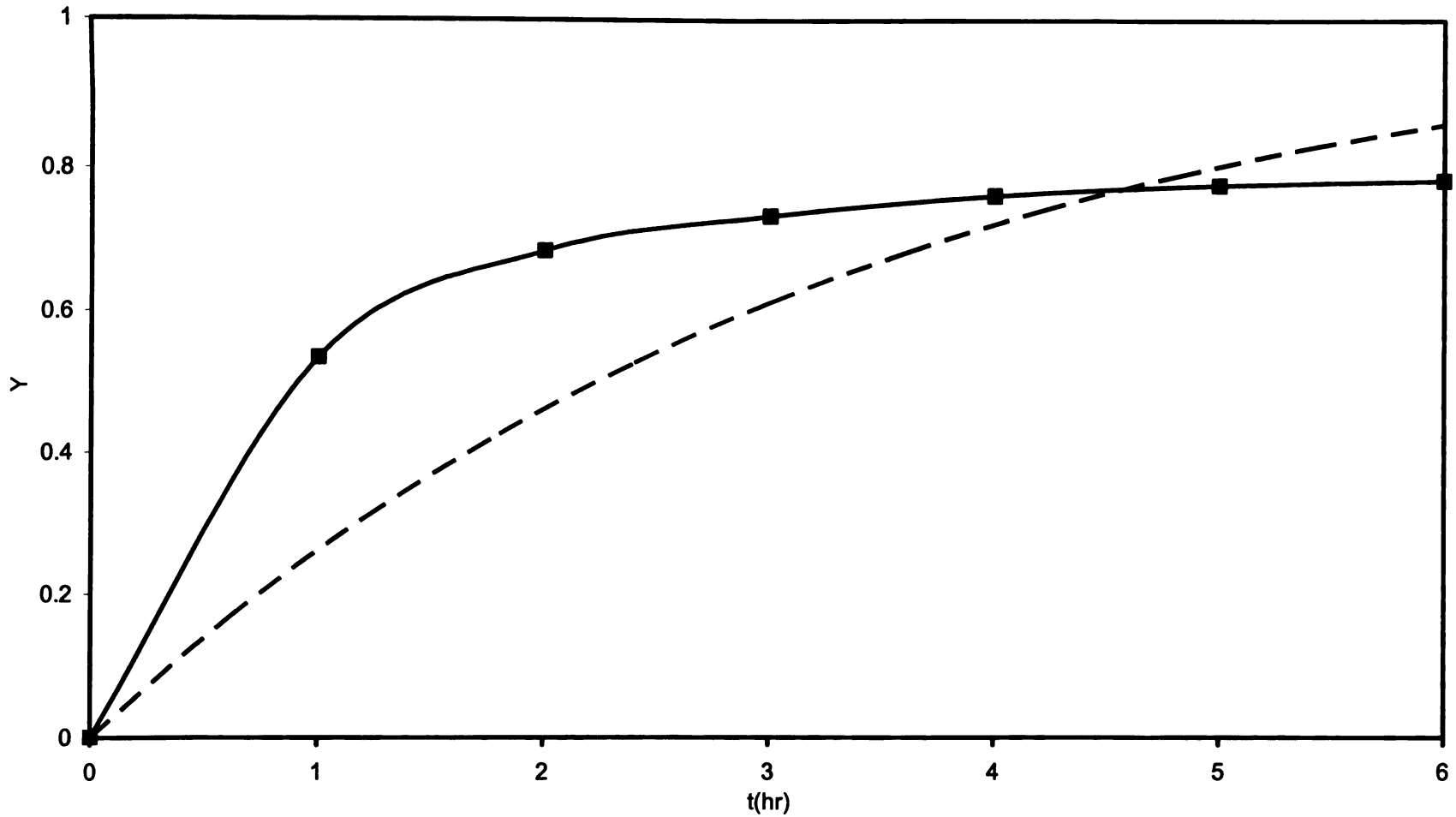

Figure 21. Comparison in the rate of formation of propylene glycol measured from PLA and predicted from lactic acid. Hydrogenation carried out with 100 grams of 1 wt% solution with 1% Ru/C catalyst at 130°C, and 1000 psi H_2. Hydrogenation results—(■)-PG yield. Predicted PG yield from lactic acid (- - - -).

selectivity). As shown in the figure, formation of PG from PLA was much faster than predicted from lactic acid. This difference in the initial rate was especially striking where at 1 hour the yields of PG from PLA and lactic acid are 53% and 26%, respectively.

Another hydrogenation experiment was performed with PLA of average molecular weight of ~ 300,000, which corresponds to a chain length of ~4,100. Hydrogenation was carried out with 100 grams of 1 wt% PLA mixture with 1 g 5% Ru/C catalyst under 1000 psi H_2 at 130°C. As shown in Figure 22, the formation of PG was very slow in the beginning of the reaction when compared to the previous case of average molecular weight 16,000 PLA. This was not surprising because hydrolysis rate is related to chain length. However, once hydrolysis has proceeded for ~6 hours, the formation of PG accelerated rapidly.

8.3.2 Use of tetrahydrofuran as hydrogenation solvent

The observations made in the initial studies of PLA hydrogenation raised several fundamental questions. Does PLA hydrogenation proceed though one or a combination of: end group hydrogenation and subsequent hydrolysis or direct ester linkage hydrogenation? Secondly, if hydrogenation of ester linkages occurs, what is the maximum chain length hydrogenated, and is the hydrogenation random? With hydrolysis and hydrogenation occurring simultaneously, these questions are difficult to answer. Therefore, experiments were planned where PLA, PLA oligomers, and lactic acid would be hydrogenated in THF (tetrahydrofuran). Performing the reaction in organic solvent eliminated hydrolysis and would thus simplify the study. However, it was found that in THF,

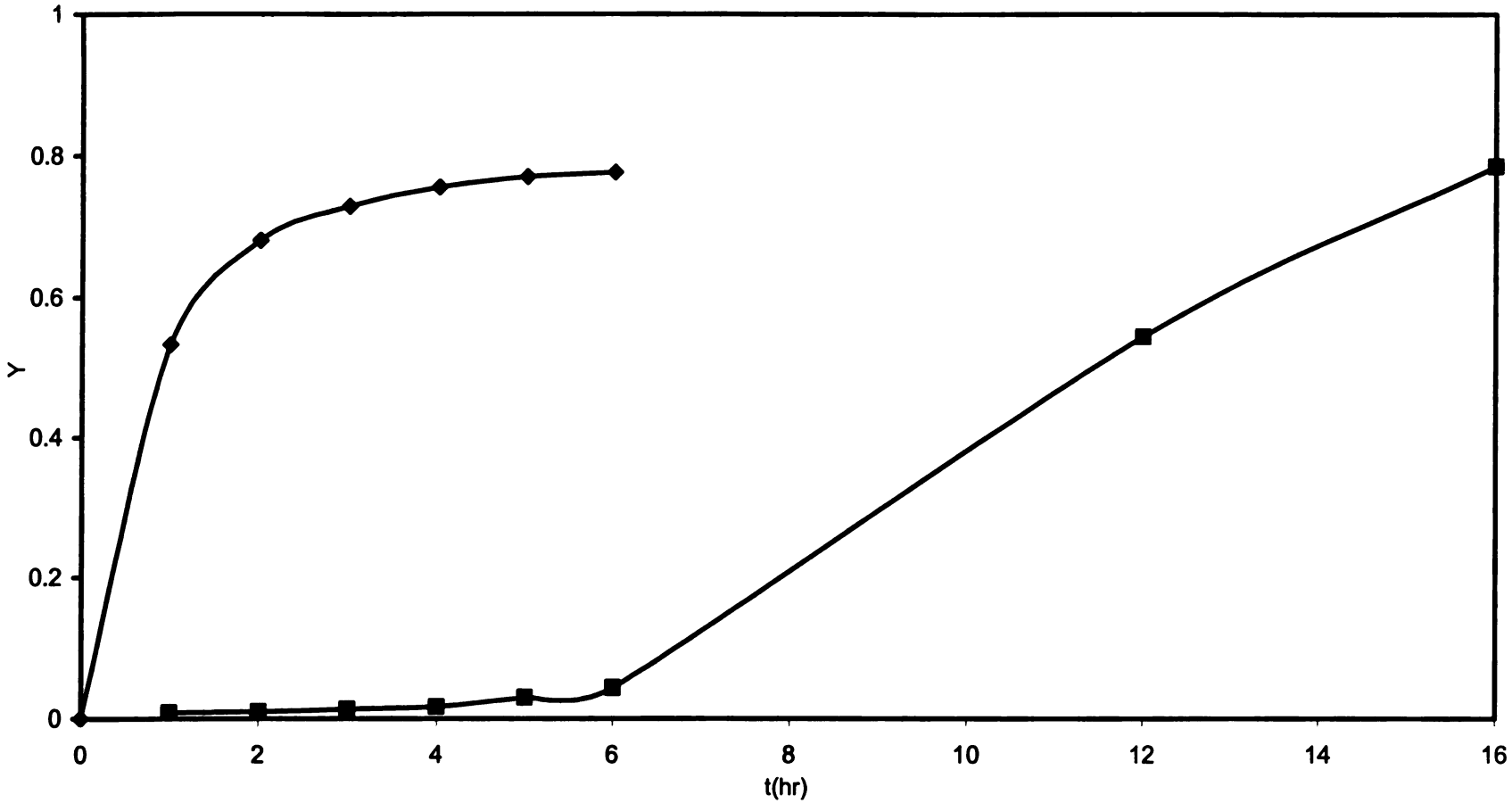

Figure 22. Comparison in the rate of formation of propylene glycol measured from high and low chain length PLA. Hydrogenations carried out with 100 grams of 1 wt% PLA solution with 1% Ru/C catalyst at 130°C, and 1000 psi H_2. PG formation from low molecular weight PLA—(♦)-PG(M). PG formation from high molecular weight PLA—(■)-PG(M).

PLA, PLA oligomers, and LA are not reactive at 130 or 150°C. Therefore, more modest goals of studying the effect of temperature and addition of wetting agent were set.

8.3.3 PLA oligomer hydrogenation and hydrolysis

Two experiments were planned using PLA oligomers that were synthesized in-house by neat condensation. The material chosen had an average chain length of 3.4 and oligomers of up to chain length 11 were observed. In the first experiment, 200 grams of a 2.5 wt% OLA mixture was hydrogenated with 1 g 5% Ru/C catalyst under 1000 psi H_2 at 130°C. For comparison, the same feed mixture was hydrolyzed at 130°C under 1000 psi helium. This feed concentration of PLA corresponded to a maximum molar concentration of monomeric lactic acid, or product PG, of 0.34 M.

After six hours under hydrogenation conditions the PG yield from PLA was 62% as shown in Figure 23. In the figure, the predicted rate of formation of PG from lactic acid was also presented and shows that in this case, the rate of PG formation from PLA and lactic acid are nearly the same.

