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peroxymonosulfate at pH < 1.7**

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ABSTRACT

OXIDATION OF CYCLOHEXENE WITH AQUEOUS POTASSIUM PEROXYMONOSULFATE AT $\text{pH} < 1.7$

by
Wen-Qing Sun

Glycols are often used as starting materials for pharmaceuticals. They are currently manufactured by reacting alkenes with organic peroxy acids in organic solutions that contain chlorinated solvents. The aim of this research is to find ways to avoid the use of hazardous organic solvents in the manufacture of pharmaceuticals in order to prevent pollution. Our approach is to find alternative synthetic methods using water as solvent.

Based on literature information, it was decided to determine if the aqueous potassium peroxymonosulfate oxidation of water-immiscible cyclohexene at room temperature can be scaled up to become a new method to manufacture glycols. Acidic ($\text{pH} \leq 1.7$) solutions of $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ in water produced trans-1,2-cyclohexanediol from cyclohexene. In a vigorously stirred two-phase mixture, 0.44 mmole KHSO_5 oxidizes cyclohexene to nearly 80% diol with no significant byproducts in 2h at room temperature.

The reaction was then scaled-up to one dm^3 . The mixture of deionized water, cyclohexene, and freshly prepared Oxone solution was stirred at 907 rpm for 2h at room temperature. In order to remove the diol from the water phase, the mixture was treated with Na_2SO_4 which quantitatively salted out the diol before extraction with ethyl ether. The extract was dried over MgSO_4 and analyzed by GC using an internal standard. Excellent carbon balances were obtained.

**OXIDATION OF CYCLOHEXENE WITH
AQUEOUS POTASSIUM PEROXYMONOSULFATE AT pH < 1.7**

by
Wen-Qing Sun

**A Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Applied Chemistry**

**Department of Chemical Engineering,
Chemistry and Environmental Science**

May 1994

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APPROVAL PAGE

OXIDATION OF CYCLOHEXENE WITH
AQUEOUS POTASSIUM PEROXYMONOSULFATE AT PH <1.7

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This thesis is dedicated to my parents

ACKNOWLEDGMENT

The author wishes to express her gratitude to her supervisors, Professor Howard Perlmutter and Professor Henry Shaw, for their guidance throughout this research.

Special thanks to Professor Gund for serving as member of the committee.

The author appreciates the help and suggestions from Mr. Chen Gu. Also thanks are given to Dr. Hung-Yi Shu for setting up the one dm³ reactor.

C. Brockway, provided gas chromatography and timely and expert assistance on analytical questions.

Mr. Yogesh Gandhi, Supervisor of stockroom of Chemistry, helped find needed glassware and the reagents used in this research.

And finally, a thank you to the group members, including: Yi Wang, Edward Chen, Paul Yu, Jonathan Yang and Sanmei Xu.

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CHAPTER 1

INTRODUCTION

1.1 Overview

There has been an increasing concern about emissions of volatile organic compounds (VOC's) from chemical industry manufacturing facilities, especially the more hazardous ones such as chlorocarbons and aromatics. For example, the Occupational Safety and Health Administration (OSHA) has recently proposed lowering from 500 ppm to 25 ppm the permitted average hourly exposure to methylene chloride, a widely used solvent¹.

The pharmaceutical and specialty chemical industries have a number of characteristics which make them ideally suited as candidates for VOC reduction:

(1) A large variety of hazardous organic solvents are used in the many chemical reactions leading to such varied chemotherapeutic agents as antibacterial and antibiotics, cardiovascular agents, CNS (central nervous system) drugs, antihistamines, analgesics, steroids, nonsteroidal anti inflammatory agents, hypoglycemic, anticholinergic and antiasthma drugs, as well as antiviral and anticancer drugs.

(2) Because of the high unit costs of the above pharmaceuticals, expensive reagents are practicable. Since the pressure to reduce costs is not as great as in the heavy chemicals industry, efforts to reduce or remove VOC's are more economically feasible. For example, pharmaceutical manufacturing costs amount to about 40% of total costs, compared to almost 90% for heavy organics².

(3) Pharmaceutical manufacturing processes themselves resemble laboratory procedures carried out on a larger scale. Problems of heat and mass transfer are certainly more important than in the laboratory, but can be overcome by scale-up laboratory techniques². Since a certain amount of scale-up is required to provide enough prospective

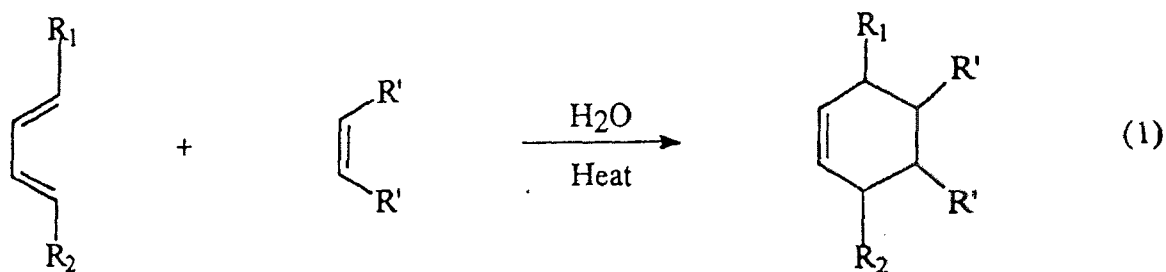
drug for testing, the scale-up of reactions involving reduced amounts of hazardous organic solvents can be a great value.

There has been recent interest among chemists doing organic synthesis research in what Grieco has called "unconventional solvents"³. These fall into 2 major categories:

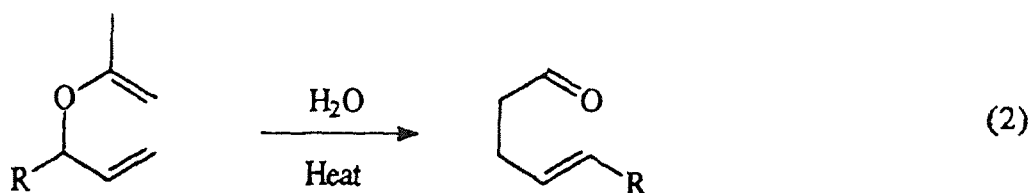
CATEGORY I - REPLACEMENT OF ORGANIC REACTION SOLVENT WITH WATER³⁻⁶

Reactions in this class are mostly of the C-C bond forming type very important in the synthesis of complex pharmaceuticals. They are:

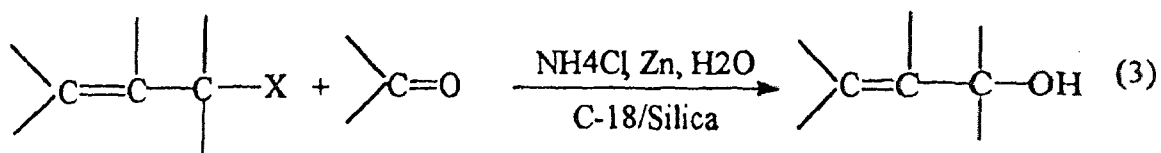
A. The Diels-Alder Reaction (Equation 1)³



B. The Claisen Rearrangement of Allyl Vinyl Ethers (Equation 2)^{3,4}

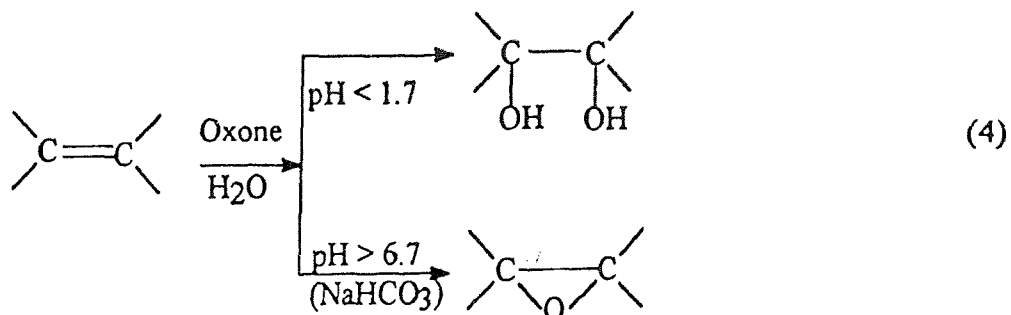


C. "Grignard-type" Organometallic Reaction (Equation 3)⁵



Another reaction where water has replaced organics as solvent is:

D. Oxidation of alkenes to glycols or epoxides (Equation 4)⁶

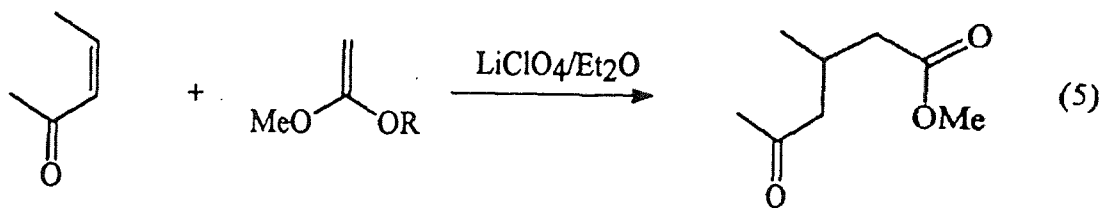


CATEGORY II - REPLACEMENT OF HAZARDOUS ORGANIC SOLVENT WITH MORE BENIGN, OXYGENATED ONES (ETHERS, ESTERS, ALCOHOLS)

These involve the following important C-C bond forming reactions:

A. Diels-Alder Reaction (see Equation 1) can be run in LiClO_4 /ethyl ether or other oxygenated solvents as opposed to the usual chlorinated or aromatic ones³.

B. Similarly, the Michael Addition of Ketene Acetals to α,β -unsaturated Carbonyls (Equation 5)³ can be run with LiClO_4 /ethyl ether instead of the traditional solvent for this reaction which is methylene chloride.



1.2 Approach

The "unconventional solvent" reactions described in CATEGORY I have all been carried out on a micro and/or semimicro scale (several mg to several g; vol. 1-500 ml). We chose the reaction, "Glycolization of Cyclohexene" as an example and demonstrated the reproducibility in the laboratory. We then scaled-up this reaction to one dm³ in order to show how scale-up affects the rate and yield of the reaction.

1.3 Potassium Peroxymonosulfate

Peroxymonosulfuric acid (Caro's acid, H₂SO₅)⁷ is a strong oxidant, but is unstable. The stable commercial triple salt, 2KHSO₅·KHSO₄·K₂SO₄ is prepared by reaction of 86% H₂O₂ with concentrated H₂SO₄, followed by neutralization with K₂CO₃⁸. By X-ray analyses of KHSO₅·H₂O and 2KHSO₅·KHSO₄·K₂SO₄, the structure of the peroxymonosulfate anion is HOOSO₃⁻, with the bond lengths of the three terminal S-O and one internal S-O (peroxo) bonds similar to those in S₂O₈²⁻ and the O-O distance similar to that in H₂O₂⁹.

Like Caro's acid¹⁰⁻¹², potassium peroxymonosulfate is a powerful oxidant. It oxidizes alcohols, ketones, carboxylic acids, alkenes, arenes, phenols, amines, and sulfides^{13,14}. It glycolizes alkanes and aromatic compounds¹⁵ and de-lignifies wood¹⁶. In biphasic mixtures of water, a ketone (usually acetone)¹⁷⁻²¹, dichloromethane, and a phase-transfer catalyst(PTC), KHSO₅ epoxidizes alkenes. The active oxidant in this system is a dioxirane generated by reaction of KHSO₅ with the ketone. Without the ketone no epoxidation occurred. The mixtures were buffered at pH 7-8 with phosphate to avoid Bayer-Villiger oxidation of ketones. Epoxidations of alkenes with KHSO₅ catalyzed by manganese porphyrins^{22,23}, and platinum complexes²⁴ also have been reported, but are impractical because organometallic complexes decompose rapidly during the epoxidation. Mixtures of water-methanol (or ethanol), or water-ethanol-acetic acid overcome the low solubility of KHSO₅ in organic solvents, but the organic solvents are also oxidized, and

large excesses of KHSO_5 are needed to obtain good yields of epoxides^{13,25}. Another problem is that organic- KHSO_5 mixtures may cause combustion¹⁰.

CHAPTER 2

LITERATURE REVIEW

2.1 Background

The glycols are compounds which contain two hydroxyl groups attached to two different carbon atoms. The hydroxyl groups in the glycols may be primary, secondary or tertiary and as such confer the characteristic properties of the kindred alcohols. By oxidation, the primary alcohol groups may be converted into aldehyde and carboxyl groups and the secondary into keto groups. Thus a large numbers of classes of compound containing two products being diketones, keto-acids or dicarboxylic acids according to the kind of alcohol groups present in the glycol.

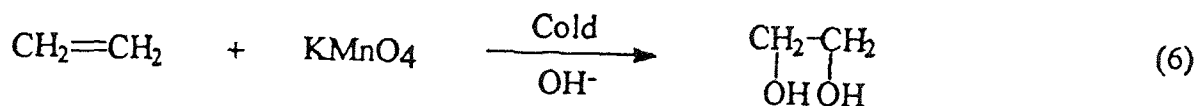
Wurtz discovered the first dihydric alcohol, ethylene glycol, and he named it glycol. Subsequently other glycols became known. Glycols are named (Geneva nomenclature) by adding the suffix "diol" to the name of the parent hydrocarbon: thus ethylene glycol is ethane-1,2-diol.

The glycols have many industrial uses. They are employed as cooling and anti-freeze media and as solvents. Of the intermediates derived from the glycols or the corresponding epoxides, the ethers and polyethylene glycols are valuable solvents, especially for resins and plastics, and the butylene glycols are used for the manufacture of butadiene. Ethylene and other glycols may be used as components of alkyd resin and of linear polymers of different types for synthetic fibers²⁶.

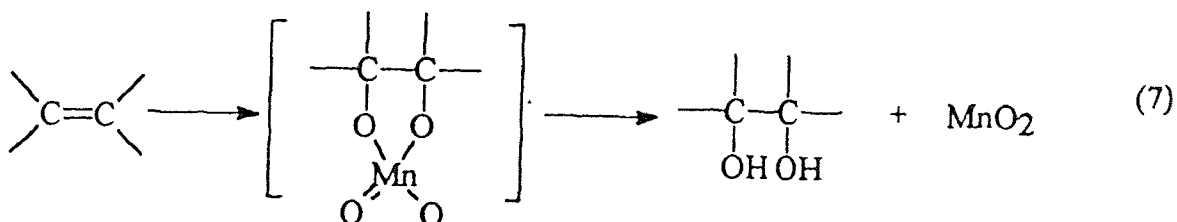
A paper in our references⁶ reported that the yield of aqueous glycolization of cyclohexene was nearly 100% in 2 hours with no significant biproducts. We studied the aqueous glycolization of cyclohexene to verify the feasibility of using water to replace hazardous solvent.

