This is to certify that the

thesis entitled

Oxidation Catalysis of Glucose
and
New α,ω-Bis Ligating Monomers

presented by

Gwen Dee Goretsas

has been accepted towards fulfillment
of the requirements for

M.S. degree in Chemistry

Michael Rathke
Major professor

Date February 22, 1980

O-7639

# OXIDATION CATALYSIS OF GLUCOSE
and
# NEW $\alpha,\omega$-BIS LIGATING MONOMERS

By

GWEN DEE GORETSAS

A Thesis

Submitted to

Michigan State University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

Department of Chemistry

1980

ABSTRACT

# OXIDATION CATALYSIS OF GLUCOSE and NEW α,ω-BIS LIGATING MONOMERS

By

GWEN DEE GORETSAS

The first project involves investigations into the catalytic oxidation of glucose. A variety of active catalysts were found, many of which have been polymer supported. A preliminary GC/MS analysis of the oxidation products was also outlined. The relevance of the project to diabetes mellitus was discussed.

The second area of research involved the synthesis of α,ω-bis(diphenylphosphine)monomers and α,ω-bis(cyclopentadienyl anion) monomer precursors. Details of the syntheses are given.

DEDICATION

To Mom and Dad. For love and encouragement above and beyond my ability to express in words.

and

To Gil. You and me-all that lights upon us, though,
brings us together like a fiddle-bow
drawing one voice from two strings it glides along.
Across what instrument have we been spanned?
And what violinist holds us in his hand?
O sweetest song.

Rainer Maria Rilke

ACKNOWLEDGEMENTS

I would like to thank my mentor, Dr. Robert H. Grubbs for his never ending support, guidance, and patience. Also, for the opportunity to be a part of that strange saga, "The Grubbies Go to California."

Thanks also to Drs. S. Pine, D. A. Evans (and his group), and D. W. Brown for providing an arena to discuss various synthetic problems at Caltech.

To JBL, I needn't say anything, you already know. Keep those turkey and chicken legs cooking!!

To my friends and coworkers at the Foothill Free Clinic in Pasadena-thanks for the time we shared.

Special appreciation to Anita King and Dr. Rathke at M.S.U. for making those 'final' arrangements and to Betty Siebert for putting me up, or is it putting up with me?!

To my coworkers on the diabetes project, Dr. Devinder Gill and Gary Smith, your enthusiasm and our productive interactions will always be remembered.

Special thanks to B. Loeffler, S. Ashoor, and G. Johnson for assistance with figures . . . misery loves company.

Finally, to the Food Research Institute bananas, thanks for making my time in Madison so a-peeling!!

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

# CHAPTER I: OXIDATION CATALYSIS OF GLUCOSE

# INTRODUCTION

This investigation was begun with a specific chemical and biological goal in mind. In order to understand the guidelines that were experimentally drawn, some general information on the disease in question, diabetes mellitus, must be established.

Diabetes mellitus or its symptoms were documented as far back as 1500 B.C.[1] But it was not until the landmark work of Banting and Best[2] in 1921 that the 'curative power' of insulin was demonstrated in this condition. Unfortunately, this discovery was not the once dreamed of panacea for diabetics. Although the useful lifetime of severe diabetics was extended there remained an unusually high incidence of heart attacks, strokes, kidney failure, gangrene, and blindness. Today, diabetes is considered to be the third leading cause of death[3] in the United States, led only by cardiovascular disease and cancer.

The debate over what causes diabetes and its complications has continued for several decades.[4] The work by the laboratories of Notkins[5] and others has given substantial evidence that diabetes is not a disease with a simple etiology, but a complex interaction between the genetic and environmental backgrounds of an individual.[6]

The causative factors aside, what is responsible for the high morbidity and mortality of the long term diabetic? The side effects present themselves in both insulin and diet controlled patients and continue to frustrate a myriad of advances in preventative medicine. The fluctuation between high and normal levels of glucose in the controlled long term diabetic has been implicated by several areas of current research as the primary source of detrimental ramifications.[7]

Normal glucose metabolism involves biosynthesis and degradation, energy production and storage. This occurs through a variety of pathways and involves a number of organs. Excess glucose levels, as expected, affect a variety of functions in the body.

Glucose reacts with hemoglobin in the blood to form glycohemoglobin $A_{1c}$ which is found in levels twice the normal concentration in diabetics.[8] The glycohemoglobin has a higher affinity for oxygen resulting in a slower release of the same and therefore a possible contribution to tissue anoxia. This disruption in normal metabolism has been implicated by R. G. Spiro as primary in causing microangiopathy or the thickening of the basement membrane which surrounds the epithelial cells of the blood vessels.[9] This can contribute to poor circulation and an acceleration in the atherosclerotic process.

One point that should be made here is that many persons afflicted with diabetes mellitus have normal or above normal

levels of insulin. But in order for the glucose to enter the cell it requires an interaction between receptor sites on the membrane with insulin and glucose. The current medical opinion is that defective receptor sites may be part of the body's inability to utilize glucose in the conventional manner.[10] When this mode of glucose depletion is blocked, the body places the excess glucose into other metabolic shunts as shown in Figure 1-1.[11] It is the overutilization of these various pathways that is believed to result in the variety of maladies commonly associated with diabetes.