That hydrogenation of this OLA was only marginally more rapid than lactic acid was not surprising after results from the hydrolysis were examined. Under hydrolysis conditions, the lactic acid concentration was 66% of the maximum achievable value after 1 hour. The brisk hydrolysis of the oligomeric feed rapidly shifted the solution mixture toward a high fraction of lactic acid monomer and enhanced hydrogenation rates as observed previously were not realized. The rapid hydrolysis rate of short chain oligomers made studying PLA oligomers

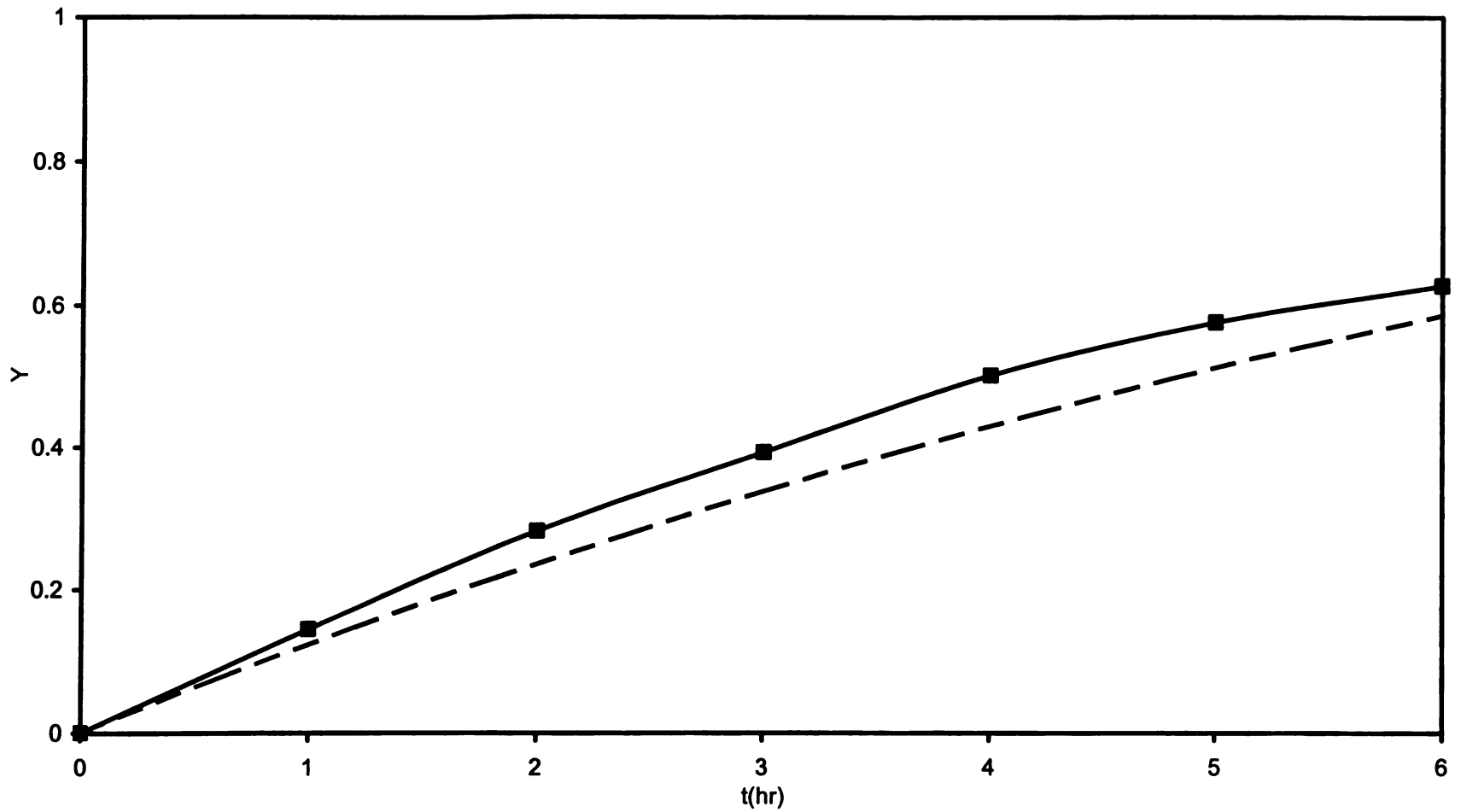

Figure 23. Comparison in the rate of formation of propylene glycol measured from oligomeric PLA and predicted from lactic acid. Hydrogenation carried out with 200 grams of 2.5 wt% solution with 1% Ru/C catalyst at 130°C, and 1000 psi H_2. Hydrogenation results—(■)-PG(M). Predicted PG yield from lactic acid (- - - -).

difficult because below 130°C the hydrogenation rate is relatively slow. Another difficulty in using PLA oligomers was that they are not water soluble and form droplets in solution. Samples taken from the reactor would appear clear with droplets of PLA and catalyst present in the sample vial. The catalyst was therefore not well dispersed in the reactor and the formation of PG was inhibited initially.

8.3.4 Temperature effect on PLA hydrogenation

The rate of PG formation from PLA is a function of temperature via four separate processes. The hydrogenation rate of ester linkages and lactic acid are both functions of temperatures as is hydrolysis rate. The physical state of PLA changes over the range of temperature studied from a hard solid at 130°C, to a leathery material at 150°C, and finally a liquid at 175°C.

The next three sets of studies were all conducted with PLA pellets with a average molecular weight of ~140,000 which were 2-3 mm in diameter.

8.3.4.1 Hydrogenation of PLA pellets at 130°C

Hydrolysis and hydrogenation experiments were performed at 130°C under 1000 psi helium and hydrogen, respectively. A feed solution of 200 grams of a 2.5% PLA solution were fed to the reactor and 1 g of 5% Ru/C catalyst was used for hydrogenation. At 130°C, PLA remains a hard solid and it appears that the breakdown of the pellets was due in large part to mechanical impact with the impeller. The presence of solid material made drawing samples from the reactor very difficult because of the small diameter of sampling tube used. Therefore, for

both hydrogenation and hydrolysis experiments usually only 3 hour and 6 hour samples were taken, thus limiting the amount of information gained.

At the end of the hydrolysis experiment (6 hours), the measured concentration of lactic acid in solution was 31% of the maximum value (if all PLA was hydrolyzed). The hydrogenation experiment at completion (6 hours) yielded 10% lactic acid and 34% PG, of the maximum values. In both cases, there was a significant amount of solid PLA left in solution. At this temperature, Zhang's model would predict a PG yield of roughly 58% if lactic acid was used as a feed material.

There are two reasons for the relatively slow rates observed in the hydrolysis and hydrogenation experiments compared to the results presented in Section 8.3.1. The relatively slow rates are explained by a combination of the relatively high molecular weight of the material and that the PLA is in pellet form. As pellets, the amount of material exposed to water is relatively small, and thus only a small amount was hydrolyzed into solution and available for hydrogenation.

8.3.4.2 Hydrogenation of PLA pellets at 150°C

Hydrolysis and hydrogenation experiments were performed at 150°C under 1000 psi helium and hydrogen, respectively. A feed solution of 200 grams of a 2.5% PLA solution were fed to the reactor and 1 g of 5% Ru/C catalyst was used for hydrogenation.

Hydrolysis experiments at this temperature were run five times, and were aborted four times due to agglomeration of pellets which disrupted the stirrer.

However, on one of these occasions this did not occur and the PLA hydrolysis was essentially complete in 4 hours.

Under hydrogenation conditions at this temperature, agglomeration of PLA did not force the reaction to be aborted. It cannot be said with any degree of certainty why this did not occur. However, hydrogenation of sticky, short chain oligomers likely reduced agglomeration.

As shown in Figure 24, formation of PG from PLA under these hydrogenation conditions was roughly at the same rate as Zhang's model would predict from lactic acid. Again in this case the enhanced rates observed in Section 8.3.1, were not realized because PLA is present in a pellet form. However, at this temperature the hydrolysis and hydrogenation rates were not as inhibited as at 130°C.

8.3.4.3 Hydrogenation of PLA pellets at 175°C

Hydrogenation and hydrolysis experiments were performed at 175°C and a pressure of 1000 psi. The feed solutions were 200 grams of 2.5% PLA and 1 g of catalyst was used for hydrogenation.

Under these conditions, both hydrolysis and hydrogenation were very rapid. Under hydrolysis conditions the yield of LA was ~90% at 2 hours and increased to 95% by the end of the run (6 hours). Hydrogenation also occurs very rapidly with a maximum yield of 57% of PG observed at two hours with only a very small amount of lactic acid observed. At 175°C, a significant amount of gas was formed with the carbon balance only 58% complete at the end of the reaction (6 hours).

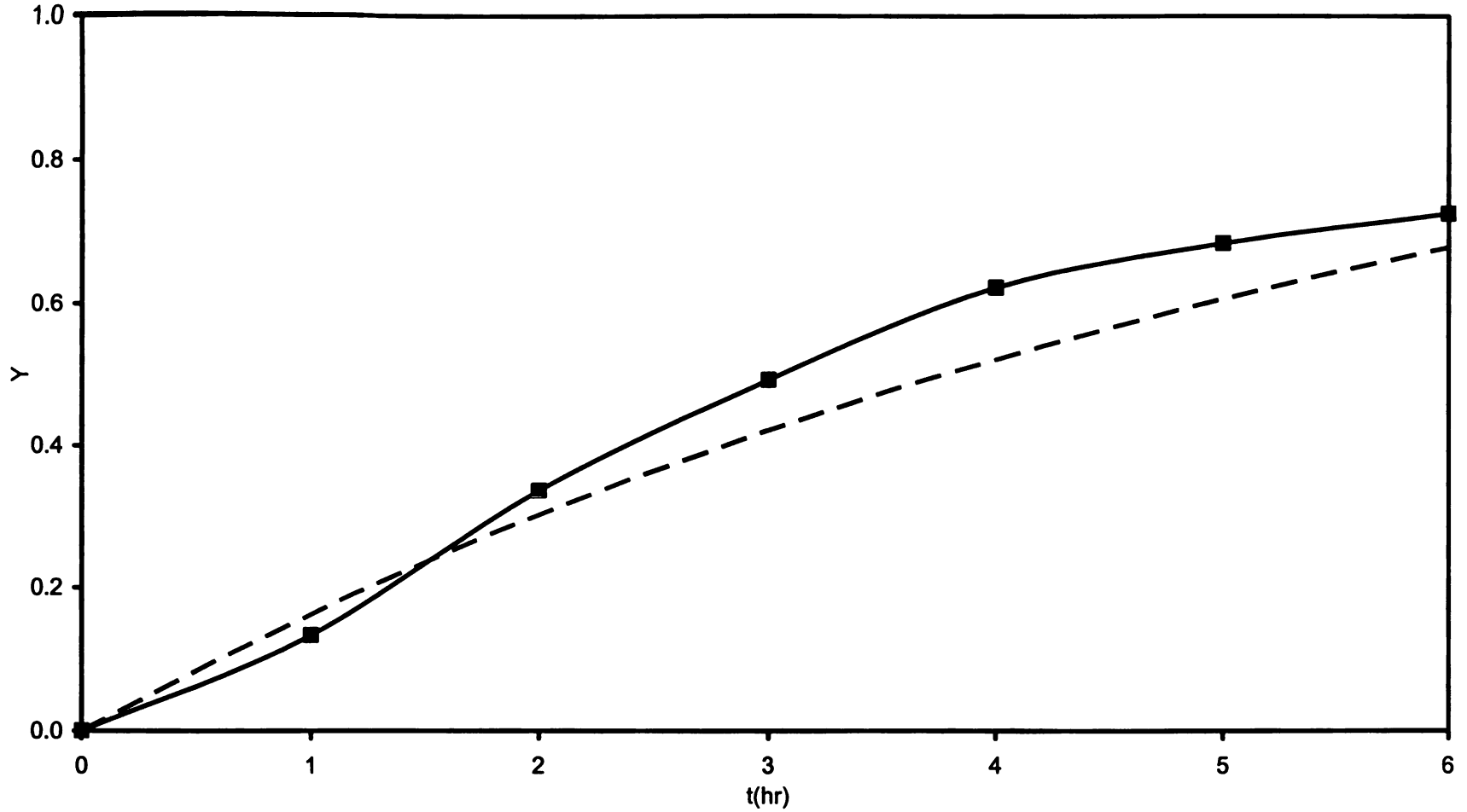

Figure 24. Comparison in the rate of formation of propylene glycol measured from PLA and predicted from lactic acid. Hydrogenation carried out with 200 grams of 2.5 wt% solution with 1% Ru/C catalyst at 150°C, and 1000 psi H_2. Hydrogenation results—(■)-PG(M). Predicted PG yield from lactic acid (- - - -).

8.3.5 Effect of PLA surface area on reaction rate

One of the primary issues when considering the combined rate of hydrolysis and hydrogenation is the PLA surface area accessible to water. Much of the work in this study has been done with PLA that was in pellet form. This was done because experiments with powderized PLA would have a significant amount of PLA stuck to metal in the headspace, particularly at 130°C.

Hydrogenation of powderized PLA was performed at 150°C under 1000 psi H_2 with 1 g 5% Ru/C. The feed solution was 200 grams of a 2.5% PLA solution. Powderized PLA was prepared from the pellets with average molecular weight of ~140,000.

The yield of PG versus time is shown in Figure 25, with an additional set of yield versus time data for the rate of PLA pellets under the same conditions. As shown in the figure, the initial rate of PG formation was much more rapid with PLA powder than with PLA in pellet form. This was expected because the powder will have much more surface than the pellet and thus more opportunity for water to attack the PLA for hydrolysis and subsequent hydrogenation. However, as shown in the Figure 24 the yield only reached roughly 65%. This was due in some part to the formation of gaseous products but primarily because some PLA remained physically trapped in the headspace.