2.2 Glycolization of Olefins

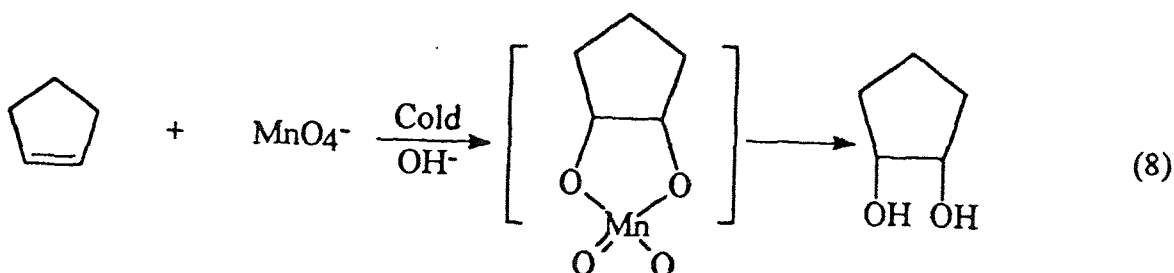
2.2.1 By Potassium Permanganate



The mechanisms for glycol formation by permanganate ion oxidations involve the formation of cyclic intermediates.



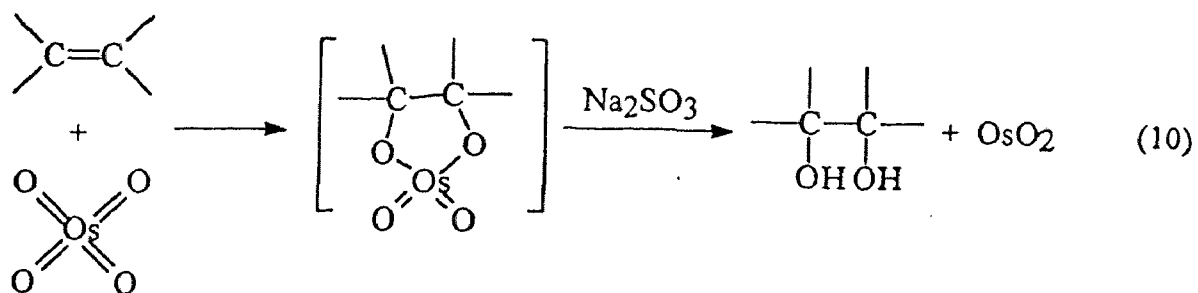
The course of this reaction is syn glycolization. This can be seen, readily, when cyclopentene reacts with cold dilute potassium permanganate (in base). The product is cis-1,2-cyclopentanediol²⁷.



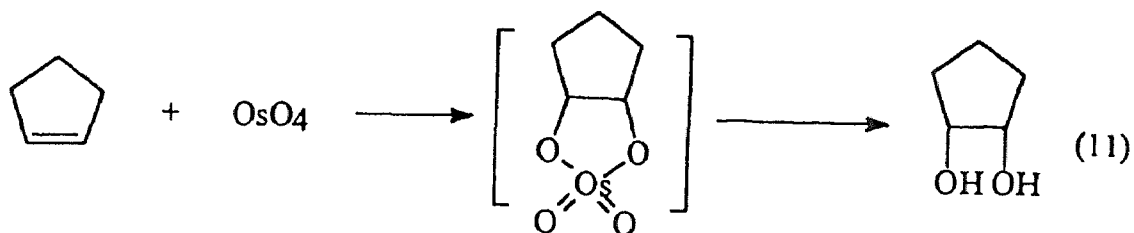
2.2.2 By Osmium Tetroxide



The mechanism for glycol formation by osmium tetroxide oxidations also involve the formation of cyclic intermediate.



This reaction is also syn glycolization. We can see from the following:



Compared with permanganate, osmium tetroxide gives the higher yield. Unfortunately, however, osmium tetroxide is highly toxic and very expensive. Potassium permanganate is a very powerful oxidizing agent and is easily capable of causing further oxidation of the glycol²⁷.

The first two methods of glycol preparation produce *syn* glycols, and many biproducts are hard to avoid. Glycols are often further oxidized to ketones or acids.

2.2.3 By Peroxytrifluoroacetic Acid

Most organic peroxyacids have at one time or another been employed for olefin glycolization *via* epoxidation (*syn* addition), acid-catalyzed ring-opening of the oxiran (most commonly with inversion of configuration) and hydrolysis of the diol monoester formed. The reagent is conventionally chosen from HCO_3H , $\text{CF}_3\text{CO}_3\text{H}$, and $\text{MeCO}_3\text{H}-\text{H}_2\text{SO}_4$ ²⁸. Peroxytrifluoroacetic acid offers some practical advantages in synthesis of water-soluble α -glycols²⁹.

Peroxytrifluoroacetic acid, prepared from trifluoroacetic anhydride and 90% hydrogen peroxide in methylene chloride, reacted almost instantaneously even at ice-bath temperatures with all the simple olefins investigated. The products obtained were hydroxytrifluoroacetates derived from the ring opening of the intermediate epoxide with trifluoroacetic acid. These esters could, however, readily be converted to the α -glycols by methanolysis³⁰. Initially it was found that the glycols were contaminated by high-boiling products of the cellosolve type. These were undoubtedly derived from condensation of the epoxide, initially formed in the reaction, with the hydroxytrifluoroacetate which accumulates as the reaction proceeds. Formation of these high boiling ethers was prevented by increasing the effective concentration of trifluoroacetate ions present in the reaction medium; this was conveniently accomplished by addition of triethylammonium trifluoroacetate to the solvent in which the oxidation was carried out, and under these conditions pure α -glycols were obtained.

The oxidations were carried out by addition of a methylene chloride solution of peroxytrifluoroacetic acid to the olefin and triethylammonium trifluoroacetate. Normally a 10% excess of the peroxyacid was employed, and considerable care was necessary in handling this very volatile reagent since it evaporates rapidly from solution.

The conversion of cyclohexene into trans-1,2-cyclohexanediol indicates that glycolization with peroxytrifluoroacetic acid is stereospecific and yields trans glycols as do other peracids¹⁸.

In this reaction, methylene chloride is used as solvent. The reaction is conducted in an ice-bath to avoid the evaporation of the peroxy acid.

2.2.4 By Potassium Peroxymonosulfate

Although potassium peroxymonosulfate is not appreciably soluble in common organic solvents, water-ethanol, water-acetic acid and water-ethanol-acetic acid mixtures have been employed successfully as solvents for the $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ mixture. A slurry of the mixed salt in glacial acetic acid has also proved to be an effective oxidant.

Olefins can be converted to glycols or glycol esters depending upon the solvent system employed. Cyclohexene is converted to trans- rather than cis-cyclohexanediol. The preferential formation of this isomer may be an indication of trans addition by an electrophilic fragment of peroxymonosulfate, but it may also indicate that epoxides are intermediates in this reaction. Attempts to isolate the epoxides, however, have been unsuccessful. A terminal, as well as an internal double bond, can be glycolized by the salt mixture if sufficiently vigorous reaction conditions are employed³¹.

At the pH 1.6, diol is produced from cyclohexene, presumably by acid-catalyzed addition of water to the epoxide. In a vigorously stirred two-phase mixture 1.7 molar equiv. of aqueous KHSO_5 glycolize cyclohexene to > 80% diol with no significant byproduct in 2 h at room temperature. In a control experiment using cyclohexene oxide in place of cyclohexene under identical conditions, the epoxide was converted completely to trans-1,2-cyclohexanediol⁶.

In this reaction, aqueous potassium peroxymonosulfate oxidizes cyclohexene to diol in acidic mixture with no added organic solvent, and so avoids the use of chlorinated solvents.

CHAPTER 3

EXPERIMENTAL

3.1 Reagents Used in the Experiments

Oxone: This product was purchased from Aldrich Chemical Company Inc. The material safety data sheet warns that it forms explosive mixtures with as little as 1% organic matter and decomposes on contact with heavy metal salts with the evolution of oxygen. Iodometric titration showed that 1g of Oxone contained 2.75 mmol KHSO_5 . A solution of 0.0101g of Oxone and 10 cm^3 of water had pH 2.93. The solution contained 0.0042g or $2.77 \times 10^{-3} \text{ M}$ of KHSO_5 and 0.0059g of $(\text{KHSO}_4 + \text{K}_2\text{SO}_4)$. From $\text{pK}_a(2)$ of $\text{KHSO}_4 = 1.92$, equilibrium calculation shows that the above solution contained 0.0022g ($1.60 \times 10^{-3} \text{ M}$) of KHSO_4 and 0.0037g ($2.14 \times 10^{-3} \text{ M}$) of K_2SO_4 . Thus, the analyzed molar ratio of $\text{KHSO}_5/\text{KHSO}_4/\text{K}_2\text{SO}_4$ in Oxone was 1.73:1.0:1.34⁶.

Cyclohexene: Reactant grade, 99+%, stabilized with 0.01% BHT, b.p. 83°C , m.p. -104°C , density=0.811, FW 82.15, Aldrich Chemical Company Inc.

Na_2SO_4 : Salting out reagent (just used in this research to salt out soluble diol from water to ethyl ether), meets A.C.S. specifications, J.T. Baker Chemical Co.

MgSO_4 anhydrous: Added after extraction to remove water from organic phase, Fisher Scientific Company.

Trans-1,2-cyclohexanediol: Standard of the product, 98%, m.p. $101-104^\circ\text{C}$, FW 116.16, Aldrich Chemical Company, Inc.

Hexadecane anhydrous: Internal standard, 99+%, Aldrich Chemical Company, Inc.

Ethyl ether: Extraction solvent, purified grade, class 1A, Fisher Chemical Company.

3.2 Experimental Procedure and Apparatus

3.2.1 2.3 cm³ Scale

The experiments were conducted in a 15 cm³ round bottom bottle with a small magnetic stirring bar in it. The magnetic stirrer, VWR Scientific 400HPS, allows precise control from 0 to 2500 rpm, also has temperature control. A schematic of the reactor system is shown in Figure 1.

Fresh Oxone solution: Exactly 2.192g of Oxone was weighed into a 10 cm³ beaker, and dissolved in deionized water. The solution was transferred into a 10 cm³ volumetric flask, adding deionized water to the limit.

A mixture of deionized water (1.57 cm³), cyclohexene (0.35 mmol, 35.5 mm³), and freshly prepared Oxone solution (0.73 cm³, 0.44 mmol KHSO₅) was stirred magnetically at 1200 rpm for 2h at room temperature. 0.5 g of Na₂SO₄ was added after the reaction, then the mixture was extracted with ethyl ether five times (total volume about 6 cm³). The extract was dried over MgSO₄. The extract was filtered into a 10 cm³ volumetric flask (containing internal standard already), adding ethyl ether to the limit. GC/FID was used to analyze the result.

3.2.2 1 dm³ Scale

A mixture of 683 cm³ deionized water, 317 cm³ (69.5g Oxone) fresh Oxone solution and 15.4 cm³ cyclohexene in the reactor (Figure 2) was stirred mechanically at 907 rpm for 2h at room temperature. The pipette was inserted and 5 cm³ of liquids quickly obtained at 5 min, 10 min, 15 min, 20 min, 30 min, 60 min, 90 min, and 120 min during the reaction with the stirrer on. Na₂SO₄ was added to salt out diol from water, then the mixture was extracted with ethyl ether five times. The extract was dried over MgSO₄ then filtered. Ethyl ether was added to the solution to make the final volume 10 cm³. Analysis was accomplished by GC/FID.