The basis of this project rests on the idea of finding a low energy pathway for the body to rid itself of excess glucose whenever the concentration begins to rise in the blood stream. It would be converted to harmless products allowing the alternative metabolic shunts to return to their normal levels of glucose usage. However, this restricts us experimentally to very stringent criteria We must develop a system (e.g. a polymer supported catalyst) which is suitable for implantation. It must be active at $37^{\circ}$, pH 7.2, and selective for glucose. The various components of blood serum cannot irreversibly poison it, nor can it be degradable under long term exposure to physiological conditions. A means of control must be built in to insure that hypoglycemia does not result.

67

With these specifics in mind, the search began.

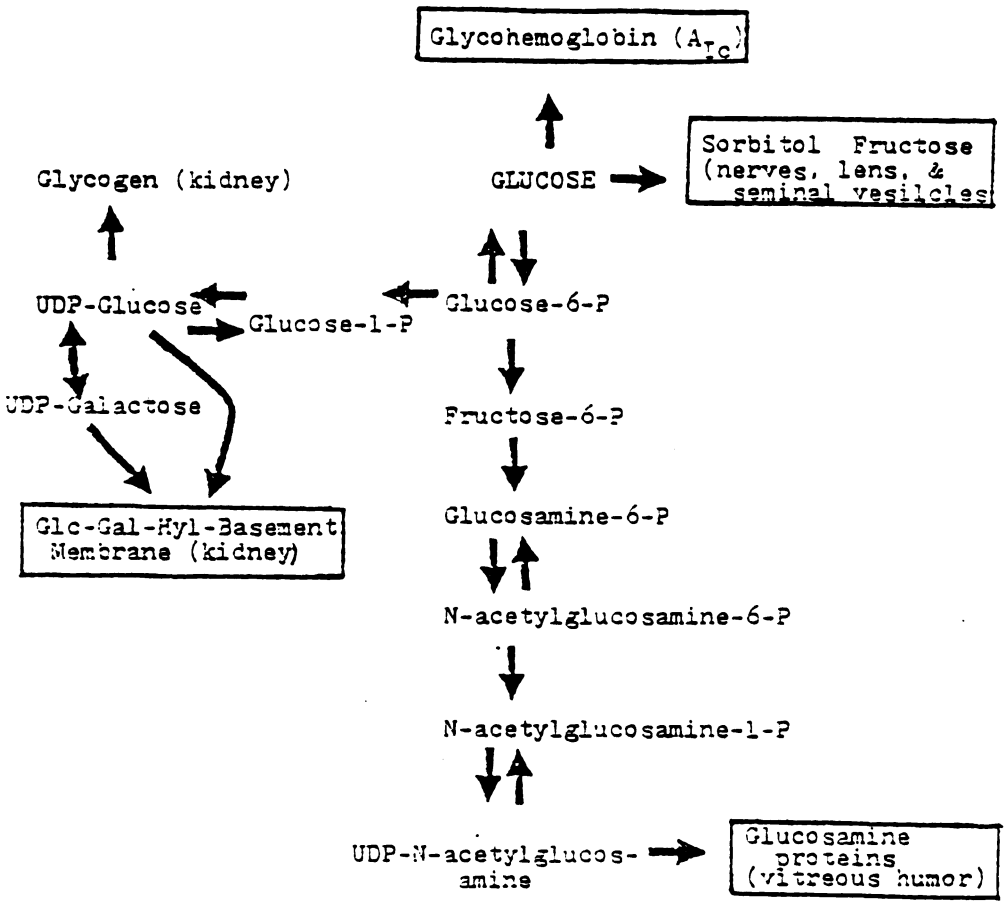



Figure 1-1. Some pathways of glucose overutilization by non-insulin requiring cells in diabetes.

## DISCUSSION and EXPERIMENTAL

The apparatus utilized for screening the activity of of catalysts was designed to maximize the number of systems checked and minimize experimental variations (Figure 1-2).

A known amount of catalyst and glucose were equilibrated separately in the desired aqueous system under positive pressure of oxygen at 37 ± 2°C, for at least twelve hours prior to mixing. A catalyst to glucose molar ratio of 1:15 was typical, the usual catalyst concentration being approximately .3mM. The glucose concentration and the pH of the solution was monitored until oxidation became negligible, usually a period of one to two weeks.

Glucose concentration was determined with a YSI 23A Glucose Analyzer. Optimum solution concentrations for the instrument (0-150 mg/dl) were obtained from the reaction mixtures by quantitative dilutions based on starting glucose concentration. Random standard runs were made to insure that experimental error did not exceed one to three percent (1-3%).

It is important to understand the operation of the Glucose Analyzer (Figure 1-3). Glucose Oxidase (EC1.1.3.4.) catalyzes the oxidation of β-D-glucopyranose to γ-D-glucono-lactone and hydrogen peroxide. The lactone rapidly hydrolyzes to D-gluconic acid.