8.3.6 Addition of surface wetting agent

Two hydrogenation experiments were performed, one with the addition of glycerol and the other propylene glycol. Due to the hydrophobic nature of PLA, it was thought that addition of a material to improve the wettability of the PLA

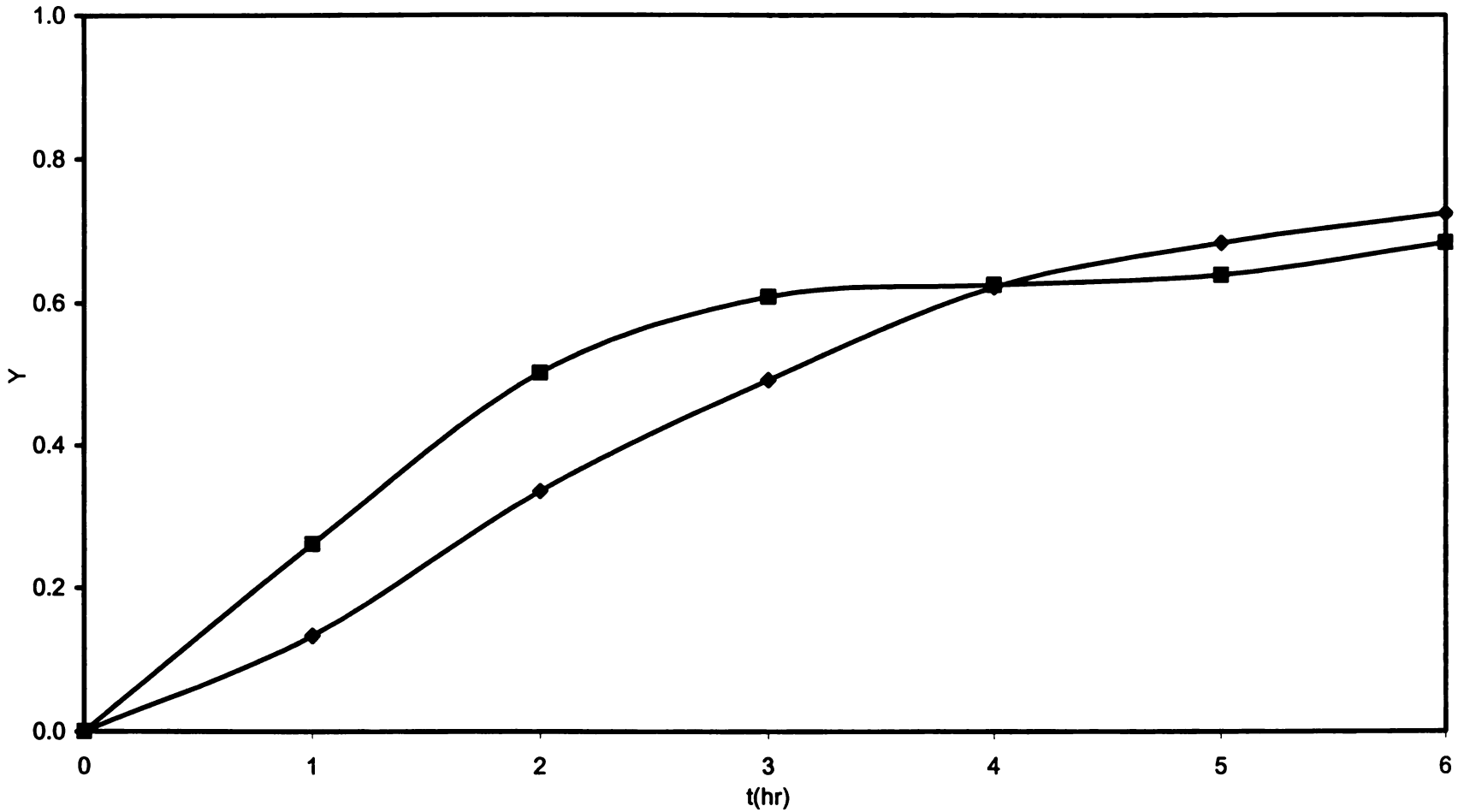

Figure 25. Comparison in the rate of formation of propylene glycol from PLA pellet and powderized PLA. Hydrogenation carried out with 200 grams of 2.5 wt% solution with 1 g 5% Ru/C catalyst at 150°C, and 1000 psi H_2. PG yield from PLA pellet—(■)-PG. PG yield from PLA powder—(♦)-PG.

would speed up the overall reaction rate. One experiment was run with PLA at 130°C, with 200 grams of 2.5% PLA fed under 1000 psi H_2 with 1 g of 5% Ru/C catalyst. The feed solution contained 5% glycerol by weight. In this case, at the conclusion of the run (6 hours) the yield to PG was 25%. For comparison in the case presented in Section 6.3.4.1, where no glycerol was added, a yield of 34% at 6 hours was achieved. Similarly, a hydrogenation experiment was performed at 150°C with 200 grams of a 2.5 wt% PLA solution with 2.5 wt% PG added to solution. In this case, the yield of PG by reaction was 68% at 6 hours (subtracting the PG fed). Under identical conditions presented in Section 8.3.4.2, with no PLA added to the reactor, a yield of 72% was observed.

In the two cases studied no improvement in conversion rate was made by adding a wetting agent. Possible improvement could be made by using different materials.

8.3.7 Conclusion for PLA

Hydrogenation of PLA may be carried under mild conditions, similar to those used for lactic acid. Several factors determine the rate of PG formation from PLA, however the most important is temperature which controls the rate of hydrogenation, and hydrolysis, and physical properties. With a Ru/C carbon catalyst, 150°C was the preferred temperature because reaction rates are high, without significant product degradation, and the physical state of PLA was favorable for hydrolysis.

8.4 Results for PHB hydrogenation

Before direct hydrogenation of PHB was carried out, two hydrogenation experiments with monomeric 3-hydroxybutyric acid were carried out at 100 and 150°C. A 100 g feed solution of 1 wt%, racemic 3-HBA was hydrogenated in water under 1000 psi H_2 with 1 g 5% Ru/C catalyst. Phosphoric acid (0.08 M) was added to the feed to ensure the carboxylic moiety was not deprotonated. At both 100 and 150°C, 5% yield of 1,3-butanediol was observed at six hours.

Lactic acid under similar conditions, reacts much more readily than 3-HBA. This is attributable to 3-HBA being a β-hydroxyacid, which are less reactive than α-hydroxy acids. Similar differences in hydrogenation behavior were noted between alpha and beta alanine as noted in Section 3.4.

An attempt at direct PHB hydrogenation was performed with 1 wt% PHB in water at 150°C with and without phosphoric acid present with 5% Ru/C catalyst under 1000 psi H_2. This material had an average molecular weight of 437,000. With 0.22 M phosphoric acid, yields of 15% 3-HBA and 13% 1,3-BDO were observed after 20 hours. Without acid present, these yields fell to 2 and 4%, respectively.

The slow rate observed for the PHB hydrogenation was probably due in part to the high molecular weight of PHB used. As noted in Section 8.3.1, as chain length increases, formation of alcohol product is delayed until hydrolysis proceeds to a sufficient degree. Under the conditions studied, PHB was apparently less susceptible to hydrolysis and hydrogenation than PLA. Because

of the low reactively of PHB, no further studies were performed and PLA became the focus of the PHA hydrogenation study.

8.5 Recommendation for PHA hydrogenation studies

The results of this study showed the viability of polylactic acid hydrogenation. The most important fundamental observation was that hydrogenation of ester linkages occurs.

This work clearly showed that hydrogenation of polylactic acid and lactic acid does not occur in organic solvents. This begs the question of whether these organic solvents occupy active sites or if the presence of water is important to the formation of reaction intermediates. Understanding the role of water in hydrogenation would add greatly to the fundamental understanding of this class of reactions.

Appendix A Alanine hydrogenation results

Table 11. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 12 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.59 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 13 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 1.2 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 14. Alanine hydrogenation: 100 grams solution, 0.46 M alanine, 0.59 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 15. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 2000 psi H_2, 1 g 5% Ru/C catalyst

Table 16. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 1500 psi H_2, 1 g 5% Ru/C catalyst

Table 17. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 500 psi H_2, 1 g 5% Ru/C catalyst

Table 18. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 250 psi H_2, 1 g 5% Ru/C catalyst

Table 19. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.19 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 20. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.15 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 21. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.08 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 22. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 23. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 90°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 24. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 110°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Table 25. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 1800 psi H_2, 1 g 5% Ru/C catalyst

Table 26. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 500 psi H_2, 1 g 5% Ru/C catalyst

Table 27. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 250 psi H_2, 1 g 5% Ru/C catalyst

Table 28. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 100 psi H_2, 1 g 5% Ru/C catalyst

Table 29. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 100 psi H_2, 1 g 5% Ru/C catalyst

Table 30. Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 100 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2096			0.0000			
1	0.1558	0.0000	0.0005	0.0477	0.0001	0.0011	0.0015
2	0.1367	0.0000	0.0007	0.0835	0.0002	0.0016	0.0022
3	0.0959	0.0000	0.0009	0.1235	0.0003	0.0021	0.0039
4	0.0640	0.0000	0.0011	0.1587	0.0004	0.0024	0.0022
5	0.0334	0.0000	0.0015	0.1792	0.0005	0.0028	0.0059
6	0.0154	0.0000	0.0013	0.2058	0.0008	0.0031	0.0072

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.69	0.000	0.000		
1	2.1	0.64	0.311	0.211	0.678	0.997
2	2.1	0.62	0.395	0.369	0.934	0.995
3	2.2	0.59	0.576	0.546	0.949	0.995
4	2.3	0.53	0.717	0.702	0.979	0.995
5	2.4	0.48	0.852	0.792	0.930	0.994
6	2.5	0.43	0.932	0.910	0.977	0.992

Table 11 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)
0	0.2175		0.0000		
0.5	0.1987	0.0000	0.0186	0.0001	0.0011
1	0.1837	0.0000	0.0367	0.0001	0.0015
2	0.1577	0.0000	0.0625	0.0002	0.0018
3	0.1334	0.0000	0.0872	0.0003	0.0022
4.3	0.0896	0.0006	0.1195	0.0003	0.0029
6	0.0687	0.0007	0.1579	0.0005	0.0034

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	1.5	0.77	0	0		
0.5	1.5	0.77	0.138	0.081	0.584	0.989
1	1.5	0.76	0.203	0.159	0.782	0.992
2	1.6	0.76	0.316	0.271	0.857	0.995
3	1.6	0.75	0.422	0.378	0.898	0.994
4	1.6	0.75	0.611	0.518	0.848	0.994
6	1.7	0.72	0.702	0.685	0.975	0.994

Table 12 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.59 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2307			0.0000			
1	0.1865	0.0000	0.0000	0.0314	0.0000	0.0015	0.0012
2	0.1771	0.0000	0.0002	0.0548	0.0000	0.0018	0.0025
3	0.1492	0.0000	0.0003	0.0781	0.0001	0.0020	0.0038
4	0.1292	0.0000	0.0005	0.0980	0.0001	0.0021	0.0043
5	0.1115	0.0000	0.0006	0.1156	0.0002	0.0023	0.0052
6	0.0911	0.0000	0.0010	0.1297	0.0003	0.0025	0.0078

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	1.0	0.96	0	0		
1	1.1	0.95	0.211	0.133	0.630	1.000
2	1.1	0.95	0.250	0.232	0.928	1.000
3	1.1	0.95	0.369	0.331	0.897	0.996
4	1.1	0.95	0.453	0.415	0.915	0.997
5	1.1	0.95	0.528	0.489	0.926	0.996
6	1.1	0.95	0.614	0.549	0.894	0.995

Table 13 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 1.2 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.4644			0.0000			
1	0.4067	0.0000	0.0000	0.0501	0.0000	0.0020	0.0020
2	0.3706	0.0000	0.0007	0.0926	0.0000	0.0024	0.0023
3	0.3158	0.0000	0.0012	0.1392	0.0000	0.0033	0.0056
4	0.2804	0.0000	0.0014	0.1813	0.0003	0.0038	0.0061
5	0.2442	0.0000	0.0016	0.2197	0.0004	0.0047	0.0077
6	0.2066	0.0000	0.0024	0.2621	0.0006	0.0051	0.0096

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.71	0	0		
1	2.0	0.69	0.131	0.107	0.815	1.000
2	2.0	0.69	0.209	0.198	0.948	1.000
3	2.0	0.67	0.326	0.297	0.913	1.000
4	2.1	0.66	0.401	0.387	0.965	0.997
5	2.1	0.63	0.478	0.469	0.981	0.996
6	2.1	0.61	0.559	0.560	1.002	0.995