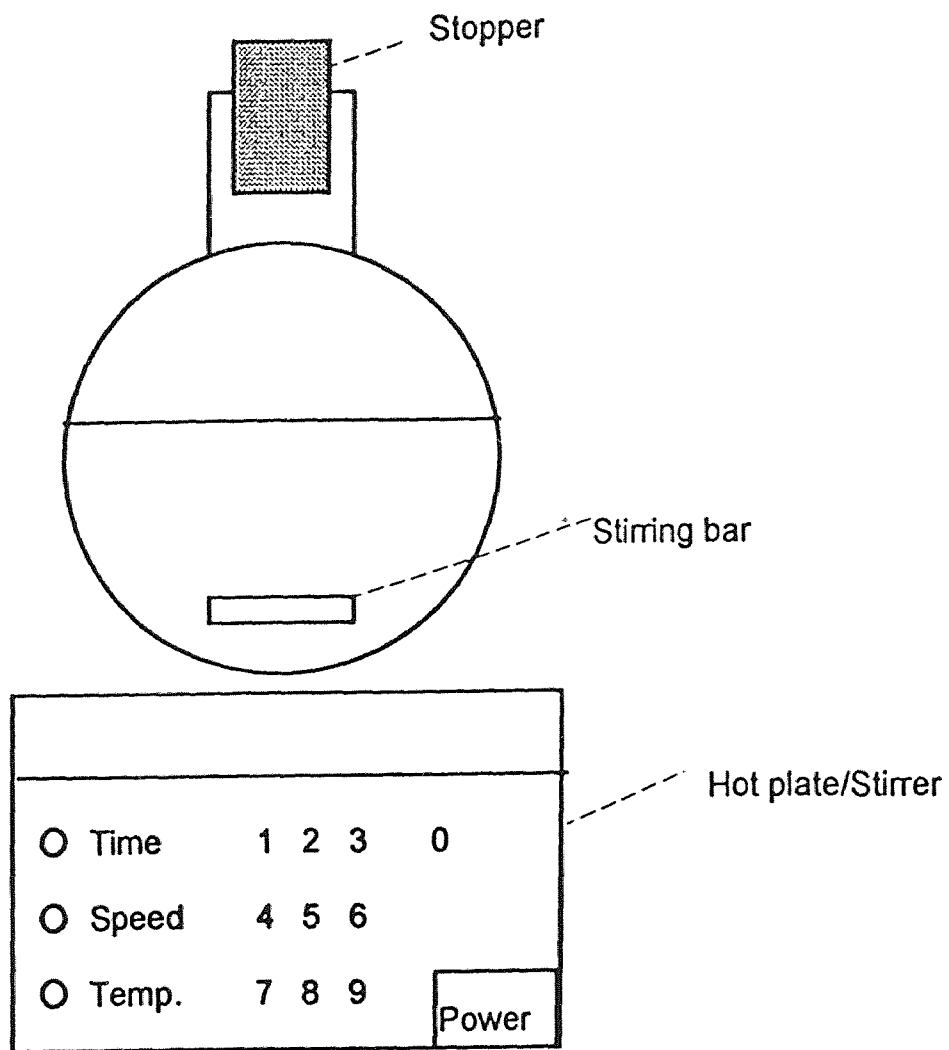


Figure 1

2.3 cm³ Reactor

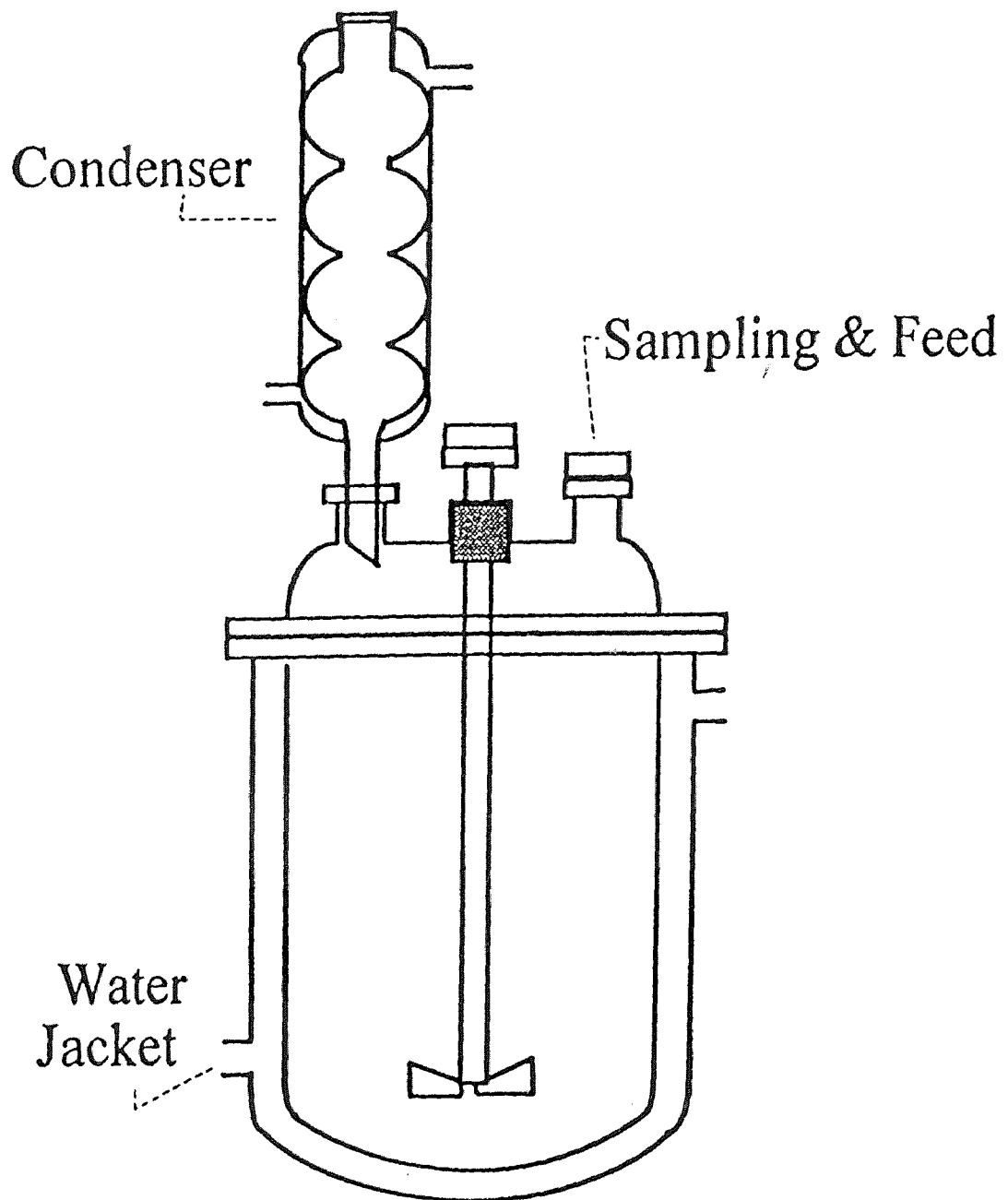


Figure 2

1 dm³ Reactor

3.3 Analytical Technique

The product compounds were measured using a Hewlett Packard 5890 gas chromatograph with Flame Ionization Detector (FID). Hewlett Packard 3396A integrator was used as both recorder and integrator.

The compounds were separated on a 1/8 inch diameter by 6 feet long stainless steel column packed with 80/100 mesh TENAX TA and temperature program was used (showed in Table 1).

Relationship Factor (R) was obtained by injection of mixed standards (cyclohexene, internal standard and trans-1,2-cyclohexanediol), whose exact amount was known, to GC.

$$R_1 = \frac{\frac{\text{peak area of internal standard}}{\text{weight of internal standard}}}{\frac{\text{peak area of cyclohexene}}{\text{weight of cyclohexene}}}$$

$$R_2 = \frac{\frac{\text{peak area of internal standard}}{\text{weight of internal standard}}}{\frac{\text{peak area of trans-1,2-cyclohexanediol}}{\text{weight of trans-1,2-cyclohexanediol}}}$$

At the beginning, n-octane was the internal standard, whose peak appeared between those of cyclohexene and trans-1,2-cyclohexanediol. We just obtained R_2 . We measured several times and obtained the median value (Table A1, Appendix A).

$$\begin{aligned} \text{The average value of } R_2 &= (1.996+1.974+2.028+2.180+1.846+1.992+2.058)/7 \\ &= 2.011 \pm 0.092 \end{aligned}$$

Evaporation of n-octane caused a large error at higher temperature. We changed internal standard to n-hexadecane whose peak occurred after that of trans-1,2-cyclohexanediol. R_1 and R_2 were measured (Table A2, Appendix A), Both the amount of cyclohexene and trans-1,2-cyclohexanediol were calculated using R.

The average values of:

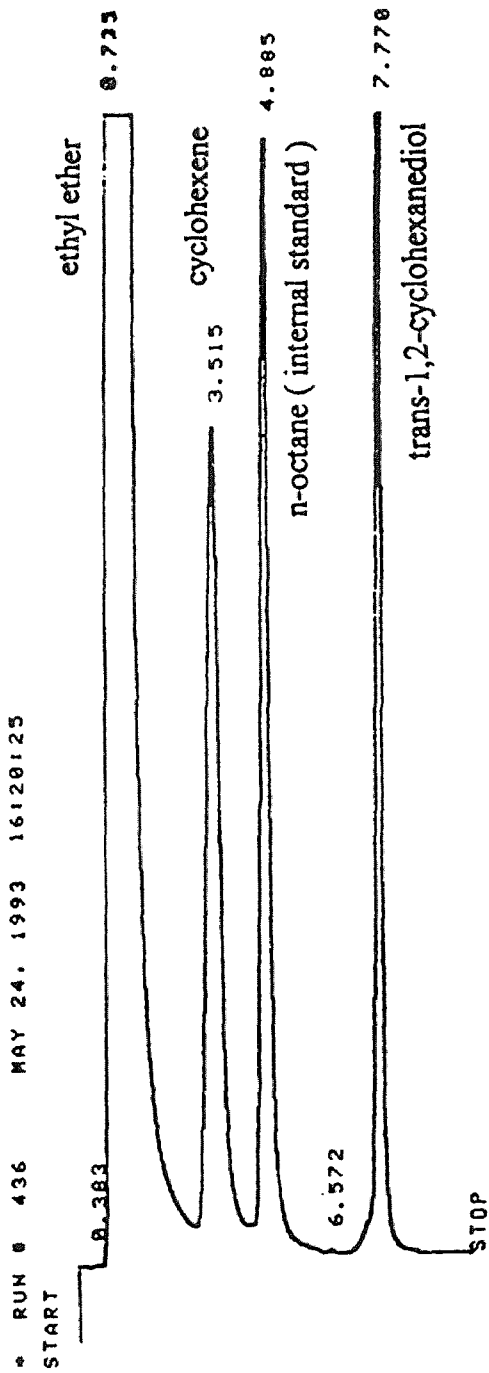
$$R_1 = (0.83+0.87+0.76+0.71+0.83)/5 = 0.80 \pm 0.6$$

$$R_2 = (1.75+1.77+1.68+1.73+1.72)/5 = 1.73 \pm 0.03$$

Figures 3 and 4 show the typical peak resolution and retention time for the cyclohexene, internal standards and trans-1,2-cyclohexanediol. Table 1 presents GC conditions.

Table 1 GC Operating Conditions

Carrier Gas	Nitrogen, 30 ml/min
Air	430 ml/min
Hydrogen	30 ml/min
Injection Temperature	300°C
Detector Temperature	310°C
Oven Starting Temperature in Programming	150°C
Time in Keeping Oven at Starting Temperature	4 min
Oven Temperature Heating Rate	25°C/min
Oven Final Temperature in Programming	300°C
Time in Keeping Oven at Final Temperature	2 min
Integrator Attenuation	6
Chart Speed	0.5 mm/min
Area Rejection	2000

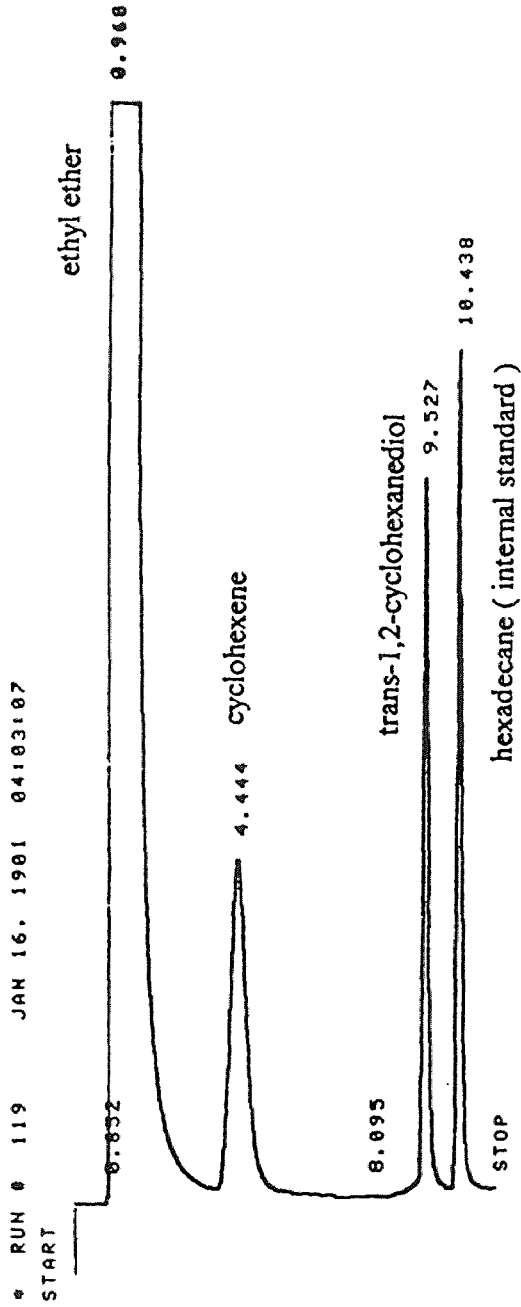


RUN# 436 MAY 24. 1993 16:20:25

AREA%	RT	AREA	TYPE	WIDTH	AREA%
.735	28878544	VH	.025	1.59255	
.773	1.762E+09	SH8	.186	97.15181	
3.515	8675354	T8V	.406	.47842	
4.885	7724410	TVP	.262	.42597	
7.770	6370352	P8	.142	.35130	

TOTAL AREA=1.8133E+09
 MUL FACTOR=1.0000E+00

Figure 3 Typical GC Chart of Cyclohexene, Trans-1,2-Cyclohexanediol, and N-Octane



RUN# 119 JAN 16, 1901 04:03:07

AREA%	RT	AREA	TYPE	WIDTH	AREA%
	.852	8483	PV	.035	.00060
	.918	18182192	VH	.028	1.28584
	.960	1.384E+09	SHB	.213	97.89901
	4.444	4911421	TBB	.525	.34733
	6.095	10074	PP	.168	.00071
	9.527	3196486	PB	.161	.22605
	10.438	3400690	PB	.145	.24050

TOTAL AREA=1.4140E+09
 MUL FACTOR=1.0000E+00

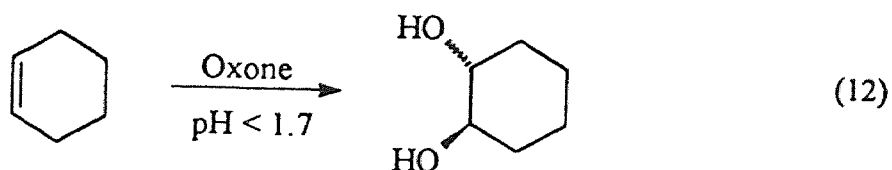
Figure 4 Typical GC Chart of Cyclohexene, Trans-1,2-Cyclohexanediol, and Hexadecane

CHAPTER 4

RESULTS AND DISCUSSION

4.1 2.3 cm³ Scale

Acidic (pH < 1.7) solutions of 2KHSO₅·KHSO₄·K₂SO₄ in water produced trans-1,2-cyclohexanediol from cyclohexene.



We verified Ford's oxidation on a 2.3 cm³ scale⁶.

We injected a series of mixed standards (cyclohexene, hexadecane and trans-1,2-cyclohexanediol) into GC to get the relationship of peak area to the weight of the compounds. Three calibration lines were obtained as shown in Figure 5. The calibration shows that for all three compounds, peak areas were proportional to the amount injected to GC. Data are shown in Table A3 (Appendix A). The Relationship Factor (R) is provided in Table 2.

Table 2 Relationship Factor (R) of the Calibration Peaks

	Cyclohexene	Trans-1,2-Cyclohexanediol	Hexadecane
R	0.9954	0.9974	0.9966

We weighed 35.5×10⁻³ cm³ of cyclohexene for seven times in order to determine the reproducibility of the feed approach. The result is shown in Table 3.

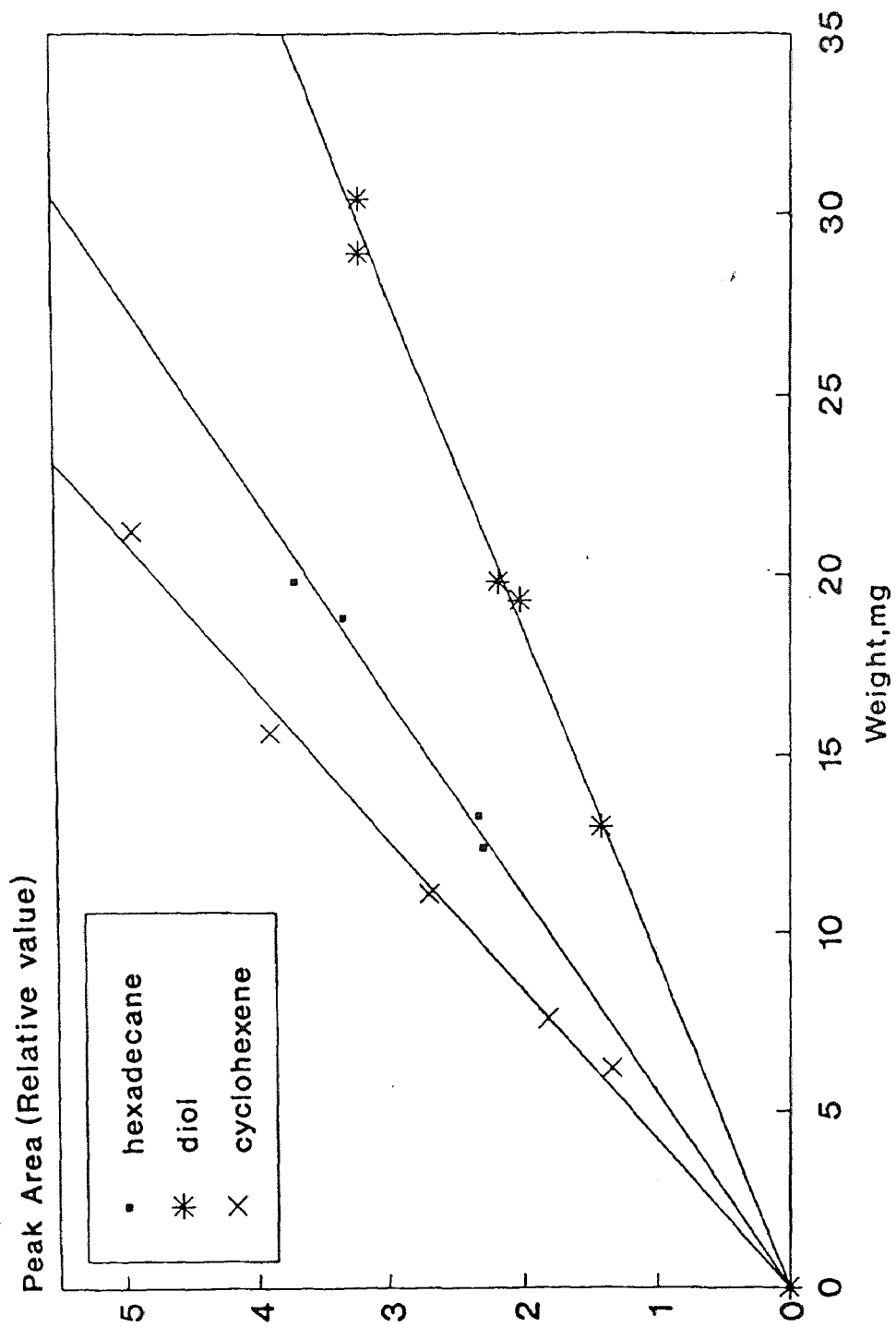


Figure 5 Relationship of Peak Area to the Amount of Cyclohexene, Trans-1,2-Cyclohexanediol, and Hexadecane Added