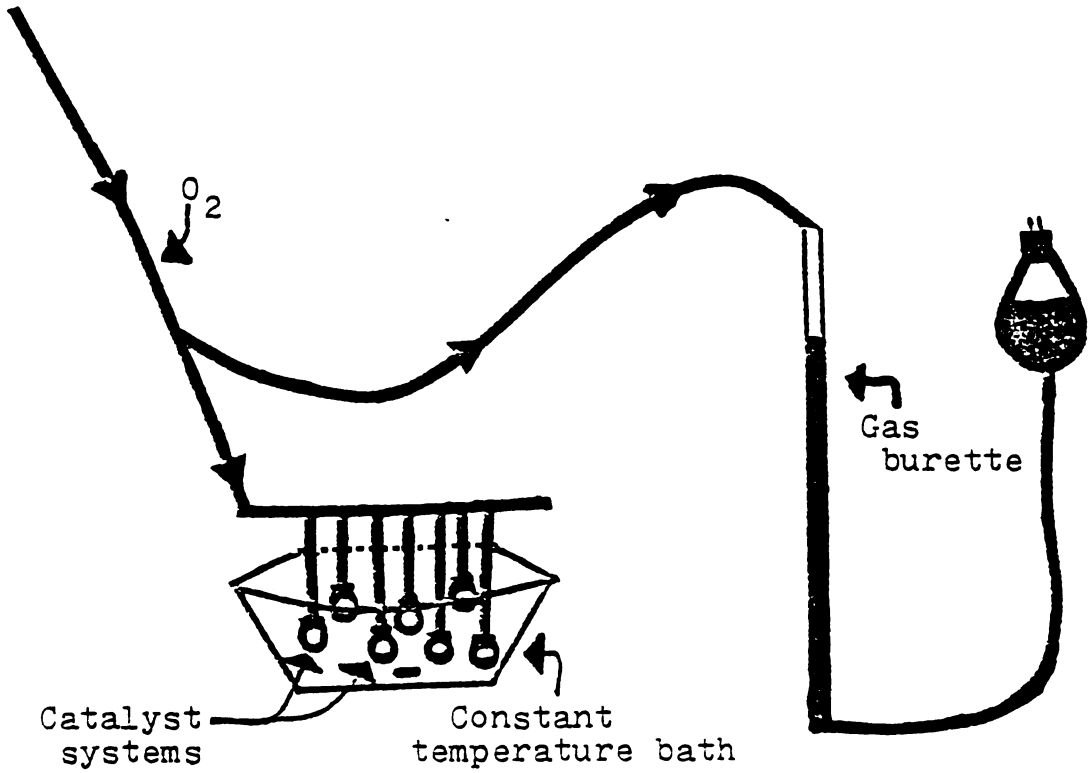
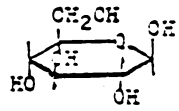



Figure 1-2. Apparatus for Screening Catalysts.

Reaction I




Glucose oxidase →

D-gluconic acid + $H_2O_2$

At the platinum anode of the instrument, $H_2O_2$ is then oxidized.

Reaction II

$$H_2O_2 \xrightarrow{\text{Pt anode}} 2H^+ + O_2 + 2e^-$$

The reaction is completed at the silver cathode.

Reaction III

$$4H^+ + O_2 \xrightarrow{\text{Silver cathode}} 2H_2O - 4e^-$$

Figure 1-3. Reactions occurring in YSI Glucose Analyzer.

The tip of the probe is covered by a porous membrane which protects the electrodes and defines the diffusion path to them. It is a two layer membrane premounted on an 'O' ring and prefilled between the layers with the enzyme.

The outer membrane is a polycarbonate material with a pore size of .03 to .06 micrometers. This allows passage of glucose, oxygen, hydrogen peroxide, and salts but it is small enough to exclude cells and restrict the diffusion of other enzymes.

The glucose oxidase is immobilized between the first membrane and the second, which is composed of cellulose acetate. This second membrane has a much smaller pore size and excludes glucose, ascorbic acid, and other interfering substances. It does allow the passage of hydrogen peroxide, water, molecular oxygen and various salts.

Glucose in the vicinity of the probe diffuses through the outer membrane where Reaction I occurs. The peroxide produced then diffuses through the inner membrane and contacts the platinum anode and silver cathode where Reactions II and III occur. This results in a current which is proportional to the quantity of hydrogen peroxide diffusing in.

The anode is polarized at 0.7 volts with respect to the cathode. This will oxidize hydrogen peroxide and several other reducing agents normally found in the blood. The inner membrane effectively minimizes the effects of the majority of interfering substances.

The glucose analyzer is ideal in many respects. It allows fast, accurate concentration readings, which are mandatory when doing rates with homogeneous catalysts or very active heterogeneous systems. There is a minimal time lag between sampling and concentration readings.

However, the instrument does present certain complications with several of our catalyst systems. It should have been noted that β-D-glucose is the species which is oxidized and results in a reading. Samples must be equilibrated for several hours in order for the alpha-beta ratio to be normalized.[12] We have found that Pt and possibly other systems selectively oxidize the beta form of glucose. Depending on the relative rate of epimerization versus oxidation we have an inherent concentration error in some of the studies.