Table 14 Alanine hydrogenation: 100 grams solution, 0.46 M alanine, 0.59 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2224			0.0000			
1	0.1587	0.0000	0.0002	0.0519	0.0000	0.0004	0.0006
2	0.1354	0.0000	0.0029	0.0943	0.0000	0.0006	0.0010
3	0.0882	0.0000	0.0003	0.1390	0.0000	0.0008	0.0015
4	0.0601	0.0000	0.0003	0.1680	0.0002	0.0009	0.0017
5	0.0337	0.0000	0.0004	0.1903	0.0000	0.0009	0.0023
6	0.0153	0.0000	0.0004	0.1968	0.0003	0.0009	0.0025

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.68	0	0		
1	2.1	0.62	0.299	0.229	0.767	1.000
2	2.2	0.60	0.402	0.417	1.037	1.000
3	2.2	0.57	0.610	0.614	1.006	1.000
4	2.3	0.55	0.734	0.742	1.011	0.998
5	2.3	0.50	0.851	0.840	0.988	1.000
6	2.4	0.46	0.932	0.870	0.933	0.997

Table 15 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 2000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2274			0.0000			
1	0.1737	0.0000	0.0000	0.0471	0.0000	0.0000	0.0000
2	0.1437	0.0000	0.0003	0.0829	0.0004	0.0006	0.0017
3	0.1092	0.0000	0.0004	0.1176	0.0000	0.0008	0.0020
4	0.0778	0.0000	0.0004	0.1556	0.0000	0.0007	0.0020
5	0.0459	0.0000	0.0004	0.1851	0.0000	0.0008	0.0018
6	0.0265	0.0000	0.0004	0.2007	0.0003	0.0010	0.0023

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.039	0.67	0	0		
1	2.124	0.62	0.2358	0.2072	0.8788	1.0000
2	2.156	0.60	0.3680	0.3646	0.9907	0.9908
3	2.225	0.57	0.5197	0.5171	0.9950	1.0000
4	2.277	0.54	0.6579	0.6847	1.0407	1.0000
5	2.338	0.50	0.7983	0.8144	1.0201	1.0000
6	2.422	0.45	0.8834	0.8830	0.9995	0.9966

Table 16 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 1500 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2196			0.0000			
1	0.1960	0.0000	0.0000	0.0278	0.0000	0.0000	0.0000
2	0.1808	0.0000	0.0003	0.0472	0.0000	0.0004	0.0009
3	0.1489	0.0000	0.0005	0.0693	0.0002	0.0005	0.0013
4	0.1320	0.0000	0.0005	0.0901	0.0000	0.0005	0.0016
5	0.1180	0.0000	0.0006	0.1201	0.0006	0.0010	0.0021
6	0.0893	0.0000	0.0007	0.1303	0.0006	0.0011	0.0029

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.66	0	0		
1	2.1	0.63	0.137	0.122	0.895	1.000
2	2.2	0.60	0.203	0.208	1.021	1.000
3	2.2	0.60	0.344	0.305	0.886	0.994
4	2.2	0.57	0.419	0.397	0.948	1.000
5	2.2	0.56	0.480	0.529	1.101	0.991
6	2.3	0.53	0.607	0.574	0.946	0.991

Table 17 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 500 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2179			0.0000			
1	0.1911	0.0000	0.0000	0.0212	0.0000	0.0012	0.0009
2	0.1900	0.0000	0.0005	0.0331	0.0002	0.0014	0.0019
3	0.1690	0.0000	0.0009	0.0475	0.0003	0.0017	0.0031
4	0.1593	0.0000	0.0011	0.0642	0.0004	0.0021	0.0053
5	0.1436	0.0000	0.0014	0.0813	0.0005	0.0025	0.0052
6	0.1266	0.0000	0.0016	0.0967	0.0007	0.0029	0.0071

Time	pH	Fraction in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.68	0	0		
1	2.1	0.66	0.155	0.094	0.605	1.000
2	2.1	0.66	0.160	0.146	0.911	0.990
3	2.1	0.64	0.253	0.210	0.829	0.986
4	2.1	0.63	0.296	0.284	0.958	0.987
5	2.2	0.61	0.365	0.359	0.984	0.987
6	2.2	0.58	0.440	0.427	0.971	0.986

Table 18 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 250 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2162			0.0000			
1	0.1562	0.0000	0.0003	0.0486	0.0000	0.0012	0.0012
2	0.1291	0.0000	0.0006	0.0862	0.0002	0.0018	0.0025
3	0.0855	0.0000	0.0007	0.1262	0.0003	0.0023	0.0040
4	0.0591	0.0000	0.0012	0.1610	0.0004	0.0028	0.0040
5	0.0329	0.0000	0.0012	0.1807	0.0008	0.0029	0.0059
6	0.0224	0.0000	0.0013	0.1953	0.0013	0.0035	0.0058

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.3	0.55	0	0		
1	2.4	0.46	0.313	0.214	0.684	1.000
2	2.5	0.40	0.432	0.379	0.878	0.995
3	2.7	0.30	0.624	0.555	0.890	0.996
4	3.0	0.19	0.740	0.709	0.957	0.995
5	3.5	0.06	0.855	0.795	0.930	0.991
6	4.4	0.01	0.901	0.859	0.953	0.987

Table 19 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.19 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)
0	0.2092		0.0000		
0.5	0.1961	0.0000	0.0246	0.0007	0.0011
1	0.1811	0.0000	0.0431	0.0000	0.0000
2.2	0.1397	0.0000	0.0759	0.0000	0.0000
3	0.1132	0.0006	0.1021	0.0004	0.0022
4	0.0864	0.0009	0.1259	0.0005	0.0026
6	0.0710	0.0008	0.1407	0.0010	0.0034

Time	measured pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.4	0.46	0	0		
0.5	2.5	0.40	0.140	0.108	0.768	0.943
1	2.5	0.39	0.206	0.189	0.917	1.000
2.2	2.7	0.28	0.388	0.333	0.858	1.000
3	3.0	0.18	0.504	0.448	0.889	0.993
4	3.6	0.05	0.621	0.552	0.888	0.992
6	4.8	0.00	0.689	0.617	0.896	0.987

Table 20 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.15 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2145			0.0000			
1	0.1634	0.0000	0.0003	0.0390	0.0000	0.0011	0.0008
2	0.1443	0.0000	0.0004	0.0599	0.0001	0.0012	0.0015
3	0.1365	0.0000	0.0004	0.0758	0.0004	0.0015	0.0015
4	0.1250	0.0000	0.0004	0.0772	0.0006	0.0017	0.0016
5	0.1234	0.0000	0.0004	0.0804	0.0008	0.0019	0.0017
6	0.1213	0.0000	0.0004	0.0844	0.0012	0.0020	0.0018

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.8	0.26	0.000	0.000		
1	3.2	0.13	0.278	0.172	0.621	0.998
2	3.8	0.04	0.362	0.265	0.732	0.997
3	5.5	0.00	0.396	0.335	0.845	0.990
4	6.1	0.00	0.447	0.342	0.764	0.984
5	6.1	0.00	0.454	0.356	0.782	0.979
6	6.2	0.00	0.463	0.373	0.806	0.972

Table 21 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.08 M phosphoric acid, 100°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2206			0.0000			
0.25	0.1743	0.0000	0.0000	0.0429	0.0003	0.0017	0.0000
0.5	0.1431	0.0000	0.0020	0.0773	0.0005	0.0030	0.0000
0.75	0.1095	0.0000	0.0023	0.1034	0.0007	0.0037	0.0000
1	0.0817	0.0000	0.0021	0.1297	0.0011	0.0046	0.0000
2	0.0285	0.0000	0.0038	0.1694	0.0019	0.0061	0.0000
4	0.0037	0.0000	0.0047	0.1912	0.0057	0.0093	0.0000
6	0.0007	0.0000	0.0054	0.2014	0.0099	0.0121	0.0000

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.68	0	0		
0.25	2.1	0.64	0.229	0.190	0.827	0.987
0.5	2.1	0.61	0.368	0.342	0.930	0.986
0.75	2.2	0.57	0.516	0.457	0.886	0.986
1	2.3	0.55	0.639	0.573	0.897	0.984
2	2.4	0.47	0.874	0.749	0.857	0.978
4	2.5	0.40	0.984	0.845	0.859	0.942
6	2.6	0.38	0.997	0.891	0.893	0.907

Table 22 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2273		0.0000			
1	0.1845	0.0000	0.0278	0.0000	0.0009	0.0018
2	0.1701	0.0003	0.0456	0.0000	0.0048	0.0034
3	0.1434	0.0000	0.0751	0.0000	0.0019	0.0031
4	0.1253	0.0003	0.0969	0.0001	0.0019	0.0041
5	0.1012	0.0005	0.1106	0.0002	0.0020	0.0042
6	0.0844	0.0003	0.1281	0.0002	0.0022	0.0052

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.70	0	0		
1	2.0	0.67	0.185	0.123	0.665	1.000
2	2.1	0.65	0.249	0.202	0.811	1.000
3	2.1	0.63	0.366	0.332	0.906	1.000
4	2.2	0.60	0.446	0.428	0.959	0.998
5	2.2	0.59	0.553	0.489	0.884	0.997
6	2.2	0.57	0.627	0.566	0.902	0.997

Table 23 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 90°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2236			0.0000			
0.33	0.1856	0.0000	0.0003	0.0320	0.0001	0.0011	0.0009
0.67	0.1745	0.0000	0.0004	0.0506	0.0001	0.0013	0.0020
1	0.1474	0.0000	0.0007	0.0820	0.0003	0.0018	0.0034
1.5	0.1054	0.0000	0.0001	0.1160	0.0004	0.0024	0.0042
2	0.0730	0.0000	0.0013	0.1431	0.0006	0.0027	0.0050
3	0.0331	0.0000	0.0017	0.1897	0.0009	0.0035	0.0076
4	0.0071	0.0000	0.0021	0.2127	0.0013	0.0040	0.0080
5	0.0015	0.0000	0.0023	0.2207	0.0018	0.0043	0.0085
6	0.0004	0.0000	0.0026	0.2241	0.0023	0.0046	0.0103

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.68	0	0		
0.33	2.1	0.66	0.180	0.141	0.788	0.995
0.67	2.1	0.64	0.228	0.224	0.979	0.994
1	2.1	0.61	0.348	0.362	1.040	0.992
1.5	2.2	0.57	0.534	0.513	0.960	0.993
2	2.3	0.53	0.677	0.633	0.934	0.992
3	2.4	0.47	0.854	0.838	0.982	0.990
4	2.5	0.41	0.969	0.940	0.971	0.988
5	2.6	0.38	0.993	0.976	0.982	0.984
6	2.6	0.38	0.998	0.991	0.993	0.980

Table 24 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 110°C, 1000 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)
0	0.2210		0.0000		
0.25	0.1930	0.0005	0.0333	0.0001	0.0014
0.5	0.1485	0.0011	0.0727	0.0003	0.0023
0.75	0.1126	0.0016	0.1114	0.0005	0.0032
1	0.0677	0.0018	0.1609	0.0009	0.0043
2	0.0080	0.0025	0.2181	0.0022	0.0057
3	0.0023	0.0030	0.2087	0.0041	0.0067
4	0.0018	0.0032	0.2206	0.0057	0.0078
6	0.0004	0.0041	0.2260	0.0094	0.0104

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.68	0	0		
0.25	2.1	0.64	0.147	0.147	1.004	0.991
0.5	2.1	0.61	0.344	0.321	0.935	0.991
0.75	2.2	0.57	0.502	0.493	0.981	0.990
1	2.3	0.55	0.701	0.711	1.015	0.989
2	2.4	0.47	0.965	0.964	0.999	0.980
3	2.5	0.40	0.990	0.923	0.932	0.961
4	2.6	0.38	0.992	0.975	0.983	0.950
6	3.6	0.06	0.998	0.999	1.001	0.921