Table 3 Weight of 35.5 cm³ of Cyclohexene

No.	1	2	3	4	5	6	7	8
wt,mg	26.1	26.0	27.0	26.6	26.8	26.3	27.4	27.6

The average weight of cyclohexene used as reactant was 26.7 ± 0.5 mg

The weight of trans-1,2-cyclohexanediol on 100% conversion was:

$$\frac{26.7 \pm 0.5}{82.15} \times 116.16 = 37.8 \pm 0.7 \text{ mg}$$

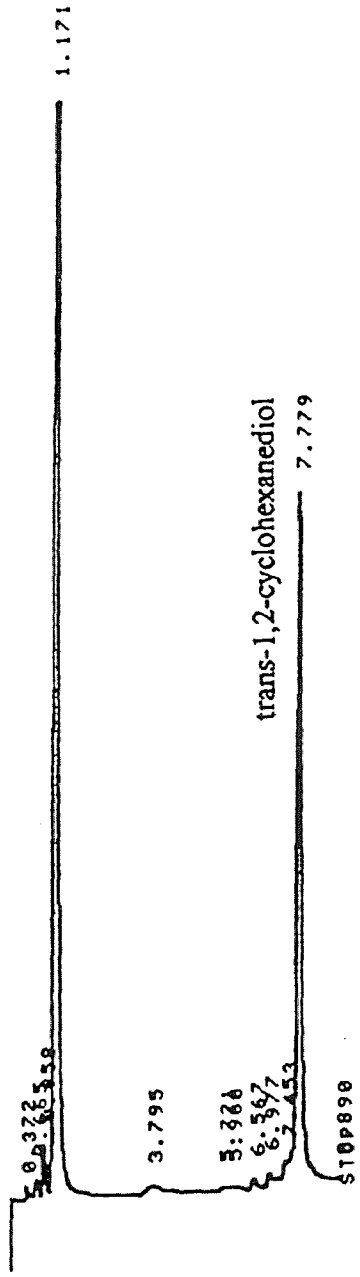
4.1.1 The Role of Na₂SO₄

At first, we extracted the mixture with ethyl ether directly after the reaction and found that the yield was less than 50%. In order to do a complete material balance, the water phase was injected into GC and a large peak was found at the retention time of trans-1,2-cyclohexanediol. Figure 6 illustrates the water injection. Since trans-1,2-cyclohexanediol is a polar compound, it is soluble in water and is difficult to extract into organic ether. However, by adding substantial quantities of salt in order to increase the ionic strength of the solution, the organic solubility is decreased. This is called salting out. At first, we used NaCl as the salting out reagent. But it was observed that after NaCl was added to the aqueous mixture it became yellow, indicating that KHSO₅ oxidized Cl⁻ to Cl₂. Consequently we switched to a SO₄²⁻ containing salt since Oxone already contained a sulfate derivative. We added Na₂SO₄ instead of NaCl. The yield was accurately determined to be over 80% and no peak of trans-1,2-cyclohexanediol was detected in water phase. Figure 7 illustrates the excellent separation of organics from inorganics.

4.1.2 Time Effect on the Oxidation of Cyclohexene

The reaction was run for up 5 hours at 1200 rpm at room temperature (19°C). The molar ratio of Oxone:cyclohexene=44:35. We found that more than 80% cyclohexene was

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 START



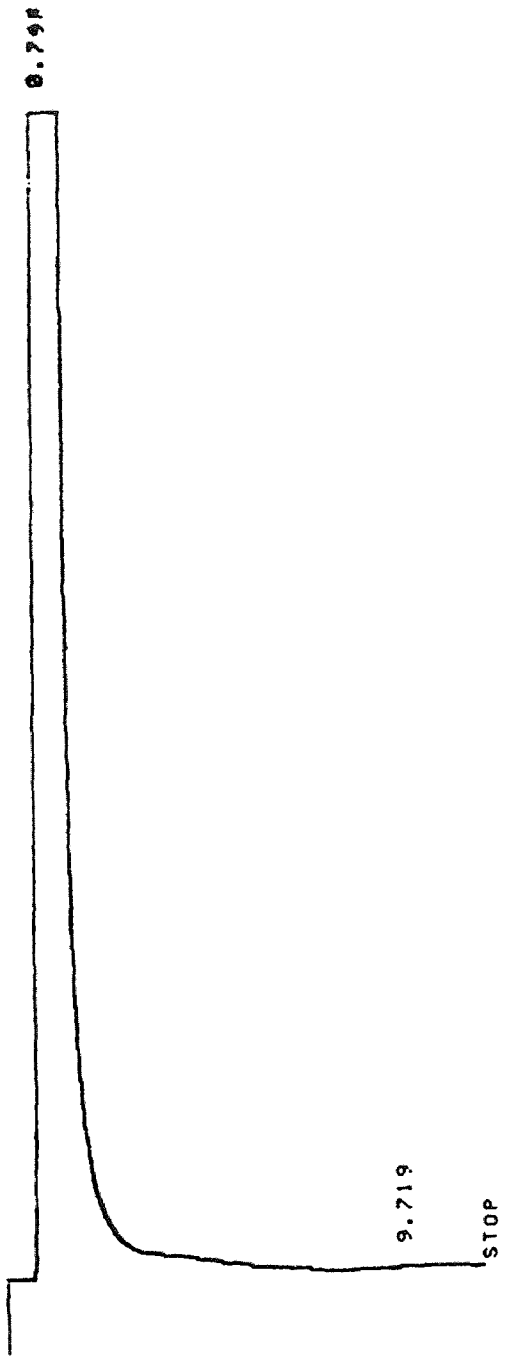
RUN# 449 MAY 24, 1993 18:55:42

AREA%	RT	AREA	TYPE	WIDTH	AREA%
.665	31825	BV	.067	.35934	
.858	139322	PP	.098	1.57318	
1.171	5670554	PB	.122	64.02691	
3.795	148669	BV	.537	1.67864	
5.721	21013	PV	.126	.23726	
5.968	45854	VP	.291	.51774	
6.567	43877	PP	.139	.48639	
6.977	43726	PV	.114	.49372	
7.453	86996	VV	.167	.98228	
7.779	2625480	VB	.137	29.64462	

TOTAL AREA=8.8565E+06
 MUL FACTOR=1.0000E+00

Figure 6 GC Chart of Extracted Water Phase Before Na₂SO₄ Was Added

* RUN # 390 MAY 21, 1993 10:21:06
 START



RUN# 390 MAY 21, 1993 10:21:06

AREA%	RT	AREA	TYPE	WIDTH	AREA%
	.744	27301008	BH	.032	1.95785
	.797	1.367E+09	SHB	.178	98.04218

TOTAL AREA=1.3944E+09
 MUL FACTOR=1.0000E+00

Figure 7 GC Chart of Extracted Water Phase After Na₂SO₄ Was Added

converted to trans-1,2-cyclohexanediol in 2 hours. The yield reached a maximum at 2 h. It remained almost constant after that. Figure 8 illustrates the change in yield with time. Table A4 provides the data (Appendix A).

Equation for yield calculation was:

$$\text{Yield} = \frac{W_1}{W_2} \times 100\%$$

Where, W_1 was the amount of diol extracted.

$$W_1 = \frac{\text{Peak Area of diol} \times R_2}{\text{Peak Area of internal standard}} \times \text{wt. of internal standard, mg}$$

$$W_2 = 37.8 \text{ mg}$$

4.1.3 Stirring Rate Effect on the Oxidation

With two miscible liquids phases, the reactants need to come in contact with each other in order to react. Stirring the two solutions can accomplish this. As expected, the yield increases with the stirring speed because fine bubbles of organics are dispersed in the aqueous layer. Figure 9 shows the effect of stirring speed on yield. The relationship between yield and stirring rate is linear. R is 0.977. The reaction was conducted at room temperature for 2 h. The initial molar ratio of Oxone:cyclohexene=44:35. Data is shown in Table A5 in Appendix A. Due to the equipment limitations, we could not increase the stirring rate sufficiently to affect the rate of the reaction. The range of stirring speeds we chose in our experiment was still within the linear range.

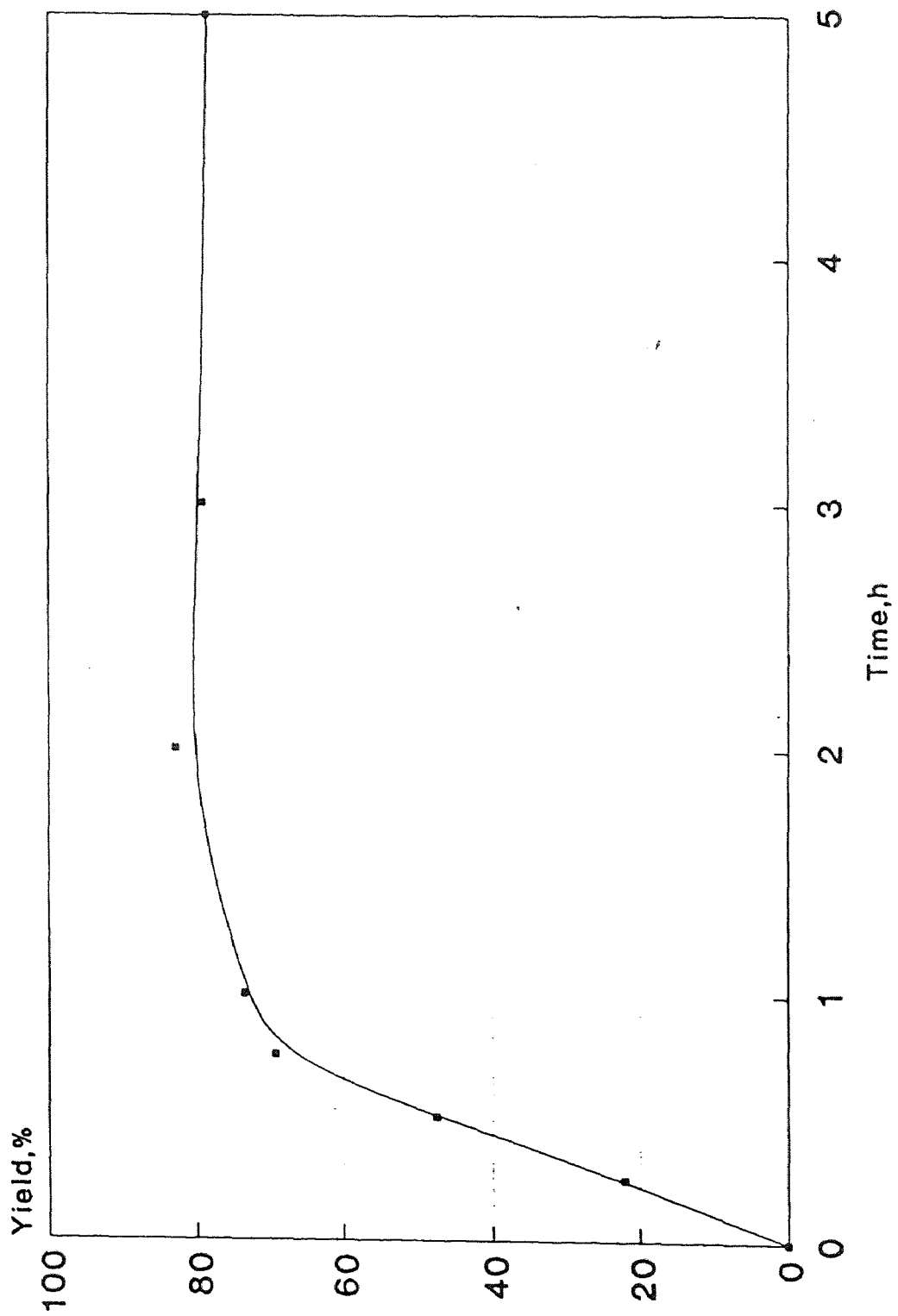


Figure 8 Time Effect on Glycolization of Cyclohexene

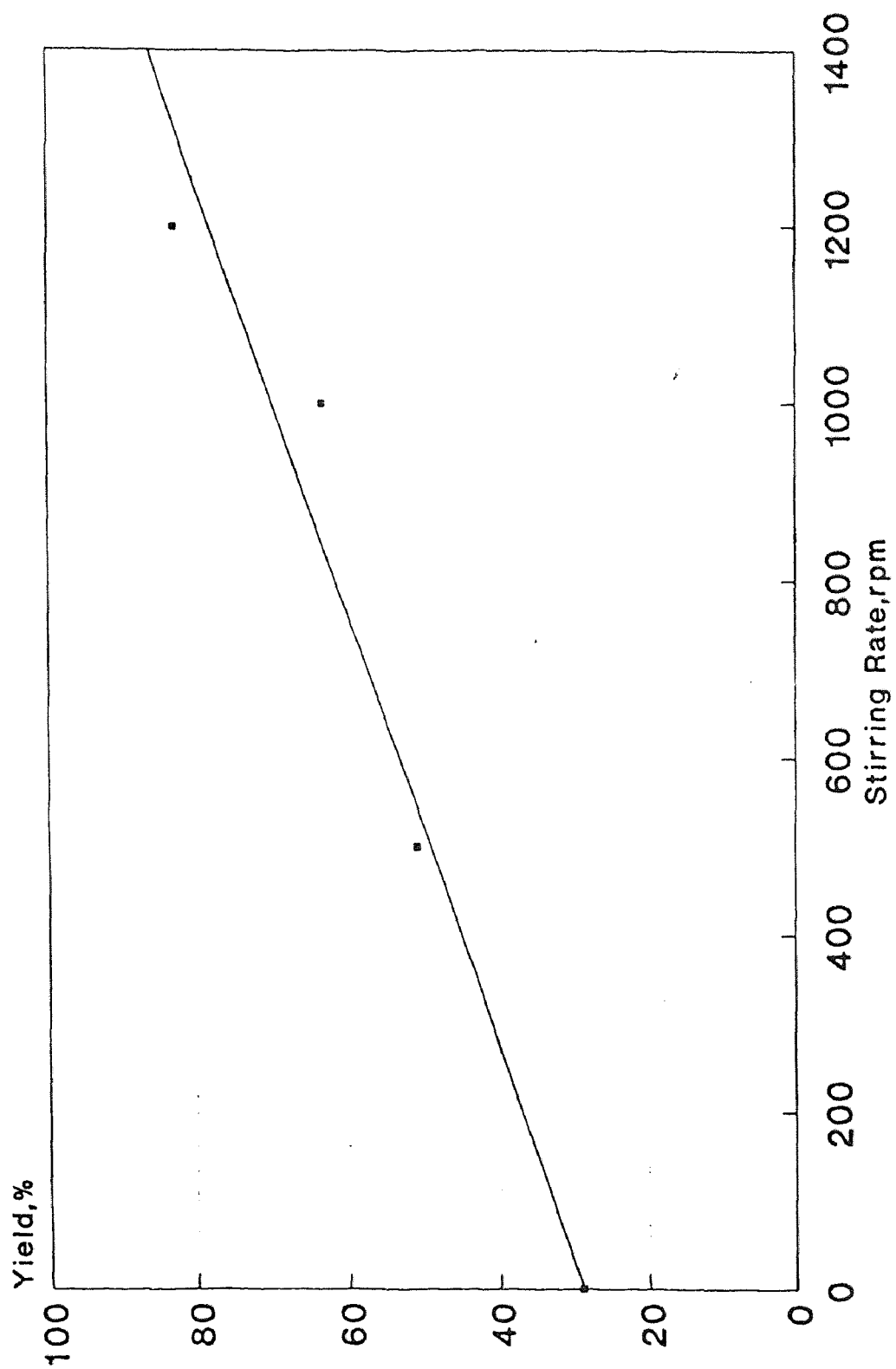


Figure 9 The Effect of Stirring Rate on Glycolization of Cyclohexene

4.1.4 Kinetics of the Oxidation

The kinetics of the oxidation over the first 20 min was studied. From Figure 10, we see $\ln(C_i/C_t)$ varies linearly with reaction time at 1200 rpm at room temperature (19°C) with the initial molar ratio of Oxone:cyclohexene=44:35. Data are shown in Table A6 (Appendix A). R for this line is 0.9887.