With the molybdenum(VI) systems another error has come to light. Molybdenum in an aqueous solution produces peroxide by the following suggested mechanism (Figure 1-4).[66]

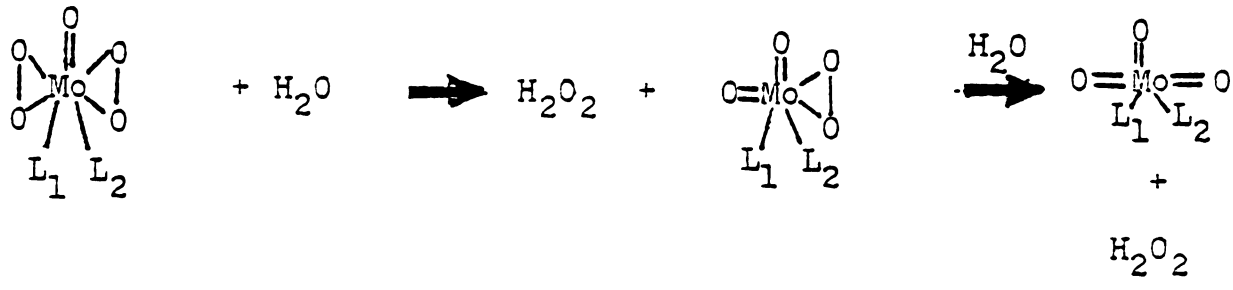



Figure 1-4. Production of hydrogen peroxide in aqueous Molybdenum (VI) systems.

Table 1-1 indicates the oxidation catalysts which under the previously described conditions have exhibited activity. It should be made clear that the active species derived from these systems are unknown.

In the majority of systems screened, the rate of glucose oxidation appears to be very dependent upon pH. In Figure 1-5 a series of solutions with varied pH values containing platinum black as the catalyst demonstrates the relative rate differences observed.[13]

In nonbuffered solutions rates are initially quite rapid and thereafter slow dramatically. Drops of more than five pH units have been observed in some systems.

It is believed that this acidification is due to product formation which ultimately decreases the catalytic activity. The dependence of reaction rate on pH may be explained by assuming that the anionic form of glucose is more reactive to catalytic degradation than the neutral molecule (Figure 1-6).[14]

Coincident with developing a biocompatible catalyst system has been the need to identify the oxidation products. In vivo toxicological studies will be necessary to verify the biological ramifications of these products. Gas liquid chromatography in conjunction with mass spectral analysis was decided on as identification method of choice.

The basic problem with the gas liquid chromatography of carbohydrates is their low volatility due to the high percentage of polar functional groups. Usually the same

Table 1-1.

Catalysts Active for the Aqueous Oxidation of Glucose.

| | |
|---|---|
| 2% Pt on PMMA | $K_3MoCl_6$ |
| Pt in poly(urethane) | $MoO_5(py)_2$ |
| Pt in poly(styrene) | $Mo(CO)_6$ |
| Pt black | ]-$CH_2(acac)_2MoO_2$ |
| ]-$CH_2C_5Me_4RhCl_2$ | $MoO_3$ |
| $C_5Me_5Rh(OAc)_2$ | $Mo(CO)_4bipy$ |
| $RhCl_3 \cdot nH_2O$ | $MoCl_6$ |
| $Rh_2(OAc)_4$ | $MoO_5(DMF)(H_2O)$ |
| ]-$CH_2C_5H_4RhCl_2$ | $MoO_5(gly)(H_2O)$ |
| Rh poly(acrylate) complex | O=Mo(OH)TPP |
| $[C_5H_5IrBr_2]_x$ | $W(CO)_4bipy$ |
| $C_5Me_5IrCl_2]_2$ | $WO_5(DMF)H_2O$ |
| $MoO_5(DMF)_2$ | $WO_5$(picolinic acid) |
| $MoO_5(gly)_2$ | $W(CO)_6$ |
| $MoO_2(acac)_2$ | $Cu(OAc)dipy(OH)H_2O$ |
| $MoO_5(py)H_2O$ | $VOSO_4 \cdot xH_2O$ |

(Catalysts were purchased or synthesized by Dr. Devinder Gill)

See Appendix 3 for explanation of all abbreviations.