Table 25 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 1800 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2259			0.0000			
0.33	0.1696	0.0000	0.0009	0.0352	0.0003	0.0018	0.0022
0.67	0.1500	0.0000	0.0017	0.0651	0.0007	0.0027	0.0045
1	0.1148	0.0002	0.0027	0.1034	0.0014	0.0040	0.0065
1.5	0.0635	0.0003	0.0047	0.1424	0.0024	0.0054	0.0102
2	0.0271	0.0000	0.0056	0.1695	0.0034	0.0065	0.0115
3	0.0063	0.0000	0.0064	0.1898	0.0056	0.0086	0.0130
4	0.0022	0.0000	0.0066	0.1935	0.0082	0.0109	0.0171
5	0.0011	0.0000	0.0080	0.1817	0.0103	0.0125	0.0197
6	0.0002	0.0000	0.0085	0.1773	0.0130	0.0147	0.0215

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.68	0	0		
0.33	2.1	0.65	0.254	0.155	0.610	0.985
0.67	2.1	0.62	0.340	0.286	0.842	0.977
1	2.2	0.58	0.495	0.455	0.919	0.974
1.5	2.3	0.52	0.721	0.626	0.869	0.967
2	2.4	0.46	0.881	0.745	0.846	0.961
3	2.5	0.41	0.972	0.835	0.859	0.943
4	2.5	0.39	0.990	0.851	0.860	0.918
5	2.5	0.38	0.995	0.799	0.803	0.892
6	2.6	0.38	0.999	0.780	0.780	0.864

Table 26 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 500 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2173			0.0000			
0.33	0.2075	0.0000	0.0012	0.0229	0.0003	0.0019	0.0022
0.67	0.1792	0.0000	0.0017	0.0408	0.0005	0.0028	0.0030
1	0.1534	0.0000	0.0025	0.0624	0.0010	0.0038	0.0049
1.5	0.1219	0.0005	0.0046	0.0897	0.0017	0.0050	0.0077
2	0.0903	0.0004	0.0056	0.1177	0.0025	0.0065	0.0089
3	0.0439	0.0005	0.0085	0.1533	0.0039	0.0079	0.0112
4	0.0129	0.0000	0.0095	0.1766	0.0060	0.0101	0.0168
5	0.0034	0.0000	0.0109	0.1776	0.0085	0.0125	0.0174
6	0.0006	0.0000	0.0123	0.1728	0.0101	0.0147	0.0222

Time	measured pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.68	0	0		
0.33	2.0	0.67	0.083	0.101	1.220	0.976
0.67	2.1	0.65	0.208	0.180	0.867	0.975
1	2.1	0.63	0.322	0.276	0.857	0.968
1.5	2.2	0.60	0.461	0.397	0.860	0.964
2	2.2	0.56	0.601	0.520	0.866	0.959
3	2.3	0.50	0.806	0.677	0.841	0.950
4	2.5	0.43	0.943	0.780	0.828	0.934
5	2.5	0.40	0.985	0.785	0.797	0.909
6	2.5	0.39	0.997	0.764	0.766	0.890

Table 27 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 250 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2283			0.0000			
1	0.1821	0.0008	0.0020	0.0148	0.0005	0.0022	0.0014
2	0.1814	0.0016	0.0033	0.0274	0.0011	0.0035	0.0028
3	0.1596	0.0019	0.0053	0.0380	0.0017	0.0048	0.0042
4	0.1409	0.0033	0.0088	0.0526	0.0026	0.0062	0.0000
5	0.1276	0.0036	0.0120	0.0629	0.0036	0.0077	0.0000

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	1.99	0.691	0	0		
1	2.03	0.671	0.1971	0.0651	0.3305	0.9330
2	2.05	0.661	0.2003	0.1209	0.6037	0.9258
3			0.2965	0.1674	0.5647	0.9156
4	2.10	0.635	0.3786	0.2318	0.6121	0.9055
5	2.12	0.624	0.4376	0.2773	0.6337	0.8920

Table 28 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 125°C, 100 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2066			0.0000			
1	0.1951	0.0000	0.0003	0.0086	0.0000	0.0009	0.0003
2	0.1993	0.0000	0.0005	0.0086	0.0001	0.0010	0.0005
4	0.1927	0.0000	0.0006	0.0154	0.0001	0.0012	0.0012
5	0.1846	0.0000	0.0010	0.0179	0.0003	0.0014	0.0016
6	0.1821	0.0000	0.0011	0.0228	0.0004	0.0015	0.0019

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.71	0	0		
1	2.0	0.70	0.137	0.038	0.277	0.992
2	2.0	0.70	0.118	0.038	0.321	0.985
4	2.0	0.69	0.147	0.068	0.462	0.982
5	2.0	0.68	0.183	0.079	0.432	0.972
6	2.0	0.68	0.194	0.101	0.520	0.969

Table 29 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 100 psi H_2, 1 g 5% Ru/C catalyst

Time	L-Alanine (mol/L)	D-Alanine (mol/L)	Ammonia (mol/L)	S-Alaninol (mol/L)	R-Alaninol (mol/L)	Ethylamine (mol/L)	IPA (mol/L)
0	0.2066			0.0000			
1	0.1951	0.0000	0.0003	0.0086	0.0000	0.0009	0.0003
2	0.1993	0.0000	0.0005	0.0086	0.0001	0.0010	0.0005
4	0.1927	0.0000	0.0006	0.0154	0.0001	0.0012	0.0012
5	0.1846	0.0000	0.0010	0.0179	0.0003	0.0014	0.0016
6	0.1821	0.0000	0.0011	0.0228	0.0004	0.0015	0.0019

Time	pH	Fraction Al in COOH form	L-Alanine Conversion	S-Alaninol Yield	S-Alaninol Selectivity	ee
0	2.0	0.71	0	0		
1	2.0	0.70	0.137	0.038	0.277	0.992
2	2.0	0.70	0.118	0.038	0.321	0.985
4	2.0	0.69	0.147	0.068	0.462	0.982
5	2.0	0.68	0.183	0.079	0.432	0.972
6	2.0	0.68	0.194	0.101	0.520	0.969

Table 30 Alanine hydrogenation: 100 grams solution, 0.22 M alanine, 0.29 M phosphoric acid, 100°C, 100 psi H_2, 1 g 5% Ru/C catalyst

Appendix B. Acid-Base calculations

As discussed throughout this work, determining the ionic state of alanine in solution is critical to understanding amino acid hydrogenation and predicting the kinetics of alanine conversion.

The Henderson-Hasselbach equation is used throughout this work to estimate the fraction of alanine protonated from measured sample pH. Another option for estimating the ionic states of all species in solution is to use an overall charge balance. This method is described in Section 4.3 for use as part of the kinetic modeling strategy. This calculation may also be used to determine the ionic state of all species in solution from concentrations determined by HPLC with some modification to system of equations in section 4.3.

To estimate ionic species the overall charge balance is expanded to included all measured species in solution.

$$0 = H^+ + A^+ + Alol^+ + Am^+ + EA^+ + IPA^+ + OH^- - A^- - P^- - 2P^{2-} - 3P^{3-} \qquad (30)$$

Where the symbols are as previously described in Section 4.3 with the addition of Am^+ as protonated ammonia, EA^+ as protonated ethylamine, and IPA^+ as protonated isopropyl amine. The charge balance now consists of 11 unknowns. The species concentrations of ammonia, ethylamine, and isopropylamine are defined similarly as alaninol is in section 4.3 by rearrangement of the Henderson-Hasselbach equation.

There is now a system of 11 equations and 11 unknowns. This method is solved in the same manner as discussed in section 4.3. The purpose of this section is to compare the estimates of the fraction protonated from measured pH values with the pH and fraction protonated from the overall charge balance. As shown in Table 31, there is good agreement between the Henderson-Hasselbach and charge balance method. Therefore, the charge balance could be used for kinetic model development with confidence.

	0.15 M				**0.29 M**				**0.58 M**			
	Measured		*Calculated*		*Measured*		*Calculated*		*Measured*		*Calculated*	
t(hr)	pH	C_{COOH}/C_t	pH	C_{COOH}/C_t	pH	C_{COOH}/C_t	pH	C_{COOH}/C_t	pH	C_{COOH}/C_t	pH	C_{COOH}/C_t
0	2.4	0.46	2.5	0.43	2.0	0.69	2.2	0.60	1.5	0.87	1.8	0.77
1	2.5	0.40	2.5	0.39	2.1	0.64	2.2	0.58	1.5	0.87	1.8	0.77
2	2.5	0.39	2.6	0.35	2.1	0.62	2.3	0.53	1.5	0.86	1.8	0.76
3	2.7	0.28	2.7	0.28	2.2	0.59	2.4	0.47	1.6	0.86	1.8	0.76
4	3.0	0.18	3.0	0.19	2.3	0.53	2.5	0.41	1.6	0.85	1.9	0.75
5	3.6	0.05	3.3	0.10	2.4	0.48	2.6	0.37	1.6	0.84	1.9	0.75
6	4.8	0.00	4.2	0.01	2.5	0.43	2.7	0.29	1.7	0.82	1.9	0.72

Table 31. Comparison of the estimated fraction of protonated alanine by use of the Henderson-Hasselbach equation and the charge balance equations.

Appendix C. Excel program for kinetic modeling

The kinetics model derived for alanine hydrogenation, as discussed in Chapter 4, involves a differential equation, the rate expression, which is dependent on a highly non-linear algebraic equation, the charge balance. This type of problem is not easily solved using the usual computational tools. Therefore, a hybrid Runge Kutta method was developed and encoded for use in the Visual Basic for Application environment of Excel. Since this represents a novel computational technique and tool, the visual basic code and discussion of the spreadsheet interface is presented.

C.1 Set Up of the spreadsheet

As shown in Figure 26, an Excel worksheet was used as the interface to the macro that performs the calculations. This worksheet is broken into two sections, one for entering independent variable information and the other for entering dependent variables, constants, initial values, differential equation, and charge balance.

In the independent variable section, the initial and final values of the independent variable are entered. In this case the variable name given to time is tau with intial and final values of 0 to 6. The number of steps is entered below as 100, which has proved adequate for this system. Also located in this box is the "Solve" button, which initiates the macro, and the "Proof Formulas" button which copies the formulas entered in the "Input" column into the "Display Formula" column.

Figure 26. Kinetic parameter Set Up page

Enter Independent Variable Information			
Name	*Initial Value*	*Final Value*	
tau	0	6	
Num of Steps		100	
Step Size (calc'd)		0.06	
Number of Points in Summary		10	

Enter Constants, Initial Values, Formulas, and Differential Equations		
Name	*Input*	*Display Formula*
c.a0	0.226	
c.ptot	0.291	
c.h2	0.004	
c.alol	0.000	=c.a0-c.a
KAl1	0.005	
KAl2	0.000	
KP1	0.007	
KP2	0.000	
KP3	0.000	
KAlol	0.000	
hplus	0.005	
p.H	2.276	=-LOG(hplus)
c.p1	0.124	=c.ptot/(1+KP1/hplus+KP1*KP2/hplus^2+KP1*KP2*KP3/hplus^3)
c.p2	0.167	=c.ptot/(1+hplus/KP1+KP2/hplus+KP3*KP2/hplus^2)
c.p3	0.000	=c.ptot/(1+KP3/hplus+hplus/KP2+hplus^2/(KP2*KP1))
c.p4	0.000	=c.ptot/(1+hplus/KP3+hplus/(KP2*KP3)+hplus^3/(KP1*KP2*KP3))
c.a	0.226	
c.a1	0.121	=c.a/(1+KAl1/hplus+KAl1*KAl2/hplus^2)
c.a2	0.105	=c.a/(1+hplus/KAl1+KAl2/hplus+KAl2/hplus)
c.a3	0.000	=c.a/(hplus^2/(KAl1*KAl2)+hplus/KAl2+1)
temp	373.000	
law	0.008	
H.P	111.310	
H.Aplus	80.929	
H.h2	68.777	
E.s	81.526	
k.s_373	0.124	
k.Aplus_373	190.617	
k.P_373	40.319	
k.h2_373	101.801	
k.s	0.124	=k.s_373*EXP(E.s/law*(-1/temp+1/373))
k.Aplus	190.617	=k.Aplus_373*EXP(-H.Aplus/law*(1/373-1/temp))
k.P	40.319	=k.P_373*EXP(-H.P/law*(1/373-1/temp))
k.h2	101.801	=k.h2_373*EXP(-H.h2/law*(1/373-1/temp))
chargebal	-0.040	=hplus+c.a1+hplus*c.alol/(KAlol+hplus)-(10^-14/hplus+c.a3+c.p2+2*c.p3+3*c.p4)
d(c.a)/d(tau)	-0.015	=-k.s*k.Aplus*c.a1*k.h2*c.h2/(1+k.Aplus*c.a1+k.P*c.p1)/(1+(k.h2*c.h2)^0.5)^2
conv	0.000	=1-c.a/c.a0

In the section below the remainder of the problem is specified. In the first column variable names and equation names are specified. In the second column, the variable values are specified and equations entered. The third column displays the formulas entered in the "Input" column. It should be noted that in addition to the code used in this program, the "accept labels" option under the Tools→Options→Calculations menu. This handy option allows the user to essentially use variable names without explicitly defining them. For example, the first variable is the feed concentration of alanine and called c.a0. The numerical value of c.a0 is entered into the adjacent cell. Now, the variable name "c.a0" may be used in equations entered in the "Input" column instead of a cell reference. The "Display Formula" column shows equations as entered into the "Input" column.