Where, $C_i = 35 \text{ mmol}/0.0023 \text{ dm}^3$

$$C_t = C_i - C_d$$

$$C_d = \frac{\text{Wd(mg) of diol at the time}}{116.16 \times 0.0023 \text{ dm}^3}$$

We know, for first order reactions, $\ln(C_i/C_t) = kt$, So, the glycolization of cyclohexene is a first order reaction. Under the conditions of this experiment, this reaction can be assumed to be a first order reaction in cyclohexene.

We had to consider the mass transfer effect in heterogeneous reaction. Also, both of the two concentrations of the reactants effected the rate of the reaction. The reaction constant is k_{obs} .

A probable mechanism for this hydroxylation is that epoxide may be an intermediate³¹. Transfer of the electrophilic perhydroxyl oxygen atom of KHSO_5 to the cyclohexene is the first step⁶. In this step, HSO_4^- is produced. The production of KHSO_4 (pKa 1.9) from KHSO_5 (pKa 9.4) causes the decrease of pH from 1.58 to 1.30 usually observed during the oxidation in the absence of NaHCO_3 . The second step is the acid-catalyzed addition of water to the epoxide. In this step, reaction rate should only change with the concentration of cyclohexene. Attempts to isolate the epoxide, however, have been unsuccessful.

The relationship of $\ln(C_i/C_t)$ vs., time was a straight line. The slope was k_{obs} .

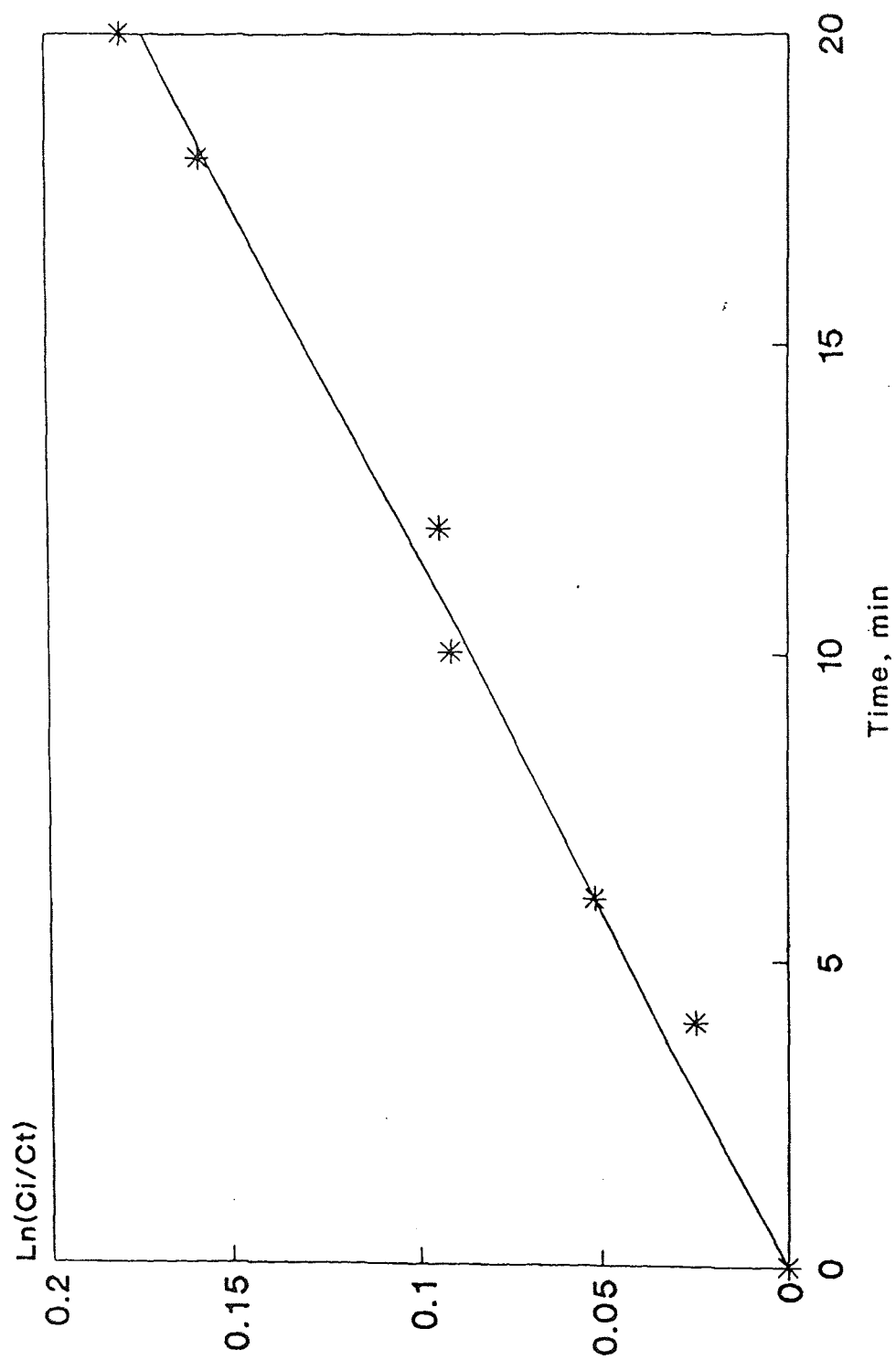


Figure 10 Kinetics of Glycolization of Cyclohexene

4.1.5 Stirring Rate Effect on k_{obs} .

The impact of stirring rate on the apparent rate constant is discussed in this section.

(1). In order to understand how stirring speed affects kinetics of the reaction, the reaction kinetics were studied at different stirring rates at 0°C. The molar ratio of Oxone:cyclohexene was 44:35. Figure B1 (Appendix B) illustrates that k_{obs} increased with the stirring rate. Data are shown in Table A7 (Appendix A).

(2). The reaction was run at room temperature (19°C) and the other conditions were kept unchanged. Figure 11 shows the effect of stirring rate on k_{obs} at 19°C. It was found that increased stirring rate enhanced k_{obs} . It was the same result as at 0°C. Table A8 (Appendix A) shows the data.

(3). The effect of stirring rate on kinetics at 40°C was also studied. The initial molar ratio of Oxone:cyclohexene was 44:35. The stirring speeds were same as those in the above two reactions. Again, the same result of k_{obs} increasing with stirring rate was obtained, as shown in Figure B2 (Appendix B). Table A9 provides the data (Appendix A).

There exists a thin liquid film between the organic phase and the surface of aqueous phase when mass transfer is considered. The thickness of this film is Δx . Δx is smaller at higher stirring speed. This means that it takes cyclohexene less time to get into the aqueous phase where hydroxylation takes place. So the reaction rate observed was faster and k_{obs} greater.

(4). The relationship of k_{obs} vs. time as a function of stirring rate at three temperatures was shown in Figure 12. The original molar ratio of Oxone: cyclohexene was 44:35. Table A10 (Appendix A) shows the data. It was found that k_{obs} increased with stirring rate at the three temperatures investigated. This also indicated that the apparent reaction rate was affected by mass transfer. Since the effect of stirring rate on k_{obs} is very complicated and is affected by temperature, it is impossible to resolve the rate expression into an independent function of stirring rate and temperature.

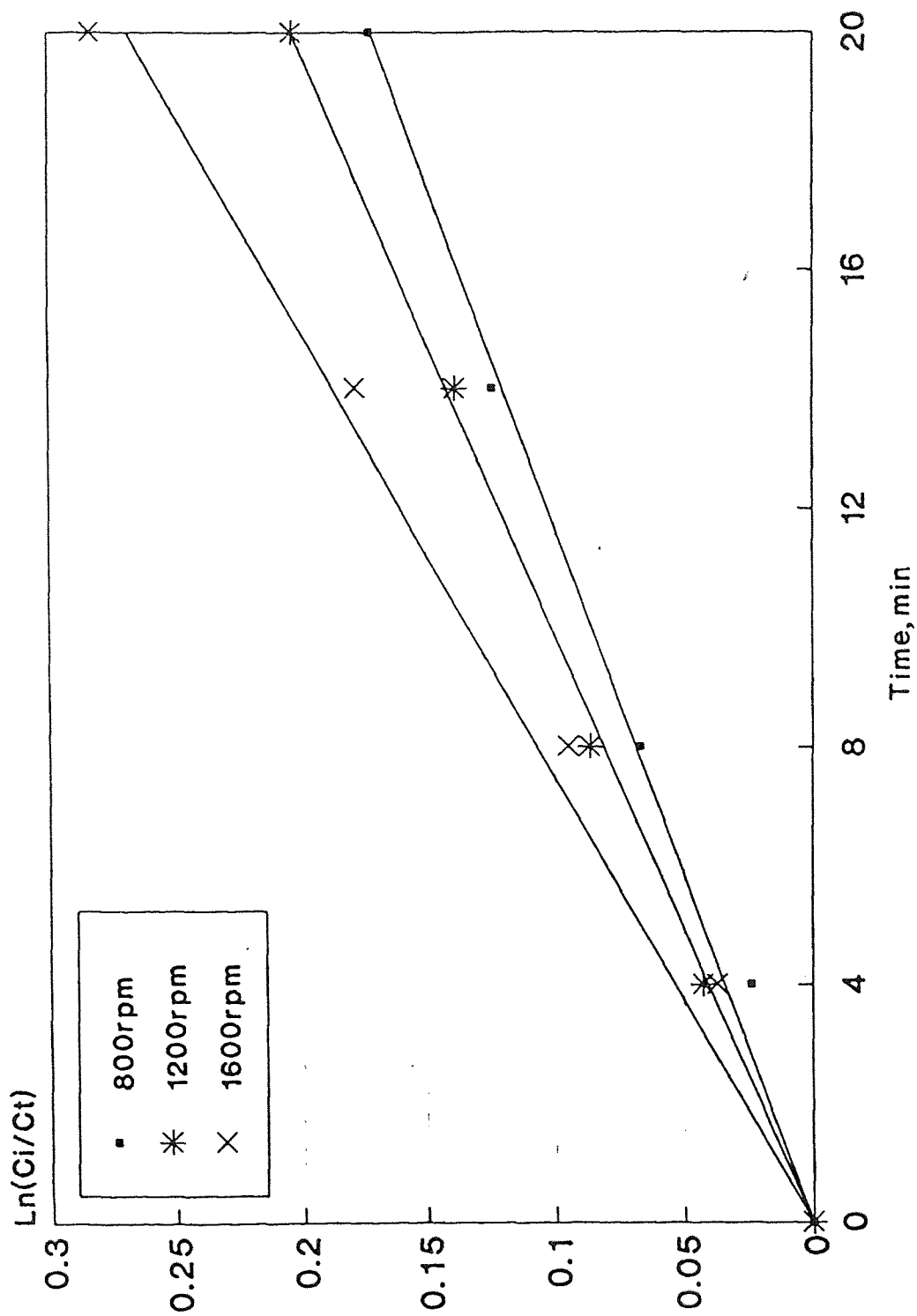


Figure 11 $\ln(C_i/C_t)$ vs. Time as a Function of Stirring Rate at 19°C-Kinetics Study of Glycolization of Cyclohexene

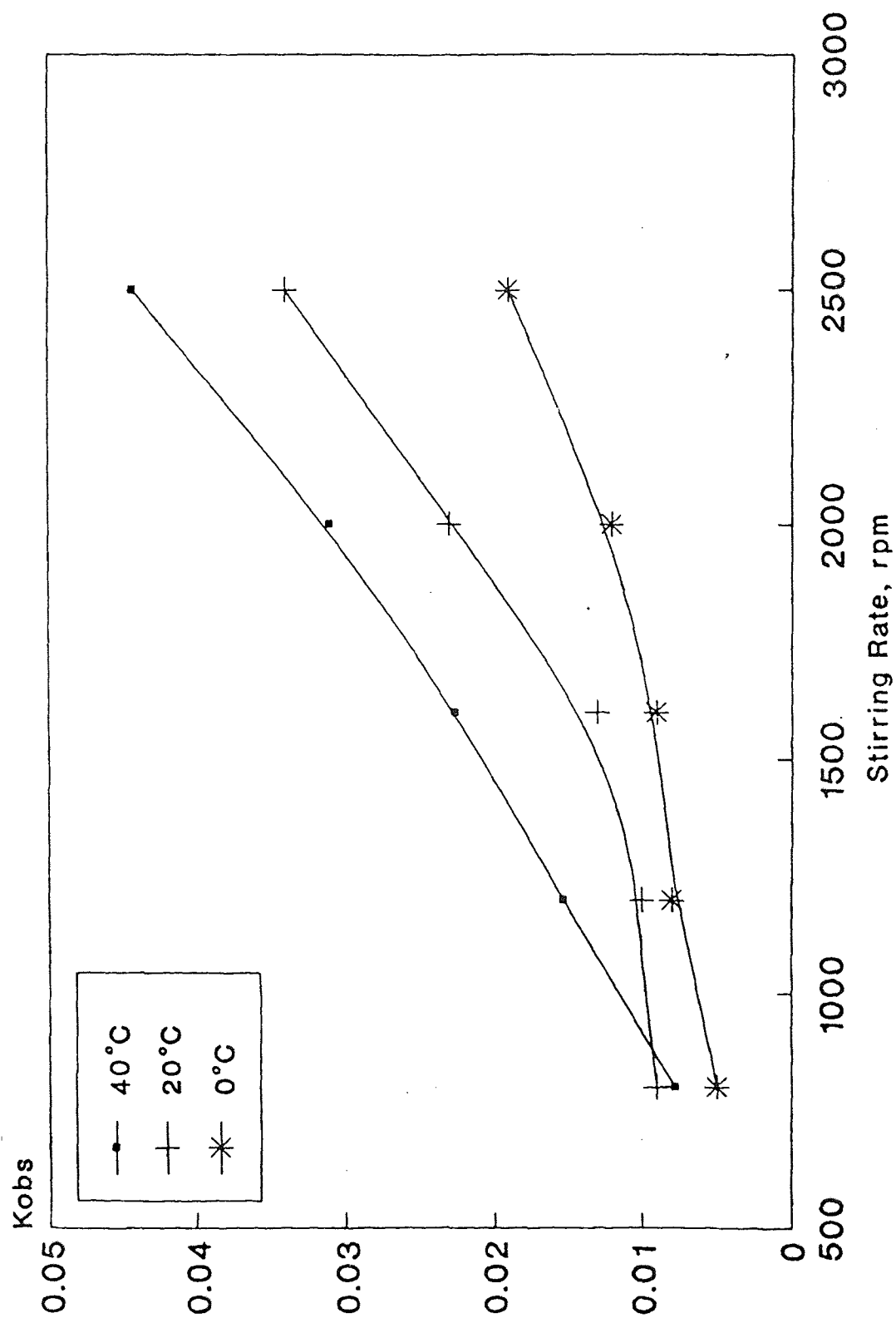


Figure 12 The Effect of Stirring Rate on k_{obs} - Kinetics Study of Glycolization of Cyclohexene

Reverting to the others, k_{obs} was higher at 19°C than k_{obs} at 40°C at 800 rpm. Most of organic cyclohexene was exposed on the surface of aqueous phase. High temperature caused more cyclohexene loss due to evaporation and k_{obs} decreased. With the increasing of stirring rate more and more cyclohexene was in the layer of aqueous phase and surrounded with water, so the evaporation became unimportant and k_{obs} increased with stirring rate as expected.