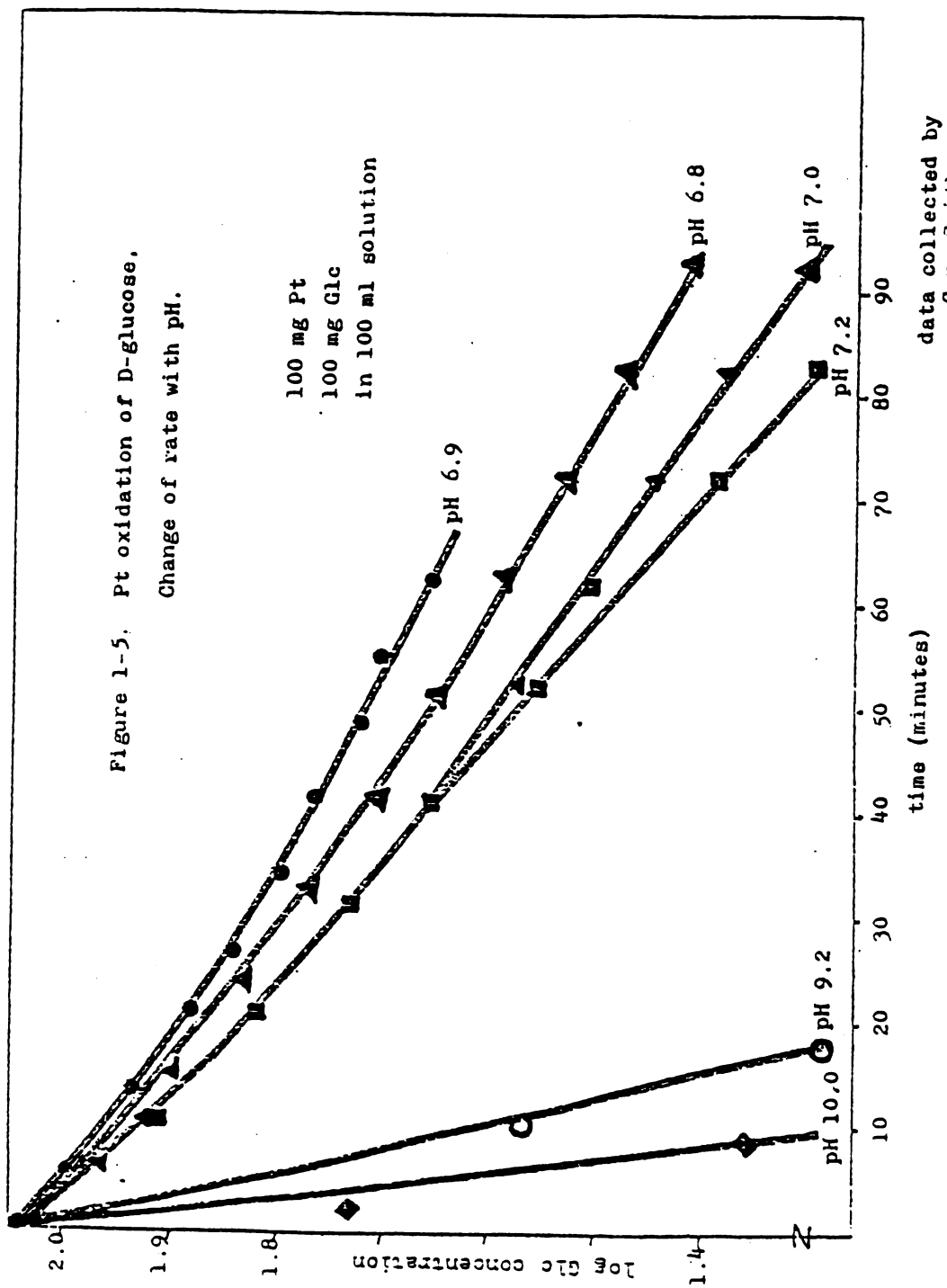
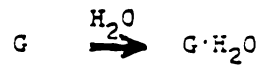


Figure 1-5. Pt oxidation of D-glucose.
Change of rate with pH.
100 mg Pt
100 mg Glc
in 100 ml solution
pH 6.9
pH 6.8
pH 7.0
pH 7.2
pH 9.2
pH 10,0
log glc concentration
time (minutes)
data collected by
Gary Smith

Figure 1-6. Kinetic model for the oxidation of glucose.



G-Glucose, Ga-Gluconic acid

*- adsorbed on heterogeneous catalyst or in contact with hybrid catalyst

intermolecular forces (hydrogen bonding) that cause the low volatility also result in such observations as assymmetric peaks in the chromatograms, measurable volatility only at decomposition temperatures and decomposition upon contact with the column surface or support. Derivatization blocks the possibility of intermolecular association and thereby increases stability and volatility. This usually renders the compound suitable for gas liquid chromatographic analysis.

Special derivatization procedures can allow selective detection of certain species or the separation of chemically very similar compounds. They can also be selected to increase detector resoponse. For example, fluorinated and chlorinated derivatives usually yield high response ratios with electron capture detectors and these are often used in trace analysis.

There are several criteria for suitable derivatization procedures. The process should be rapid and quantitative with any carbohydrate. It is best if carried out at room temperature and must be suitable for a wide range of concentrations of starting materials.

Nonpolar derivatives are usually less reactive to the analysis conditions and therefore are more suitable for quantitative determinations. Trimethylsilyl derivatives are ideal in these respects.

Other types of derivatives which can be used are dimethylsilyl ethers,[15] methyl ethers,[16] acetates,[17] and trifluoroacetates.[18] Dimethylsilylation increases the volatility of the compounds and permits faster elution

times on the same columns used with the trimethylsilyl derivatives.[19] Methyl ethers do not usually allow separation of anomers.[20] In Table 1-2 a list of the most commonly used derivatizing reagents for carbohydrates is given.