There are several other worksheets in this program. The "Data" worksheet contains the initial conditions and experimental data for the 20 experiments used for parameter determination. The output of the macro is written to a different worksheet for each of the twenty experiments.

C.2 Description of calculation procedure

Calculations are performed in the following manner. For each of the 20 experiments used to determine the kinetic parameters, alanine concentration versus time is predicted. These trajectories are compared to the concentration data points from experimental works. The sum of the squared differences (SS) between the predicted and 109 experimental points are calculated at the conclusion of each run through the entire set experiments. The goal is then to

minimize the SS, which is done by random walk where at the beginning of each set of calculations, one of the 8 kinetic parameters is randomly chosen and then randomly increased or decreased by a specific percent. If at the conclusion of the run the sum of squares is reduced, the parameter change is retained, if the SS increases the original value is restored. If after 83 cycles the SS is not reduced, the set of parameters have reached a minimum and the calculation is terminated.

The mathematics involved in predicting these trajectories makes use of the Runge Kutta method in conjunction with the Excel Solver add-in. Runge Kutta is a predictor method where small time steps are taken and estimates of the derivative at these points is used to predict the next value of the dependent variable. In this particular case, between time steps the Solver add-in is called to set the solution charge balance to zero.

In the next section, the code is provided as it appears in the program file. The code contains comment lines which explain the function of various section of code.