4.1.6 Temperature Effect on k_{obs} .

The results on the effect of temperature on the apparent rate constant are described in this section.

(1) Temperature effect on k_{obs} was obtained from the data we have. Figure 13 illustrates that k_{obs} increased with temperature at 800 rpm when the initial molar ratio of Oxone:cyclohexene was 44:35.

(2) Stirring rate was kept at 1200 rpm, temperature was changed in each run in order to get the temperature effect on k_{obs} . It was found that k_{obs} increased with temperature at 1200 rpm when the initial molar ratio of Oxone:cyclohexene was 44:35 (Figure 14), the same result as at 800 rpm.

(3) Temperature effect on k_{obs} was also studied at 1600 rpm with the initial molar ratio of Oxone:cyclohexene = 44:35. The result was that k_{obs} increased with temperature, as shown in Figure 15.

The first probable reason for this temperature effect is that more cyclohexene is dissolved into water at higher temperature. Higher concentration of cyclohexene in the aqueous phase produced more trans-1,2-cyclohexanediol after the same time as occurs at the lower temperature, that is, C_d is larger at higher temperature. The concentration of cyclohexene in aqueous phase cannot be measured and should appear in the final rate expression. The concentration of organic cyclohexene added into the system was known

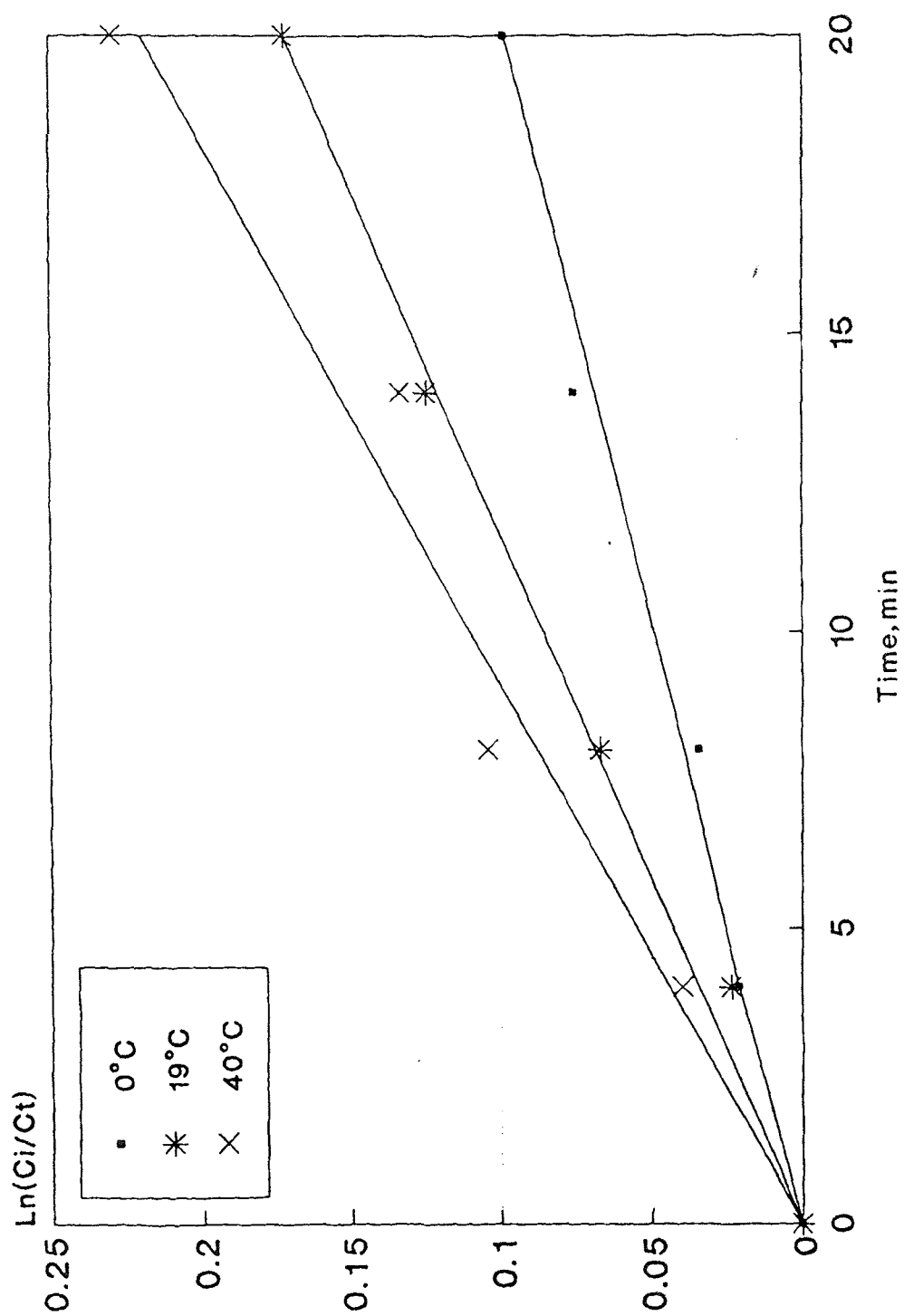


Figure 13 Ln(Ci/Ct) vs. Time as a Function of Temperature at 800 rpm-Kinetics Study of Glycolization of Cyclohexene

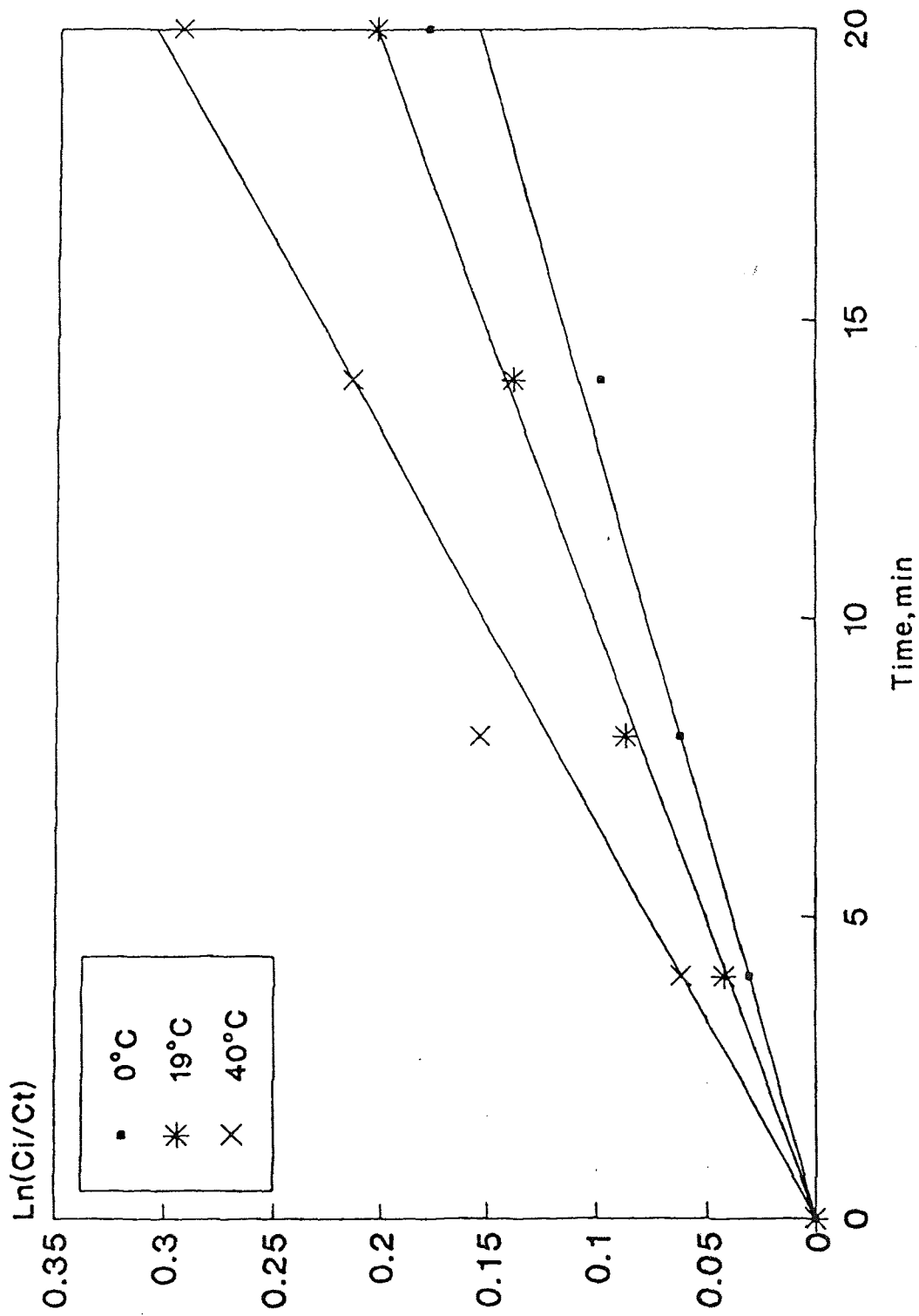


Figure 14 $\ln(C_i/C_t)$ vs. Time as a Function of Temperature at 1200 rpm-Kinetics Study of Glycolization of Cyclohexene

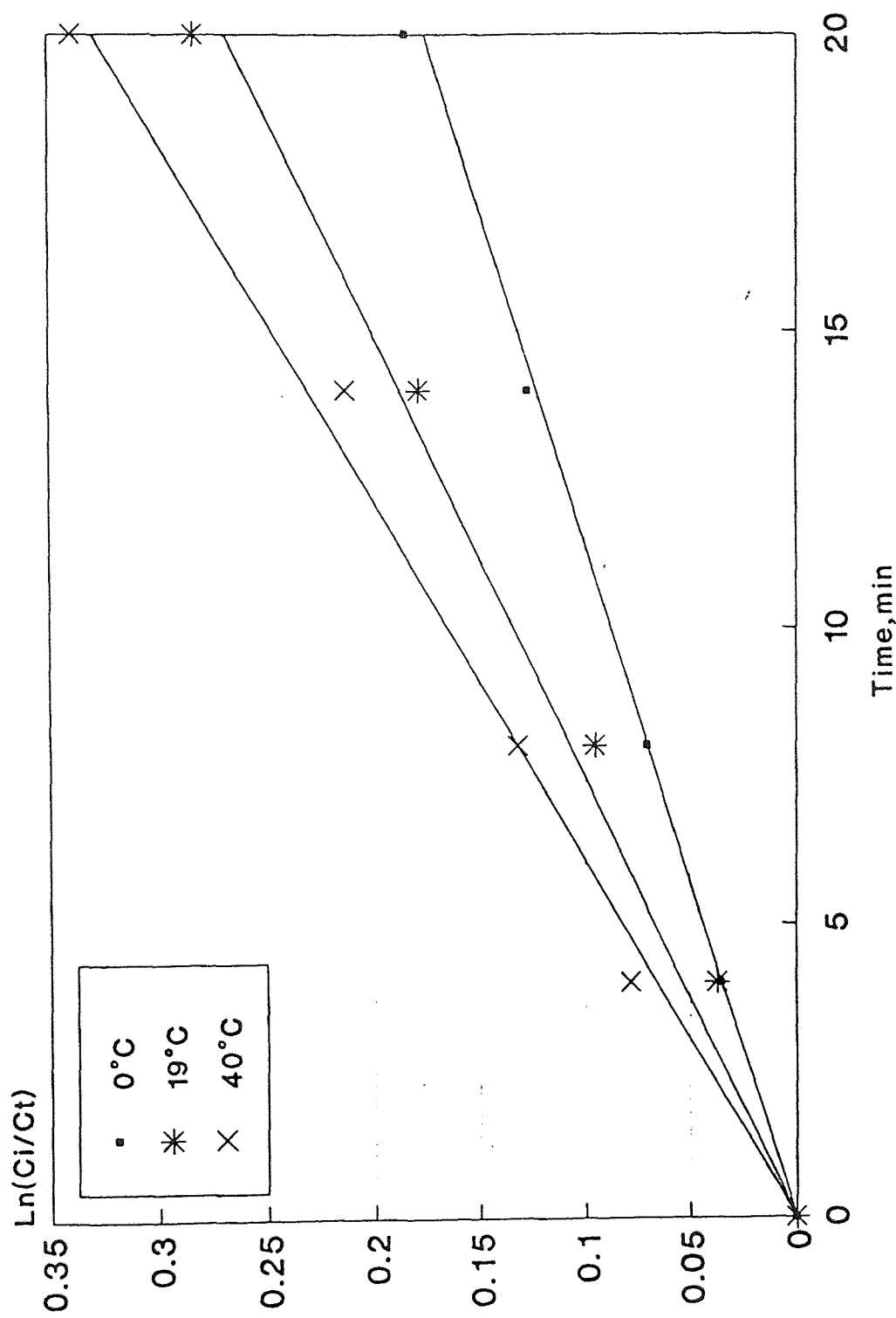


Figure 15 Ln(Ci/Ct) vs. Time as a Function of Temperature at 1600 rpm-Kinetics Study of Glycolization of Cyclohexene

and was kept the same, this means that C_i is constant. So $C_t = C_i - C_d$ is smaller. Thus, $\ln(C_i/C_t)$ is greater at higher temperature at the same time as at lower temperature. And k_{obs} , the slope of the straight line of $\ln(C_i/C_t)$ vs. time is larger.

Second, viscosity of the mixture decreases with increasing temperature. We know that stirring efficiency is higher at lower viscosity. So increasing temperature enhances stirring efficiency, and as a consequence, k_{obs} is increased.

4.1.7 The Effect of Oxone

The reaction rate constant depended upon the amount of excess KHSO_5 in a surprising way. By doubling the amount of Oxone in the mixture, but keeping total volume of 2.3 cm^3 unchanged, we found that the k_{obs} decreased as the concentration of KHSO_5 increased at room temperature (20°C) (Figure 16). Table A11 shows the data. We hypothesized that the reaction occurred in the aqueous phase and that the lower rate at higher KHSO_5 concentration might be due to lower concentration of cyclohexene in the aqueous phase at high ionic strength.

4.2 1 dm^3 Scale

In order to make the reaction useful, we scaled up the reaction from 2.3 cm^3 to 1 dm^3 . Since the evaporation effect was important on the larger scale, a condenser was needed to condense the evaporated cyclohexene.