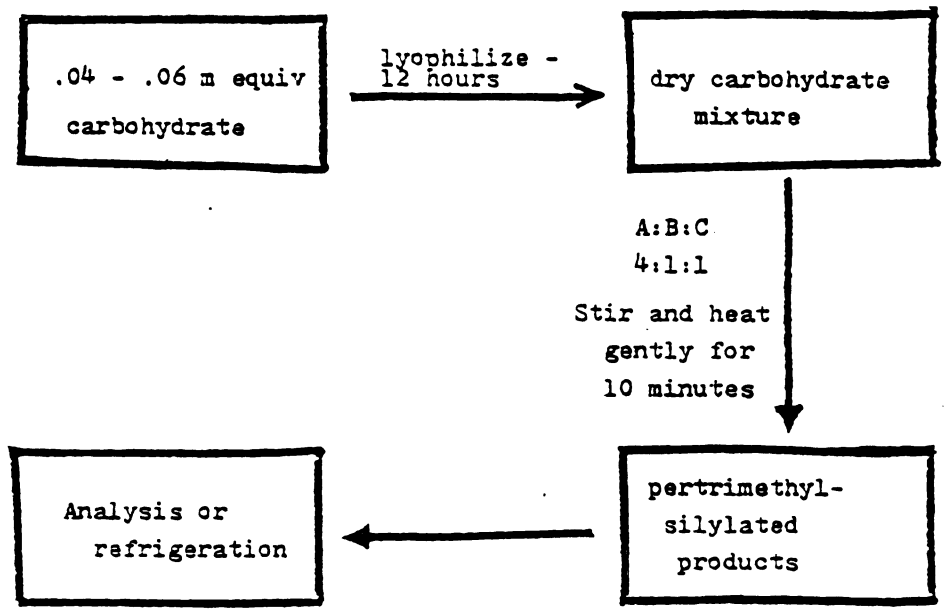
Table 1-2. Commonly Used Derivatizing Agents

1. N-(trimethylsilyl)imidazole (TMSIM)
2. N,O-Bis(trimethylsilyl)acetamide (BSA)
3. Bis(trimethylsilyl)trifluoroacetamide (BSTFA)
4. Silyl amines such as trimethylsilyldiethylamine (TMSDEA)
5. Hexamethyldisilazane (HMDS) with trimethylchlorosilane (TMCS) as catalyst

The procedure normally used for trimethylsilylation is shown in Figure 1-7. The free sugar can usually be recovered in a near quantitative yield by refluxing in 50% aqueous methanol for approximately five hours.[21]

Difficult silylations have been aided by the use of ultrasonic agitation.[22] In the presence of trace amounts of water, trifluoroacetic acid has been found to be more advantageous than the normally used trimethylchlorosilane.[23] Partial silylation resulting in spurious peaks still remains as a problem even with the added potency of this catalyst.

There has been some discussion in the literature as to the solvent of choice in silylation procedures. Some investigators claim that pyridine (the most frequently used solvent) inhibits the formation of trimethylsilyl esters and have recommended the use of petroleum ether, acetone,




A-pyridine; B-hexamethyldisilazane; C-trimethylchlorosilane
Analysis conditions: 10ft. glass SE-52, 100/120 mesh, AW/DMCS flow rate: 36 ml/min; temp: 140° for 5 min., 140° to 250° at .5°/min

Figure 1-7. Derivatization procedure.

or carbon disulfide.[24] Pyridine also presents problems with solvent tailing during chromatography. This has been dealt with in several cases by evaporation of the solvent and subsequent dissolution in dimethylformamide, acetonitrile or hexane.

These analyses are further complicated by the fact that when aldopentoses and higher glycoses are converted into their trimethylsilyl derivatives, there is the possibility that four or more isomers will be produced.[25] Both the alpha and beta anomers are possible for the furanosides and pyranosides. Small peaks may also be present due to partial silylation or to glucose anhydrides formed during the derivatization procedure.[26]

Heating of reducing sugars in pyridine may lead to the establishment of an equilibrium mixture of different composition than the normal aqueous ratio. Sweeley has shown that with crystalline monosaccharides the rate of reaction during derivatization is greater than the rate of mutarotation.[27] Reaction conditions similar to those used during the study were followed to minimize any such reequilibration.

Many types of column packings have been used in gas chromatography for the separation of carbohydrate derivatives. Usually nonpolar and nonselective phases have been preferred. The support is deactivated by acid washing followed by silylation which helps to produce a higher separation efficiency for the column. Commonly used columns are OV-1, SE-30 (dimethyl silicone polymer), SE-52 (methyl phenyl

silicone polymer), TCEPE (tetra(cyanoethyl)pentaerythritol) or Carbowax 20M.[28]

Derivatization and proper column preparation minimizes secondary adsorption effects which may cause nonlinearity in the calibration graph. Several internal standards have been recommended. These are sorbitol, methyl-α-galactopyranoside, and methyl-α-mannopyranoside.[29] The latter is the most favored as it occurs midway between the pentoses and hexoses.

For minimum expense and optimum sensitivity a flame ionization detector (FID) is used. FID response values are similar for structural isomers if their retention times do not differ greatly.[30] However, upon combustion of the silicaceous materials, an aerosol of silica is produced which is deposited upon the electrodes. This deposit can decrease sensitivity or alter the response factor and must be dealt with regularly in routine analysis.