C.3 Visual Basic Code

```
Public rowdeq(1 To 10)
Public f(10) As Double          'holds derivative values
Public z(1 To 50) As Double     'Variable used to hold onto initial values
Public initial                  'holds the initial value of the indep variable
Public columnvar
Public CurrentRow
Public rowvar(1 To 10) As Single
Public expnames(21) As Double
Sub Caller()
```

```
row1 = ActiveWorkbook.Names("startingpt").RefersToRange.Row + 1
column1 = ActiveWorkbook.Names("startingpt").RefersToRange.Column

For i = 0 To 50
If (Not IsEmpty(Worksheets("Set Up").Cells(row1 + i, column1))) _
And (Worksheets("Set Up").Cells(row1 + i, column1)) _
Like "d(*" Then
subcaller = Worksheets("Set Up").Cells(row1 + i, column1).Value
End If
Next i

For i = 0 To 50
If (Not IsEmpty(Worksheets("Set Up").Cells(row1 + i, column1))) _
And (Worksheets("Set Up").Cells(row1 + i, column1)) _
Like "f(*" Then
subcaller = Worksheets("Set Up").Cells(row1 + i, column1).Value
End If
Next i

If subcaller Like "d(*" Then
Call RungeKutta4
End If

If subcaller Like "f(*" Then
Dim solverpath As String
On Error Resume Next
If Application.IsNA(Workbooks("Solver.xla")).Name Then
solverpath = Application.LibraryPath & "\solver\solver.xla"
ThisWorkbook.VBProject.References.AddFromFile solverpath

End If
On Error GoTo 0
Call SolverSub
End If

End Sub
Sub FuncList(t, y, f, i)
temp = Worksheets("Set Up").Cells(rowdeq(i), columnvar).Value
If (Not IsNumeric(temp)) Then
msg = "There was a problem with the calculation. "
msg = msg & "At least one derivative"
msg = msg & " has become non-numeric due to an error."
msg = msg & " You will need to reinitialize all dependent variables after"
msg = msg & " you find the error. Be sure to reinitialize the"
msg = msg & " independent variable also."
notice = MsgBox(msg, vbOKOnly, "Runtime Error")
```

```
End
End If
f(i) = Worksheets("Set Up").Cells(rowdeq(i), columnvar).Value
End Sub
Sub Addworksheets()
jump = 1
For i = 1 To 19
expnames(i) = Worksheets("Experiments").Cells(1, jump).Value
Sheets.Add.Name = expnames(i) & "Output"

jump = jump + 5
Next i
End Sub
Sub RungeKutta4()
'Call displayformula
'Worksheets("Output").UsedRange.ClearContents
'Worksheets("Summary").UsedRange.ClearContents

' Adapted using notation and methods described in
' Reference B. Carnahan, H. Luther, J. Wilkes, "Applied Numerical
' Methods", Wiley, New York, 1969.
Dim rowvar(1 To 50)            'Used to keep keep track of rows in loop below
Dim y(1 To 50) As Double       'Array variable used for transfering dependent
variable values
Dim k1(10) As Double           'k values are part of Runge Kutta calculation
Dim k2(10) As Double
Dim k3(10) As Double
Dim k4(10) As Double
Dim expnames(1 To 22) As Variant
Dim cao(22) As Double
Dim cpo(22) As Double
Dim ch2(22) As Double
Dim temperature(22) As Double
Dim parameters(9) As Double

walks = 125

' start number of random steps
initialave = Worksheets("Summary").Cells(27, 2).Value
frankjump = 0
For frank = 0 To walks
Worksheets("Set Up").Range("h15").Value = frank
For pmer = 1 To 9
parameters(pmer) = _
Worksheets("Set Up").Cells(30 + pmer, 8).Value
Next pmer
```

```
'Select cell to change randomly

Randomize

random1 = Int((38 - 31 + 1) * Rnd + 31)
random2 = Int((2 - 1 + 1) * Rnd + 1)

If random2 = 1 Then
Worksheets("Set Up").Cells(random1, 8).Value = _
Worksheets("Set Up").Cells(random1, 8).Value * 1.005
Else
Worksheets("Set Up").Cells(random1, 8).Value = _
Worksheets("Set Up").Cells(random1, 8).Value * 0.995
End If

For pmer = 1 To 8
Worksheets("Set Up").Cells(30 + pmer, 2).Value = _
Worksheets("Set Up").Cells(30 + pmer, 8).Value
Next pmer

jump = 1
For i = 1 To 21
expnames(i) = Worksheets("Experiments").Cells(1, jump).Value
cao(i) = Worksheets("Experiments").Cells(6, jump + 1).Value
cpo(i) = Worksheets("Experiments").Cells(5, jump + 1).Value
ch2(i) = Worksheets("Experiments").Cells(4, jump + 1).Value
temperature(i) = Worksheets("Experiments").Cells(2, jump + 1).Value

jump = jump + 5
Next i
runs = 20

For reaction = 1 To runs
Worksheets("Set Up").Range("h14").Value = reaction
If reaction = 5 Then
Worksheets("Set Up").Cells(44, 2).Formula = Worksheets("Set Up").Cells(45,
7).Formula
End If

If reaction = 8 Then
Worksheets("Set Up").Cells(44, 2).Formula = Worksheets("Set Up").Cells(46,
7).Formula
End If

j = 0
```

```
jj = 0
m = 0
Worksheets("Set Up").Range("b9").Value = cao(reaction)
Worksheets("Set Up").Range("b25").Value = cao(reaction)
Worksheets("Set Up").Range("b10").Value = cpo(reaction)
Worksheets("Set Up").Range("b11").Value = ch2(reaction)
Worksheets("Set Up").Range("b29").Value = temperature(reaction)

'Puts the name of the independent variable into the Output Sheet
Worksheets(expnames(reaction) & " Output").Cells(2, 1) = Worksheets("Set
Up").Range("indepvar").Value

'Puts the initial value of the independent variable into the Output Sheet
Worksheets(expnames(reaction) & " Output").Cells(3, 1) = Worksheets("Set
Up").Range("initialindep").Value

'These variables used to keep track of the rows and columns of variables in Set
Up
row1 = ActiveWorkbook.Names("startingpt").RefersToRange.Row + 1
column1 = ActiveWorkbook.Names("startingpt").RefersToRange.Column

'columnvar holds the value of the column with variable values
columnvar = column1 + 1

'The following two nested loops find the initial values and names of the
'dependent variables
For i = 0 To 50
If (Not IsEmpty(Worksheets("Set Up").Cells(row1 + i, column1))) _
And (Worksheets("Set Up").Cells(row1 + i, column1)) _
Like "d(*" Then
'store the rows of the diffeqs
jj = jj + 1
'check number of diffeqs
If (jj > 10) Then
notice = MsgBox("You have more than 10 Diff Eqns. The program can only solve
10.", vbOKOnly, "Error")
End
End If
rowdeq(jj) = row1 + i
temp = Worksheets("Set Up").Cells(row1 + i, column1).Value
temp = Right(temp, Len(temp) - 2)
temp = Left(temp, InStr(temp, ")"))
temp = Left(temp, Len(temp) - 1)
   For k = 0 To 50
   If (Not IsEmpty(Worksheets("Set Up").Cells(row1 + k, column1))) _
   And (Worksheets("Set Up").Cells(row1 + k, column1)) _
```

```
   Like temp Then
   j = j + 1
   'rowvar holds the rows that correspond to dependent variable derivatives.
   'z(j) holds the initial value
   rowvar(j) = row1 + k
   z(j) = Worksheets("Set Up").Cells(row1 + k, column1 + 1)
   Worksheets(expnames(reaction) & " Output").Cells(3, 1 + j) = _
   Worksheets("Set Up").Cells(row1 + k, column1 + 1)
   Worksheets(expnames(reaction) & " Output").Cells(2, 1 + j) = _
   Worksheets("Set Up").Cells(row1 + k, column1).Value
   End If
   Next k
End If
Next i
'check that initial values exist for all indep variables
If (jj <> j) Then
notice = MsgBox("The program cannot continue because initial values were not
found for every dependent variable.", vbOKOnly, "Error")
End
End If


'This loop finds the location of the formulas
Dim rowform(1 To 50) As Single
For i = 0 To 50
   If (Not Worksheets("Set Up").Cells(row1 + i, column1).Value Like "d(*)") _
   And Worksheets("Set Up").Cells(row1 + i, column1 + 1).HasFormula Then
      m = m + 1
      rowform(m) = row1 + i
      Worksheets(expnames(reaction) & " Output").Cells(3, 1 + j + m) = _
      Worksheets("Set Up").Cells(row1 + i, column1 + 1).Value
      Worksheets(expnames(reaction) & " Output").Cells(2, 1 + j + m) = _
      Worksheets("Set Up").Cells(row1 + i, column1).Value
   End If
Next i

'Formats Runge Kutta Sheet
Worksheets(expnames(reaction) & " Output").Range("A1") = expnames(reaction)
& " Output"
Worksheets(expnames(reaction) & " Output").Range("A1").HorizontalAlignment =
xlLeft
Worksheets(expnames(reaction) & " Output").Range("A1").Font.Bold = True
Worksheets(expnames(reaction) & " Output").Range("A1").Font.Italic = True
Worksheets(expnames(reaction) & " Output").Range("A1").Font.Size = 12
Worksheets(expnames(reaction) & " Output").Range("2:2").HorizontalAlignment
= xlCenter
```

```
Worksheets(expnames(reaction) & " Output").Range("2:2").Font.Bold = True
Dim CurrentRow
row1 = 3
row2 = row1 + 1
column1 = 1
Stoprow = row1 + Worksheets("Set Up").Range("numsteps")

' Sets up for main calculation loop
h = Worksheets("Set Up").Range("stepsize")
CurrentRow = row1
initial = Worksheets("Set Up").Range("initialindep").Value
'Worksheets("Output").Cells(3, 12).Value = Worksheets("Set
Up").Range("b25").Value
'Main calculation loop
'Solves inital charge balance

SolverReset
SolverOptions Scaling:=True
   SolverOk SetCell:=Worksheets("Set Up").Range("b43"), MaxMinVal:=3,
ValueOf:=0, _
  ByChange:=Worksheets("Set Up").Range("b19")
   SolverAdd CellRef:=Worksheets("Set Up").Range("b19"), Relation:=3,
FormulaText:=".000000001"
   SolverAdd CellRef:=Worksheets("Set Up").Range("b19"), Relation:=1,
FormulaText:=".99"
   SolverSolve UserFinish:=True

SolverDelete CellRef:=Worksheets("Set Up").Range("b19"), Relation:=3,
FormulaText:=".000000001"
  SolverDelete CellRef:=Worksheets("Set Up").Range("b19"), Relation:=1,
FormulaText:=".99"

Do While CurrentRow < Stoprow
t = Worksheets(expnames(reaction) & " Output").Cells(CurrentRow,
column1).Value
Worksheets("Set Up").Range("initialindep").Value = t

For i = 1 To j
y(i) = Worksheets(expnames(reaction) & " Output").Cells(CurrentRow, column1 +
i).Value
Next i



For i = 1 To j
Worksheets("Set Up").Cells(rowvar(i), columnvar) = y(i)
```

```
Next i

SolverReset
SolverOptions Scaling:=True
   SolverOk SetCell:=Worksheets("Set Up").Range("b43"), MaxMinVal:=3,
ValueOf:=0, _
  ByChange:=Worksheets("Set Up").Range("b19")
   SolverAdd CellRef:=Worksheets("Set Up").Range("b19"), Relation:=3,
FormulaText:=".000000001"
   SolverAdd CellRef:=Worksheets("Set Up").Range("b19"), Relation:=1,
FormulaText:=".99"
   SolverSolve UserFinish:=True

   SolverDelete CellRef:=Worksheets("Set Up").Range("b19"), Relation:=3,
FormulaText:=".000000001"
  SolverDelete CellRef:=Worksheets("Set Up").Range("b19"), Relation:=1,
FormulaText:=".99"


For i = 1 To m
Worksheets(expnames(reaction) & " Output").Cells(CurrentRow, column1 + j + i)
= _
Worksheets("Set Up").Cells(rowform(i), 2).Value
Next i

For i = 1 To j
FuncList t, y, k1, i
FuncList t + h / 2, y(i) + h * k1(i) / 2, k2, i
FuncList t + h / 2, y(i) + h * k2(i) / 2, k3, i
FuncList t + h, y(i) + h * k3(i), k4, i
Next i


CurrentRow = CurrentRow + 1

Worksheets(expnames(reaction) & " Output").Cells(CurrentRow, column1).Value
= t + h
Worksheets("Set Up").Range("initialindep").Value = t + h

For i = 1 To m
Worksheets(expnames(reaction) & " Output").Cells(CurrentRow, column1 + j + i)
= _
Worksheets("Set Up").Cells(rowform(i), 2).Value
Next i
```

```
Worksheets(expnames(reaction) & " Output").Cells(CurrentRow, column1 + 1) =
_
y(1) + h / 6 * (k1(1) + 2 * k2(1) + 2 * k3(1) + k4(1))

Loop


'End of main calculation loop

'Adds final values of dependent variables to Runge Kutta Sheet
For i = 1 To j
y(i) = Worksheets(expnames(reaction) & " Output").Cells(Stoprow, column1 +
i).Value
Next i
For i = 1 To j
Worksheets("Set Up").Cells(rowvar(i), columnvar) = y(i)
Next i
For i = 1 To m
Worksheets(expnames(reaction) & " Output").Cells(Stoprow, column1 + j + i) = _
Worksheets("Set Up").Cells(rowform(i), 2).Value
Next i

'Resets initial values
For i = 1 To j
Worksheets("Set Up").Cells(rowvar(i), columnvar) = z(i)
Next i
Worksheets("Set Up").Range("initialindep") = initial
Worksheets("Set Up").Activate
Next reaction

'Graphs Values

jump2 = 1

For i = 1 To 20
expnames(i) = Worksheets("Experiments").Cells(1, jump2).Value
'cao(i) = Worksheets("Experiments").Cells(6, jump2 + 1).Value
'cpo(i) = Worksheets("Experiments").Cells(5, jump2 + 1).Value
'ch2(i) = Worksheets("Experiments").Cells(4, jump2 + 1).Value
'temperature(i) = Worksheets("Experiments").Cells(2, jump2 + 1).Value

jump2 = jump2 + 5
Next i
runs2 = 20
jump2 = 1
For reaction2 = 1 To runs2
```

```
'Clears previous chart values
Charts(expnames(reaction2) & " Plot").ChartArea.ClearContents

'Adds dependent variable series to chart
Worksheets(expnames(reaction2) & " Output").Activate
With Charts(expnames(reaction2) & " Plot").SeriesCollection.NewSeries
.Name = "Predicted"
.Values = Worksheets(expnames(reaction2) & " Output").Range(Cells(3, 2),
Cells(1003, 2))
.XValues = Worksheets(expnames(reaction2) & " Output").Range(Cells(3, 1),
Cells(1003, 1))
End With

Worksheets("Experiments").Activate
With Charts(expnames(reaction2) & " Plot").SeriesCollection.NewSeries
.Name = "Data"
.Values = Worksheets("Experiments").Range(Cells(9, jump2 + 1), Cells(17,
jump2 + 1))
.XValues = Worksheets("Experiments").Range(Cells(9, jump2), Cells(17, jump2))
End With

Worksheets("Experiments").Activate
With Charts(expnames(reaction2) & " Plot").SeriesCollection.NewSeries
.Name = "Fit"
.Values = Worksheets("Experiments").Range(Cells(9, jump2 + 2), Cells(17,
jump2 + 2))
.XValues = Worksheets("Experiments").Range(Cells(9, jump2), Cells(17, jump2))
End With

'Gives X axis name of independent variable and sets to the range to
'be the initial to final value
If Worksheets("Set Up").Range("finalindep").Value > _
Worksheets("Set Up").Range("initialindep").Value Then
minx = Worksheets("Set Up").Range("initialindep").Value
maxx = Worksheets("Set Up").Range("finalindep").Value
Else
minx = Worksheets("Set Up").Range("finalindep").Value
maxx = Worksheets("Set Up").Range("initialindep").Value

End If

With Charts(expnames(reaction2) & " Plot").Axes(xlCategory)
  .HasTitle = True
  .AxisTitle.Caption = "t(hr)"
   .MinimumScale = minx
```

```
  .MaximumScale = maxx
End With

With Charts(expnames(reaction2) & " Plot").Axes(xlValue)
  .HasTitle = True
  .AxisTitle.Caption = "C.a(M)"
  .MinimumScale = 0

End With

With Charts(expnames(reaction2) & " Plot")
    .HasTitle = True
    .ChartTitle.Text = expnames(reaction2)
End With

jump2 = jump2 + 5

Next reaction2

jump3 = 1

For i = 1 To 20
expnames(i) = Worksheets("Experiments").Cells(1, jump3).Value
cao(i) = Worksheets("Experiments").Cells(6, jump3 + 1).Value
cpo(i) = Worksheets("Experiments").Cells(5, jump3 + 1).Value
ch2(i) = Worksheets("Experiments").Cells(4, jump3 + 1).Value
temperature(i) = Worksheets("Experiments").Cells(2, jump + 1).Value

jump3 = jump3 + 5
Next i

runs3 = 20
jump3 = 1

For reaction3 = 1 To runs3

For p = 0 To 9

If IsEmpty(Worksheets("Experiments").Cells(8 + p, jump3).Value) Then