4.2.1 Evaporation of Cyclohexene

Under stirring, 15.4 cm^3 of cyclohexene was added into 984.6 cm^3 deionized water (pH<1.7, adjusted with concentrated H_2SO_4) at room temperature. 5 cm^3 mixture was taken from the middle of the reaction system where the mixture was stirred vigorously every 30 min. It was extracted with ethyl ether after salting out by Na_2SO_4 and dried over MgSO_4 . Then the extract was analyzed by GC/FID. The result was that more than 60% of

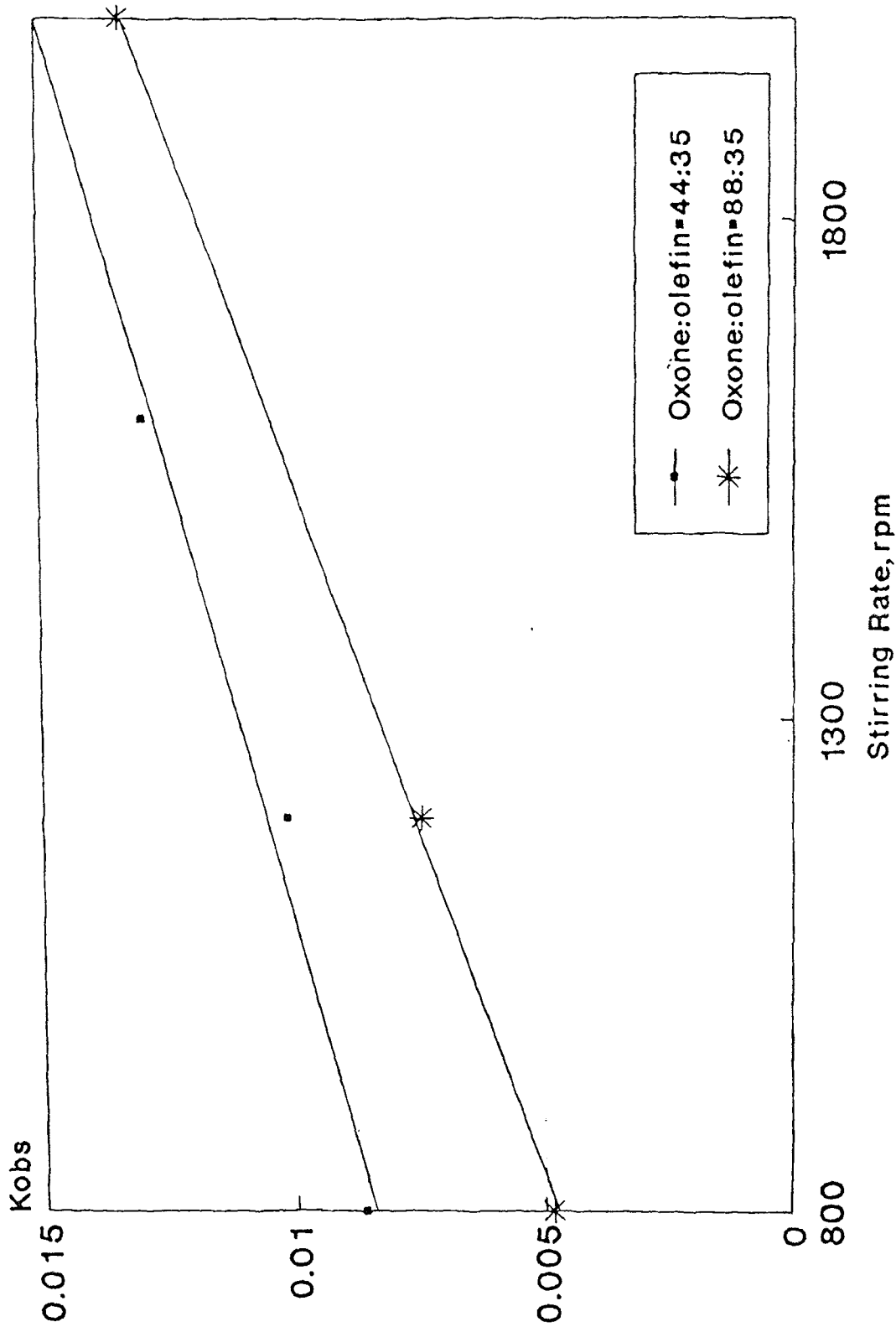


Figure 16 The Effect of the Amount of Oxone on K_{obs} .

cyclohexene was lost in 2 h without any reaction taking place at 907 rpm at room temperature (Figure 17). Data are shown in table A12 (Appendix A).

If the reaction was run in an ice-bath, the problem of evaporation should be minimized. However, the reaction rate would be very slow. A good yield could still be obtained after a long reaction time.

4.2.2 Yield of the Reaction

We injected 15.4 cm³ of cyclohexene into 984.6 cm³ Oxone solution (contained 69.5g Oxone) with the mechanical stirrer on at room temperature. The stirring speed was 907 rpm. We took 5 cm³ of sample from the middle of the reaction system at 5 min, 10 min, 15 min, 20 min, 30 min, 60 min, 90 min and 120 min. The mixture was salted out by Na₂SO₄ and extracted with ethyl ether, the extract was dried over MgSO₄ and filtered. Ethyl ether was added to make the final volume 10 cm³ then analyzed by GC. Result is shown in Figure 18. Table A13 (Appendix A) presents the data.

The yield was calculated by the following equation.

$$\text{Yield(\%)} = \frac{\text{mole of diol produced} \times 100\%}{\text{mole of diol corrected}}$$

The moles of diol obtained were corrected as if there were no evaporation of cyclohexene. It was calculated based on the amount of cyclohexene in the system at the time. At the end of 1 hour of the reaction, the amount of cyclohexene left could not be detected by GC. We did not consider the evaporation after 1h.

From this plot, we can see that at the end of 2 hours, over 90% cyclohexene was converted to trans-1,2-cyclohexanediol with no significant byproduct.

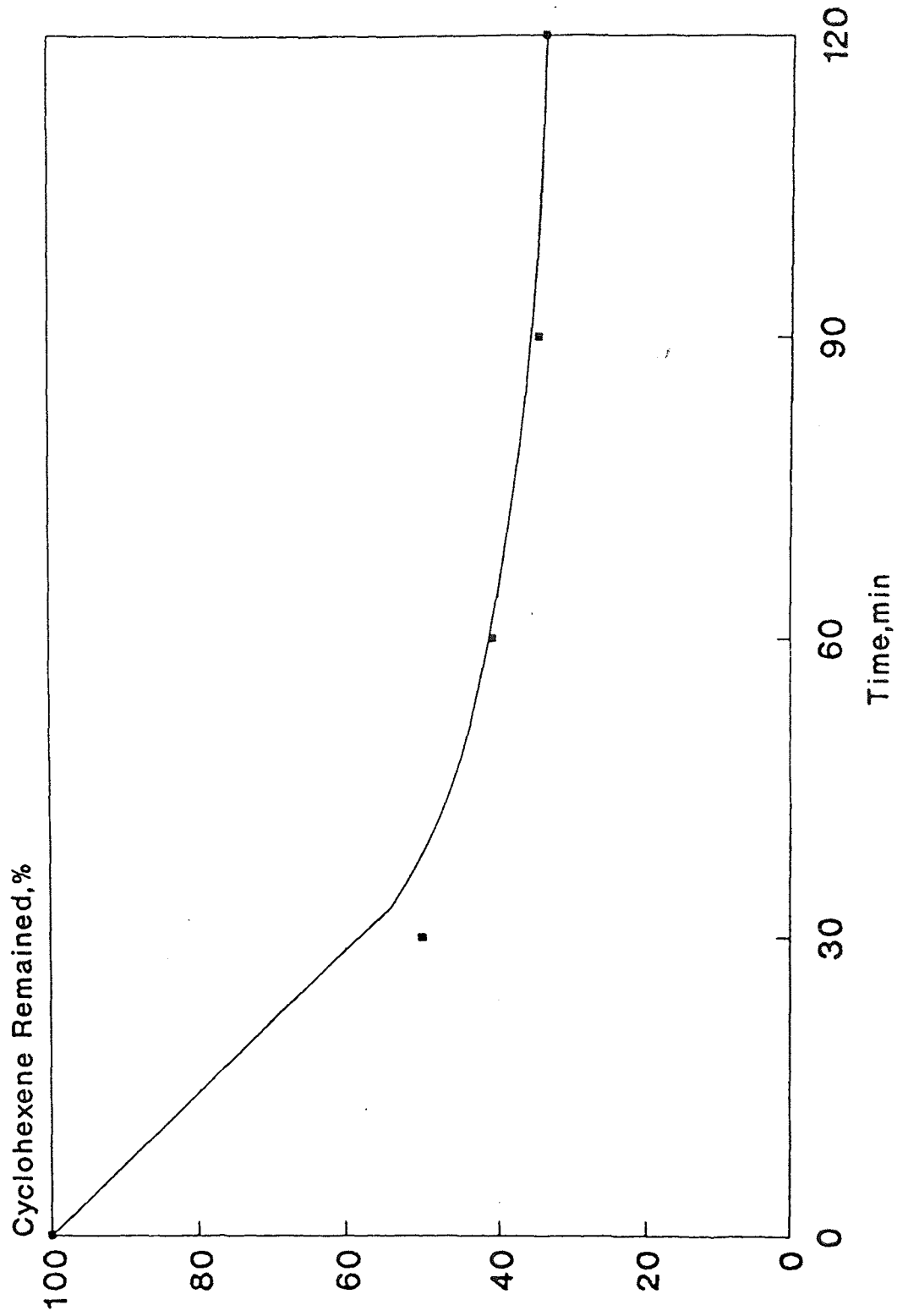


Figure 17 Evaporation of Cyclohexene at pH < 1.7 - 1 dm³ Scale-up

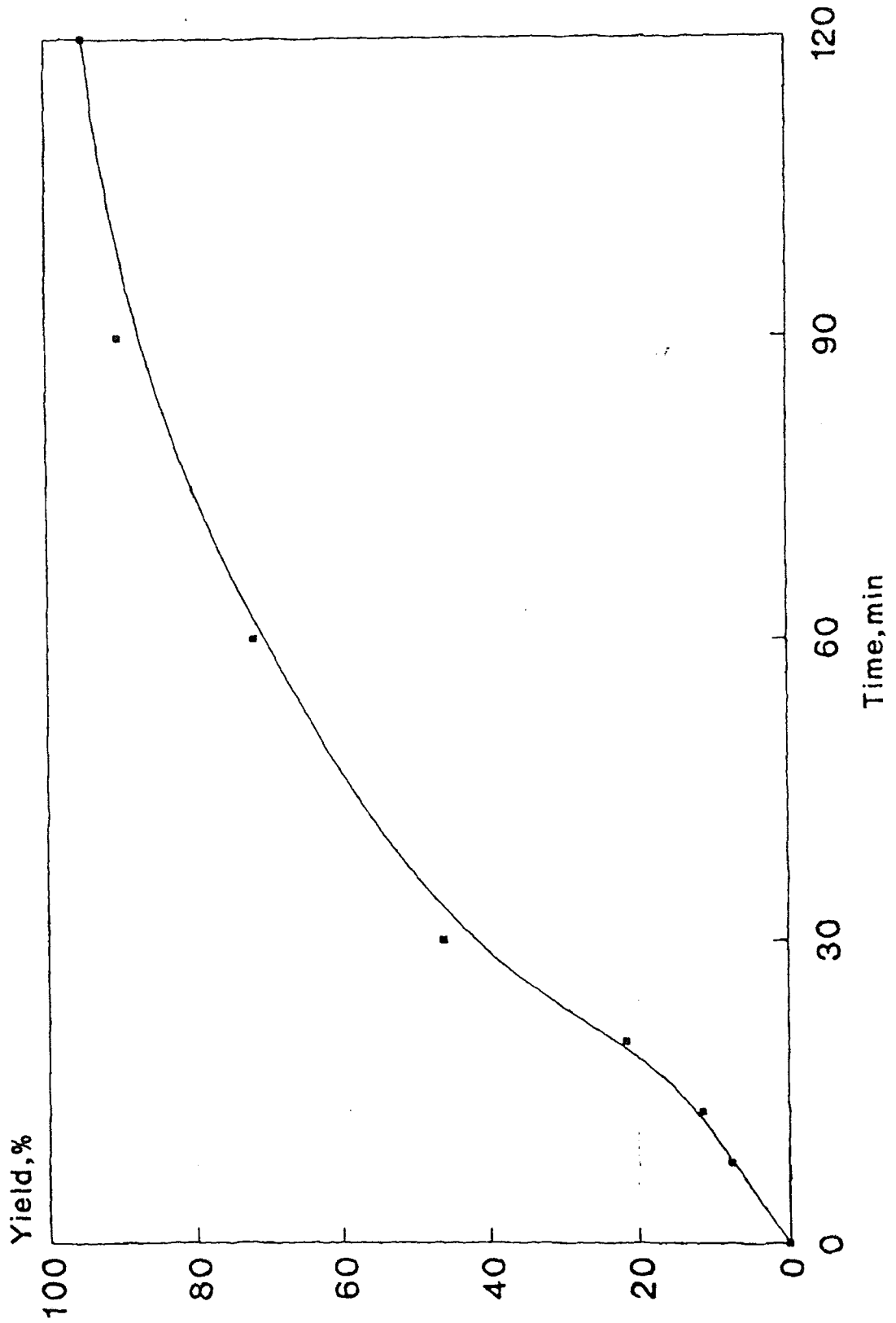


Figure 18 1 dm³ Scale-up Reaction

Table 4 presents the carbon balance in the 1 dm³ system. As can be seen, excellent recovery of carbon was obtained. This shows that there are, at least, no trace amounts of byproducts. Furthermore, these results illustrate one of the advantages of scale-up, which is to allow sufficient material to be reacted in order to conduct material balances.

Table 4 Carbon Balance in 1 dm³ System

Time ,min	0	30	60	90	120
Wt.of C evaporated ,mg	0	11.7	13.8	15.3	15.6
Wt.of C in cyclohexene ,mg	23.4	4.5	1.3		
Wt.of C in diol ,mg	0	5.4	6.8	7.3	9.1
Carbon balance ,%	100	92.3	93.6	96.6	105

CHAPTER 5

CONCLUSIONS

Cyclohexene was oxidized to trans-1,2-cyclohexanediol by aqueous potassium peroxymonosulfate at $\text{pH} < 1.7$ without any organic solvent or phase transfer catalyst. As a consequence of the research, the following conclusion were reached:

1. Trans-1,2-cyclohexanediol dissolved partially in water. Na_2SO_4 was needed to salt it out in order to obtain good recovery.
2. The yield was nearly 80% in 2h of reaction at room temperature on 2.3 cm^3 scale.
3. The yield increased with the stirring speed.
4. Observed rate constants increased with stirring speed.
5. Observed rate constants increased with temperature.
6. Observed rate constant decreased with increasing amounts of KHSO_5 .
7. In an open reaction system of 1 dm^3 scale, 60% of cyclohexene was evaporated in 2h under vigorous mechanically stirring.

CHAPTER 6

FUTURE WORK FOR SCALE-UP

Scale up the reaction to larger scale (5 to 30 kg, 5-22 dm³) in order to show how scale-up affects the rate and yield of the reaction. The specific effects of heat and mass transfer on yield need be investigated.

Heat transfer is an area or surface related operation which strongly depends on thermal conductivity. Consequently, scale-up in glass vessels results in poorer heat transfer unless the equipment is specifically designed to avoid this problem. In this reaction, we do not anticipate heat transfer problem since it is carried out at room temperature in fairly dilute solvent where exothermic effect will play a minimal role.