Since the basis of identification for oxidation products rests with mass spectrometry, a few general words on the principals should be discussed. The mass spectral analysis of organic compounds relies on specific fragmentations of these molecules under electron impact. The resulting particles can be differentiated by the use of mass to charge ratios. It is usually possible to obtain a mass spectrum of a compound if the substance provides a vapor pressure of at least $10^{-2}$ mm of mercury at 150° to 250°C.

The abundance of an ion depends on: 1) stability; 2) the stability of neutral particles formed concurrently with the ion and 3) the energy of the bonds cleaved during the formation of the ion.

The parent ion ($M^+$) which is usually an ion radical with an odd number of electrons, is involved in two types of reactions after its formation. These are fragmentation and rearrangement.

Fragmentation is the decomposition of the parent ion into two or more particles, one of which is charged and the other(s) neutral.

The decomposition is termed a rearrangement if bond cleavage is accompanied by new bond formation. Rearrangement ions are of great diagnostic value in structural analysis. They are relatively more abundant at lower electron voltages. At 20 ev, they are frequently the base peaks.[31]

The McLafferty rearrangement refers to the specific migration of a γ-hydrogen atom to a functional group in an odd electron ion. Similar processes are frequently seen in the analysis of trimethylsilyl derivatives of carbohydrates.[32]

Another diagnostic tool often found in the mass spectra of carbohydrates are metastable peaks. If ion A gives rise to another ion B and to a noncharged particle C on the way from the ion source chamber to the magnetic field, the registering recorder indicates a diffuse peak of low intensity known as a metastable peak M. Its position is related to the mass to charge ratio (m/e) of A and B

(a and b) by the equation:

$$M = b^2/a.$$ [33]

The mass spectral method was first applied to carbohydrate chemistry in 1958 by Reed et al.[34] They reported the spectra of D-glucose, D-galactose and others demonstrating the utility of the technique.

Due to the instability of the derivatives of carbohydrates, the molecular ion can only be occasionally found in the spectra of carbohydrate derivatives. Usually the most characteristic feature of the mass spectrum is the absence of this peak.[35]

The elimination of a silicon linked methyl (M-15) and the loss of trimethylsilanol (90 amu) are characteristic fragmentations of carbohydrate trimethylsilyl derivatives.

Several rearrangement ions can be classified as involving the migration of a trimethylsilyl (TMS) group to an oxygen atom or migration of an ester '-OTMS' group to a silicon atom. Concomittant loss of a stable molecule often provides the driving force. The odd electron ions formed by migration of a TMS group are termed McLafferty type rearrangements. The decomposition of several even electron ions can be can be considered analagous to that (Figure 1-8).[36] Extra stability is usually found with the odd electron ions due to the delocalization of the positive charge and the unpaired electron.

Distinguishing between sugar epimers can be difficult. Usually only relative variations in peak intensities are