Exit For
End If

For q = 0 To 1000

If Worksheets(expnames(reaction3) & " Output").Cells(3 + q, 1).Value >= _
Worksheets("Experiments").Cells(8 + p, jump3).Value Then
```

```
Worksheets("Experiments").Cells(8 + p, jump3 + 3).Value = _
Worksheets(expnames(reaction3) & " Output").Cells(3 + q, 2).Value
Exit For

End If

Next q

Next p

jump3 = jump3 + 5

Next reaction3

Worksheets("Set Up").Activate

jump4 = 5

For i = 1 To 20
expnames(i) = Worksheets("Experiments").Cells(1, jump4 - 4).Value
Worksheets("Summary").Cells(9 + i, 1 + frankjump).Value = _
Worksheets("Experiments").Cells(1, jump4).Value
Worksheets("Summary").Cells(9 + i, 2 + frankjump).Value = _
Worksheets("Experiments").Cells(18, jump4).Value
jump4 = jump4 + 5
Next i

For k = 0 To 7
Worksheets("Summary").Cells(2 + k, frankjump + 1).Value = _
Worksheets("Set Up").Cells(31 + k, 1).Value
Worksheets("Summary").Cells(2 + k, frankjump + 2).Value = _
Worksheets("Set Up").Cells(31 + k, 2).Value
Next k

Worksheets("Summary").Cells(27, frankjump + 1).Value = "SSq"
Worksheets("Summary").Cells(27, frankjump + 2).Value = _
Worksheets("Experiments").Cells(18, 2).Value
Worksheets("Summary").Cells(28, frankjump + 1).Value = "Desired"
Worksheets("Summary").Cells(28, frankjump + 2).Value = _
Worksheets("Experiments").Cells(20, 2).Value

If parameters(9) < _
Worksheets("Experiments").Cells(18, 2).Value Then
For pmer = 1 To 9
Worksheets("Set Up").Cells(30 + pmer, 8).Value = _
```

```
parameters(pmer)
Next pmer
End If

If parameters(9) > _
Worksheets("Experiments").Cells(18, 2).Value Then
Worksheets("Set Up").Cells(39, 8).Value = _
Worksheets("Experiments").Cells(18, 2).Value
End If

Worksheets("Set Up").Cells(40, 8).Value = _
Worksheets("Experiments").Cells(19, 2).Value
Worksheets("Set Up").Activate
frankjump = frankjump + 2
Next frank

End Sub
Sub Grapher()
Dim expnames(1 To 19) As Variant
Dim cao(19) As Double
Dim cpo(19) As Double
Dim ch2(19) As Double
Dim temperature(19) As Double

'Get names, put in array, add sheets
jump2 = 1

For i = 1 To 19
expnames(i) = Worksheets("Experiments").Cells(1, jump2).Value
cao(i) = Worksheets("Experiments").Cells(6, jump2 + 1).Value
cpo(i) = Worksheets("Experiments").Cells(5, jump2 + 1).Value
ch2(i) = Worksheets("Experiments").Cells(4, jump2 + 1).Value
temperature(i) = Worksheets("Experiments").Cells(2, jump2 + 1).Value

jump2 = jump2 + 5
Next i
runs2 = 19
jump2 = 1
For reaction2 = 1 To runs2

'Clears previous chart values
Charts(expnames(reaction2) & " Plot").ChartArea.ClearContents

'Adds dependent variable series to chart
Worksheets(expnames(reaction2) & " Output").Activate
With Charts(expnames(reaction2) & " Plot").SeriesCollection.NewSeries
```

```
.Name = "Predicted"
.Values = Worksheets(expnames(reaction2) & " Output").Range(Cells(3, 2),
Cells(1003, 2))
.XValues = Worksheets(expnames(reaction2) & " Output").Range(Cells(3, 1),
Cells(1003, 1))
End With

Worksheets("Experiments").Activate
With Charts(expnames(reaction2) & " Plot").SeriesCollection.NewSeries
.Name = "Data"
.Values = Worksheets("Experiments").Range(Cells(9, jump2 + 1), Cells(17,
jump2 + 1))
.XValues = Worksheets("Experiments").Range(Cells(9, jump2), Cells(17, jump2))
End With

Worksheets("Experiments").Activate
With Charts(expnames(reaction2) & " Plot").SeriesCollection.NewSeries
.Name = "Fit"
.Values = Worksheets("Experiments").Range(Cells(9, jump2 + 2), Cells(17,
jump2 + 2))
.XValues = Worksheets("Experiments").Range(Cells(9, jump2), Cells(17, jump2))
End With

'Gives X axis name of independent variable and sets to the range to
'be the initial to final value
If Worksheets("Set Up").Range("finalindep").Value > _
Worksheets("Set Up").Range("initialindep").Value Then
minx = Worksheets("Set Up").Range("initialindep").Value
maxx = Worksheets("Set Up").Range("finalindep").Value
Else
minx = Worksheets("Set Up").Range("finalindep").Value
maxx = Worksheets("Set Up").Range("initialindep").Value

End If

With Charts(expnames(reaction2) & " Plot").Axes(xlCategory)
  .HasTitle = True
  .AxisTitle.Caption = "t(hr)"
   .MinimumScale = minx
   .MaximumScale = maxx
End With

With Charts(expnames(reaction2) & " Plot").Axes(xlValue)
  .HasTitle = True
  .AxisTitle.Caption = "C.a(M)"
  .MinimumScale = 0
```

```
End With

With Charts(expnames(reaction2) & " Plot")
   .HasTitle = True
   .ChartTitle.Text = expnames(reaction2)
End With

jump2 = jump2 + 5

Next reaction2
End Sub
Sub Fitter()
Dim expnames(1 To 19) As Variant
Dim cao(19) As Double
Dim cpo(19) As Double
Dim ch2(19) As Double
Dim temperature(19) As Double

'Get names, put in array, add sheets
jump3 = 1

For i = 1 To 19
expnames(i) = Worksheets("Experiments").Cells(1, jump3).Value
cao(i) = Worksheets("Experiments").Cells(6, jump3 + 1).Value
cpo(i) = Worksheets("Experiments").Cells(5, jump3 + 1).Value
ch2(i) = Worksheets("Experiments").Cells(4, jump3 + 1).Value
temperature(i) = Worksheets("Experiments").Cells(2, jump + 1).Value

jump3 = jump3 + 5
Next i


runs3 = 19
jump3 = 1



For reaction3 = 1 To runs3

For p = 0 To 9

If IsEmpty(Worksheets("Experiments").Cells(8 + p, jump3).Value) Then
Exit For
End If
```

```
For q = 0 To 1000

If Worksheets(expnames(reaction3) & " Output").Cells(3 + q, 1).Value >= _
Worksheets("Experiments").Cells(8 + p, jump3).Value Then

Worksheets("Experiments").Cells(8 + p, jump3 + 3).Value = _
Worksheets(expnames(reaction3) & " Output").Cells(3 + q, 2).Value
Exit For

End If

Next q

Next p

jump3 = jump3 + 5
frankjump = frankjump + 2
Next reaction3

End Sub
Sub SolverSub()
Call displayformula
Worksheets("Output").UsedRange.ClearContents
Worksheets("Summary").UsedRange.ClearContents



'These variables used to keep track of the rows and columns of variables in Set
Up
row1 = ActiveWorkbook.Names("startingpt").RefersToRange.Row + 1
column1 = ActiveWorkbook.Names("startingpt").RefersToRange.Column

'columnvar holds the value of the column with variable values
columnvar = column1 + 1

'The following two nested loops find the initial values and names of the
'dependent variables
For i = 0 To 50
If (Not IsEmpty(Worksheets("Set Up").Cells(row1 + i, column1))) _
And (Worksheets("Set Up").Cells(row1 + i, column1)) _
Like "f(*" Then
'store the rows of the diffeqs
jj = jj + 1
'check number of diffeqs
If jj = 1 Then
```

```
balance1 = Cells(row1 + i, column1 + 1).Address

End If

If jj = 2 Then
balances = balances & Cells(row1 + i, column1 + 1).Address & ":"
End If

If (jj > 10) Then
notice = MsgBox("You have more than 10 Diff Eqns. The program can only solve
10.", vbOKOnly, "Error")
End
End If

rowdeq(jj) = row1 + i
temp = Worksheets("Set Up").Cells(row1 + i, column1).Value
temp = Right(temp, Len(temp) - 2)
'temp = Left(temp, InStr(temp, ")"))
temp = Left(temp, Len(temp) - 1)
   For k = 0 To 50
   If (Not IsEmpty(Worksheets("Set Up").Cells(row1 + k, column1))) _
   And (Worksheets("Set Up").Cells(row1 + k, column1)) _
   Like temp Then
   j = j + 1
'rowunk(j) = row1 + k
   varied = varied & Cells(row1 + k, column1 + 1).Address & ","

' rowvar holds the rows that correspond to dependent variable derivatives.
' z(j) holds the initial value
   rowvar(j) = row1 + k
   z(j) = Worksheets("Set Up").Cells(row1 + k, column1 + 1)

  ' Worksheets("Output").Cells(3, 1 + j) = _
  ' Worksheets("Set Up").Cells(row1 + k, column1 + 1)
   Worksheets("Output").Cells(2, 1 + j) = _
   Worksheets("Set Up").Cells(row1 + k, column1).Value
   End If
   Next k
End If
Next i

'check that initial values exist for all indep variables
If (jj <> j) Then
notice = MsgBox("The program cannot continue because initial values were not
found for every dependent variable.", vbOKOnly, "Error")
End
```

```
End If


'This loop finds the location of the formulas
Dim rowform(1 To 50) As Single
For i = 0 To 50
   If (Not Worksheets("Set Up").Cells(row1 + i, column1).Value Like "d(*)") _
   And Worksheets("Set Up").Cells(row1 + i, column1 + 1).HasFormula Then
      m = m + 1
      rowform(m) = row1 + i
'      Worksheets("Output").Cells(3, 1 + j + m) = _
'      Worksheets("Set Up").Cells(row1 + i, column1 + 1).Value
      Worksheets("Output").Cells(2, 1 + j + m) = _
      Worksheets("Set Up").Cells(row1 + i, column1).Value
   End If
Next i

'Formats Runge Kutta Sheet
Worksheets("Output").Range("A1") = "Solver Output"
Worksheets("Output").Range("A1").HorizontalAlignment = xlLeft
Worksheets("Output").Range("A1").Font.Bold = True
Worksheets("Output").Range("A1").Font.Italic = True
Worksheets("Output").Range("A1").Font.Size = 12
Worksheets("Output").Range("2:2").HorizontalAlignment = xlCenter
Worksheets("Output").Range("2:2").Font.Bold = True
Dim CurrentRow
'row1 = ActiveWorkbook.Names("indep0").RefersToRange.Row
'row2 = row1 + 1
'column1 = ActiveWorkbook.Names("indep0").RefersToRange.Column
'stoprow = row1 + Worksheets("Set Up").Range("numsteps")

' Sets up for main calculation loop

Range(balance1).Select
bal1 = Selection.Address
ActiveSheet.Names.Add Name:="bal1", RefersTo:="=" & bal1

balances = balances & Cells(rowdeq(jj), column1 + 1).Address & ":"
balances = Left(balances, Len(balances) - 1)
Range(balances).Select
bals = Selection.Address
ActiveSheet.Names.Add Name:="bals", RefersTo:="=" & bals

varied = Left(varied, Len(varied) - 1)
Range(varied).Select
vary = Selection.Address
```

```
ActiveSheet.Names.Add Name:="vary", RefersTo:="=" & vary
final = Worksheets("Set Up").Range("finalindep").Value
'Main calculation loop

CurrentRow = 3
h = Worksheets("Set Up").Range("stepsize")
initial = Worksheets("Set Up").Range("initialindep").Value
initial2 = Worksheets("Set Up").Range("initialindep").Value
Stoprow = 4 + Worksheets("Set Up").Range("numsteps")
initial = Worksheets("Set Up").Range("initialindep").Value
initial2 = Worksheets("Set Up").Range("initialindep").Value


If Not (IsEmpty(Worksheets("Set Up").Range("indepvar"))) Then

Do While CurrentRow < Stoprow
SolverReset
SolverOptions Scaling:=True
   SolverOk SetCell:=Range("bal1"), MaxMinVal:=3, ValueOf:=0, _
   ByChange:=Range("vary")
' ByChange:="c.h, c.x, c.h"
   SolverAdd CellRef:=Range("bals"), Relation:=2, FormulaText:="0"
  ' SolverAdd CellRef:=Range("$b$4:$b$6"), Relation:=3, FormulaText:="0"
   SolverSolve UserFinish:=True

   SolverDelete CellRef:=Range("bals"), Relation:=2, FormulaText:="0"
   'SolverDelete CellRef:=Range("$b$4:$b$6"), Relation:=3, FormulaText:="0"
Worksheets("Output").Cells(CurrentRow, 1).Value = _
Worksheets("Set Up").Range("initialindep").Value

For i = 1 To j
Worksheets("Output").Cells(CurrentRow, 1 + i).Value = _
Worksheets("Set Up").Cells(rowvar(i), 2).Value
Next i
For i = 1 To m
Worksheets("Output").Cells(CurrentRow, 1 + j + i).Value = _
Worksheets("Set Up").Cells(rowform(i), 2).Value
Next i

CurrentRow = CurrentRow + 1

Worksheets("Set Up").Range("initialindep").Value = _
Worksheets("Set Up").Range("initialindep").Value + h

Loop
```

```
Worksheets("Set Up").Range("initialindep").Value = initial2
For i = 1 To j

Worksheets("Set Up").Cells(rowvar(i), 2).Value = z(i)
Next i

'Summary

Worksheets("Summary").Range("A1") = "Summary of Output"
Worksheets("Summary").Range("A1").HorizontalAlignment = xlLeft
Worksheets("Summary").Range("A1").Font.Bold = True
Worksheets("Summary").Range("A1").Font.Italic = True
Worksheets("Summary").Range("A1").Font.Size = 12

'Resets initial values
For i = 1 To j
Worksheets("Set Up").Cells(rowvar(i), columnvar) = z(i)
Next i

Worksheets("Set Up").Range("initialindep") = initial2

'Creates Summary Table
summarypts = Worksheets("Set Up").Range("summarypts").Value
For i = 1 To summarypts
Worksheets("Summary").Cells(2, i) = _
Worksheets("Output").Cells(2, i)
Worksheets("Summary").Cells(2, i).Font.Bold = True
Worksheets("Summary").Cells(2, i).HorizontalAlignment = xlCenter
Next i
step = Worksheets("Set Up").Range("numsteps").Value
For i = 0 To summarypts
Worksheets("Output").Activate
Worksheets("Output").Range(Cells(3 + step / summarypts * i, 1), Cells(3 + step /
summarypts _
* i, 20)).Copy Worksheets("Summary").Cells(3 + i, 1)
Next i
End If

If (IsEmpty(Worksheets("Set Up").Range("indepvar"))) Then

SolverReset
SolverOptions Scaling:=True
   SolverOk SetCell:=Range("bal1"), MaxMinVal:=3, ValueOf:=0, _
   ByChange:=Range("vary")
' ByChange:="c.h, c.x, c.h"
   SolverAdd CellRef:=Range("bals"), Relation:=2, FormulaText:="0"
```

```
  ' SolverAdd CellRef:=Range("$b$4:$b$6"), Relation:=3, FormulaText:="0"
   SolverSolve UserFinish:=True

   SolverDelete CellRef:=Range("bals"), Relation:=2, FormulaText:="0"
   'SolverDelete CellRef:=Range("$b$4:$b$6"), Relation:=3, FormulaText:="0"
End If

'Clears previous chart values
'Charts("RK Plot").ChartArea.ClearContents

'Adds dependent variable series to chart
'For i = 1 To j
'With Charts("RK Plot").SeriesCollection.NewSeries
'.Name = Worksheets("Output").Cells(2, 1 + i)
'.Values = Worksheets("Output").Range(Cells(3, 1 + i), Cells(3 + stoprow, 1 + i))
'.XValues = Worksheets("Output").Range(Cells(3, 1), Cells(3 + stoprow, 1))
'End With
'Next i
'Gives X axis name of independent variable and sets to the range to
'be the initial to final value
'If Worksheets("Set Up").Range("finalindep").Value > _
'Worksheets("Set Up").Range("initialindep").Value Then
'minx = Worksheets("Set Up").Range("initialindep").Value
'maxx = Worksheets("Set Up").Range("finalindep").Value
'Else
'minx = Worksheets("Set Up").Range("finalindep").Value
'maxx = Worksheets("Set Up").Range("initialindep").Value

'End If

'With Charts("RK Plot").Axes(xlCategory)
 '  .HasTitle = True
  '  .AxisTitle.Caption = Worksheets("Output").Cells(2, 1).Value
  '  .MinimumScale = minx
'    .MaximumScale = maxx
'End With
'Worksheets("Set Up").Activate
End Sub

'Displays formulas in Set Up Sheet
Sub displayformula()
'Worksheets("Output").UsedRange.ClearContents
row1 = ActiveWorkbook.Names("startingpt").RefersToRange.Row + 1
column1 = ActiveWorkbook.Names("startingpt").RefersToRange.Column
For i = 0 To 50
If Worksheets("Set Up").Cells(row1 + i, column1 + 1).HasFormula _
```

```
Then
Worksheets("Set Up").Cells(row1 + i, column1 + 2) = "'" & Cells(row1 + i,
column1 + 1).Formula
Else
Worksheets("Set Up").Cells(row1 + i, column1 + 2) = ""
End If
Next i
End Sub
```

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