The other effect of scale-up is mass transfer. In this case, the chemical kinetics follow the path determined in the microscale experiments, but because of the large volume, it takes longer for the reactants to meet. Thus, the apparent rate may become mass transfer limited unless mixing or recirculation procedures are instituted to avoid such problems.

This combined "micro-semimacro-kilo" scale data is essential in the early stage of drug manufacture since scale-up is needed to produce sufficient quantities for testing.

APPENDIX A

Tables

Table A1 Relationship Factor (R) of n-Octane to Trans-1,2-Cyclohexanediol

n-octane		trans-1,2-cyclohexanediol		R
wt.,mg	peak area	wt.,mg	peak area	
10.5	3501819	13.1	2188677	1.996
18.1	6201082	37.3	6475104	1.974
34.7	12687720	36.3	6544279	2.028
10.6	3790821	45.9	7529210	2.180
22.6	8041676	36.2	6979490	1.846
22.8	8342547	37.4	6869847	1.992
18.4	6609997	36.9	6440266	2.058

Table A2 Relationship Factor (R) of Hexadecane to Cyclohexene and to Diol

hexadecane	wt.,mg	12.4	12.4	19.8	13.3	18.8
	peak area	2186886	2400233	3718334	2140577	3255822
cyclohexene	wt.,mg	6.2	7.6	15.6	11.1	21.2
	peak area	1318657	1704613	3891885	2518040	4435642
R_1		0.83	0.87	0.76	0.71	0.83
hexadecane	wt.,mg	12.4	12.4	19.8	13.3	18.8
	peak area	2186886	2400233	3718334	1959455	3255822
diol	wt.,mg	19.8	19.3	28.9	13.0	30.4
	peak area	2004228	2122559	3235479	1106634	3059253
R_2		1.75	1.77	1.68	1.73	1.72

APPENDIX A
(Continued)

Table A3 Calibration Factors Used in the GC Analysis of Reactants and Products

	Cyclohexene		Hexadecane		Trans-1,2-cyclohexanediol	
	Wt.,mg	Peak Area	Wt.,mg	Peak Area	Wt.,mg	Peak Area
1	0	0	0	0	0	0
2	6.2	1332863	12.4	2291282	13.0	1412887
3	7.6	1810307	13.3	2321698	19.3	2008920
4	11.1	2691117	18.8	3328256	19.8	2167830
5	15.6	3889813	19.8	3695782	28.9	3192958
6	21.2	4911421			30.4	3196486

Table A4 Yields of Glycol Obtained as a Function of Time at 1200 rpm and 19°C on 2.3 cm³ Scale

Time,h	0	0.25	0.5	0.75	1	2	3	5
Wt. of diol,mg	0	8.3	17.9	26.2	27.8	31.3	29.9	29.7
Yield,%	0	22.0	47.4	69.3	73.5	82.8	79.1	78.6

Table A5 Stirring Rate Effect on the Yield of Diol at 19°C on 2.3 cm³ Scale

Stirrer speed,rpm	0	500	1000	1200
Wt,mg	10.9	19.3	23.9	31.3
Yield,%	28.8	51.1	63.2	82.8

APPENDIX A
(Continued)

Table A6 The Change of $\ln(C_i/C_t)$ with Time at 1200 rpm and 19°C on 2.3 cm³ Scale

Time,min	Wd,mg	Cd,mM	C _i /C _t	Ln(C _i /C _t)	Corr.Ln(C _i /C _t)
0	0	0	1	0	0
4	0.9	3.37	1.02	0.0241	0.0346
6	1.9	7.11	1.05	0.0516	0.0519
10	3.3	12.4	1.09	0.0915	0.0865
12	3.4	12.7	1.10	0.0944	0.104
18	5.5	20.6	1.17	0.157	0.156
20	6.2	23.2	1.20	0.179	0.173

Where C_i is the initial cyclohexene concentration in moles/dm³ and C_t is the cyclohexene concentration at a given time.

Table A7 The Effect of the Stirring Rate on k_{obs} (min⁻¹) at 0°C on 2.3 cm³ Scale

	Time,min	0	4	8	14	20	k_{obs}
	800 rpm	wt. of diol,mg	0	0.8	1.3	2.8	
	Ln(C _i /C _t)	0	0.0211	0.0343	0.0753	0.0979	
1200 rpm	wt. of diol,mg	0	0.4	1.2	3.6	6.3	0.008
	Ln(C _i /C _t)	0	0.0365	0.0623	0.0979	0.1782	
1600 rpm	wt. of diol,mg	0	0.9	1.7	4.6	6.5	0.009
	Ln(C _i /C _t)	0	0.0350	0.0700	0.1269	0.1844	

APPENDIX A
(Continued)

Table A8 The Effect of Stirring Rate on k_{obs} (min^{-1}) at 19°C on 2.3 cm^3 Scale

	Time,min	0	4	8	14	20	k_{obs} .
800 rpm	wt.of diol,mg	0	0.9	2.5	4.5	6.1	0.009
	Ln(Ci/Ct)	0	0.0236	0.0670	0.1239	0.1720	
	wt.of diol,mg	0	1.6	3.2	5.0	7.1	
1200 rpm	Ln(Ci/Ct)	0	0.0423	0.0865	0.1387	0.2032	
1600 rpm	wt.of diol,mg	0	1.4	3.5	6.3	9.5	0.013
	Ln(Ci/Ct)	0	0.0369	0.0950	0.1782	0.2825	

Table A9 The Effect of Stirring Rate on k_{obs} (min^{-1}) at 40°C on 2.3 cm^3 Scale

	Time,min	0	4	8	14	20	k_{obs} .
800 rpm	wt.of diol,mg	0	1.0	2.0	3.9	5.6	0.008
	Ln(Ci/Ct)	0	0.0270	0.0542	0.1091	0.1609	
	wt.of diol,mg	0	1.3	3.2	5.8	8.2	
1200 rpm	Ln(Ci/Ct)	0	0.0353	0.0889	0.1684	0.2452	
1600 rpm	wt.of diol,mg	0	2.4	6.2	10.3	13.8	0.023
	Ln(Ci/Ct)	0	0.0659	0.1810	0.3192	0.4552	

APPENDIX A
(Continued)

Table A10 The Relationship of k_{obs} vs., Time as a Function of Stirring Rate and Temperature

	800 rpm	1200 rpm	1600 rpm	2000 rpm	2500 rpm
0°C	0.005	0.008	0.009	0.012	0.019
19°C	0.009	0.010	0.013	0.023	0.034
40°C	0.008	0.015	0.023	0.031	0.044

Table A11 The Effect of Oxone on k_{obs} (min^{-1})

	Oxone:cyclohexene = 44:35			Oxone:cyclohexene = 88:35		
	800 rpm	1200 rpm	1600 rpm	800 rpm	1200 rpm	2000 rpm
k_{obs}	0.0086	0.0102	0.0134	0.0048	0.0075	0.0140

Table A12 The Evaporation of Cyclohexene

Time, min	0	30	60	90	120
Wt. of cyclohexene, mg	26.7	13.3	10.9	9.2	8.9
Cyclohexene in the system, %	100	49.8	40.7	34.4	33.5

Table A13 Yield on 1 dm^3 Reaction

Time, min	0	8	13	20	30	60	90	120
Wt. of diol, mg	0	2.5	3.5	5.9	8.7	11.0	11.7	14.7
Yield, %	0	7.6	11.5	21.5	46.2	71.8	90.1	94.9

APPENDIX B

Figures

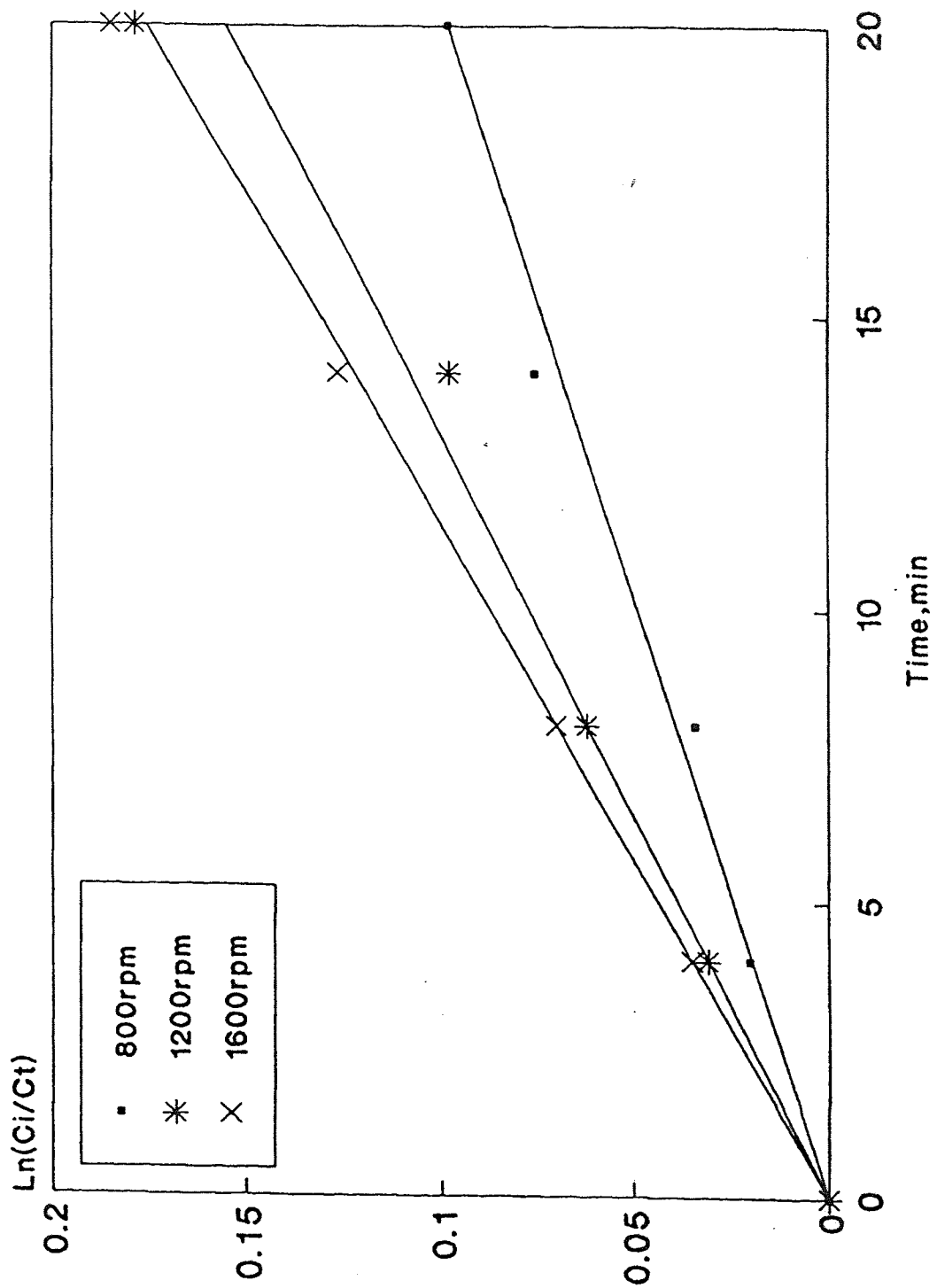


Figure B1 $\ln(C_i/C_t)$ vs. Time as a Function of Stirring Rate at 0°C-Kinetics Study of Glycolization of Cyclohexene

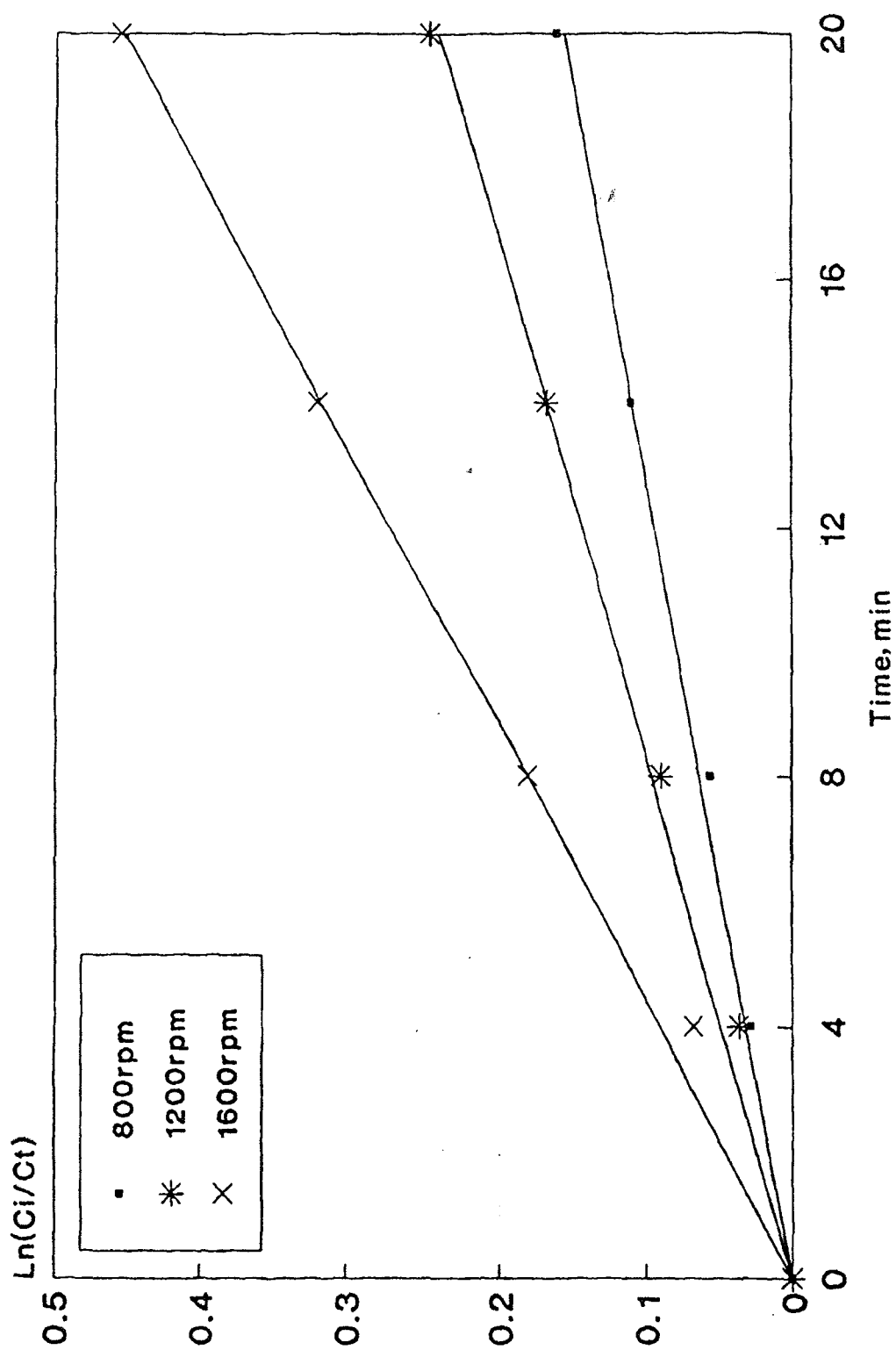
APPENDIX B
(Continued)

Figure B2 $\ln(C_i/C_t)$ vs. Time as a Function of Stirring Rate at 40°C-Kinetics Study of Glycolization of Cyclohexene

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