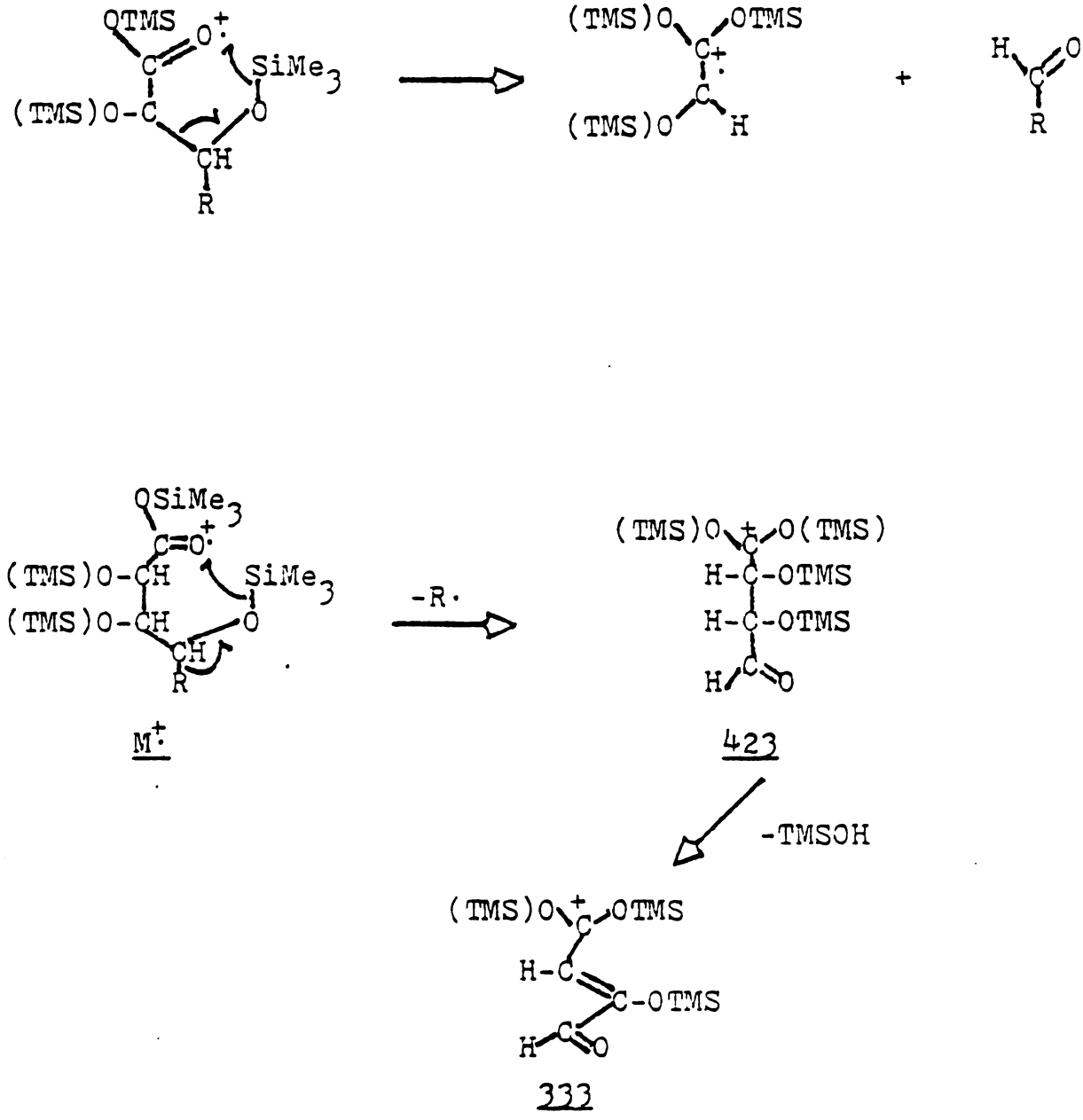



Figure 1-8. McLafferty-type rearrangements seen during mass spectral analyses of carbohydrates.

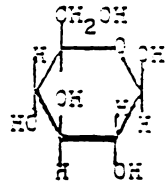
noted and care must be taken for positive assignments.[37]

In this research, specific fragmentation patterns of products obtained during mass spectral analysis were compared with standard spectra available in large quantities in the literature. Identifications were made on this basis (Figure 1-9). Due to the large volume of publications available on the subject, no attempt will be made here to rationalize these patterns.[38] Actual spectra along with their associated reference spectra are located in Appendix 1.

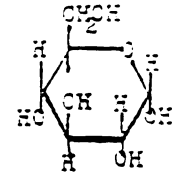
The products identified in Figure 1-9 were obtained through the oxidation of glucose by platinum black and platinum trapped within a poly(methylmethacrylate) matrix. Unfortunately, during the two hours required for the gas liquid chromatographic runs, slight variations in retention times of the peaks were noted. This results in our inability to positively identify the products through comparison of retention times. Unambiguous identification of products from other catalytic systems is not possible until more GC/MS work is completed. In Figure 1-10 the relative retention times (based on β-D-glucose) are plotted versus relative intensity. Certain relationships between oxidation products of different catalysts should be noted. Tabulation of this data can be found in Appendix 2.

For example, with the molybdenum(VI) systems, a similar product distribution is seen for nearly all catalyts. This implicates minimally some similarity in the active species. Unfortunately, few of these peaks appear in the

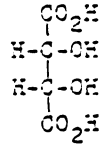
Figure 1-9 Known oxidation products of glucose.



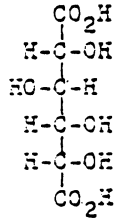
β-D-Glucopyranose



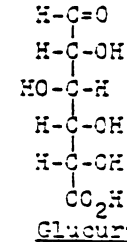
α-D-Glucopyranose



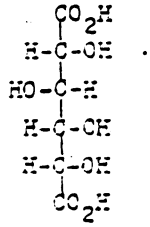
Tartaric Acid
Tetra(TMS)



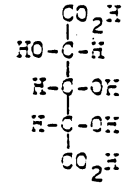
Gluconic Acid
Hexa(TMS)



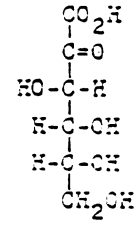
Glucuronic Acid
Penta(TMS)



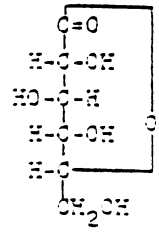
Glucaric Acid
Hexa(TMS)



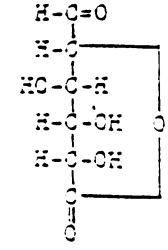
Arabinaric Acid
Penta(TMS)



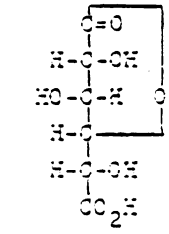
Galacturonic Acid
Penta(TMS)



Gluconc-1,5-lactone
Tetra(TMS)



Glucuronolactone
Tri(TMS)



Saccharo-1,4-lactone
Tetra(TMS)

Figure 1-10. Relative retention times of glucose oxidation products versus relative intensities.

——— -Oxidation products.

------ -Glucose.

Figure 1-10

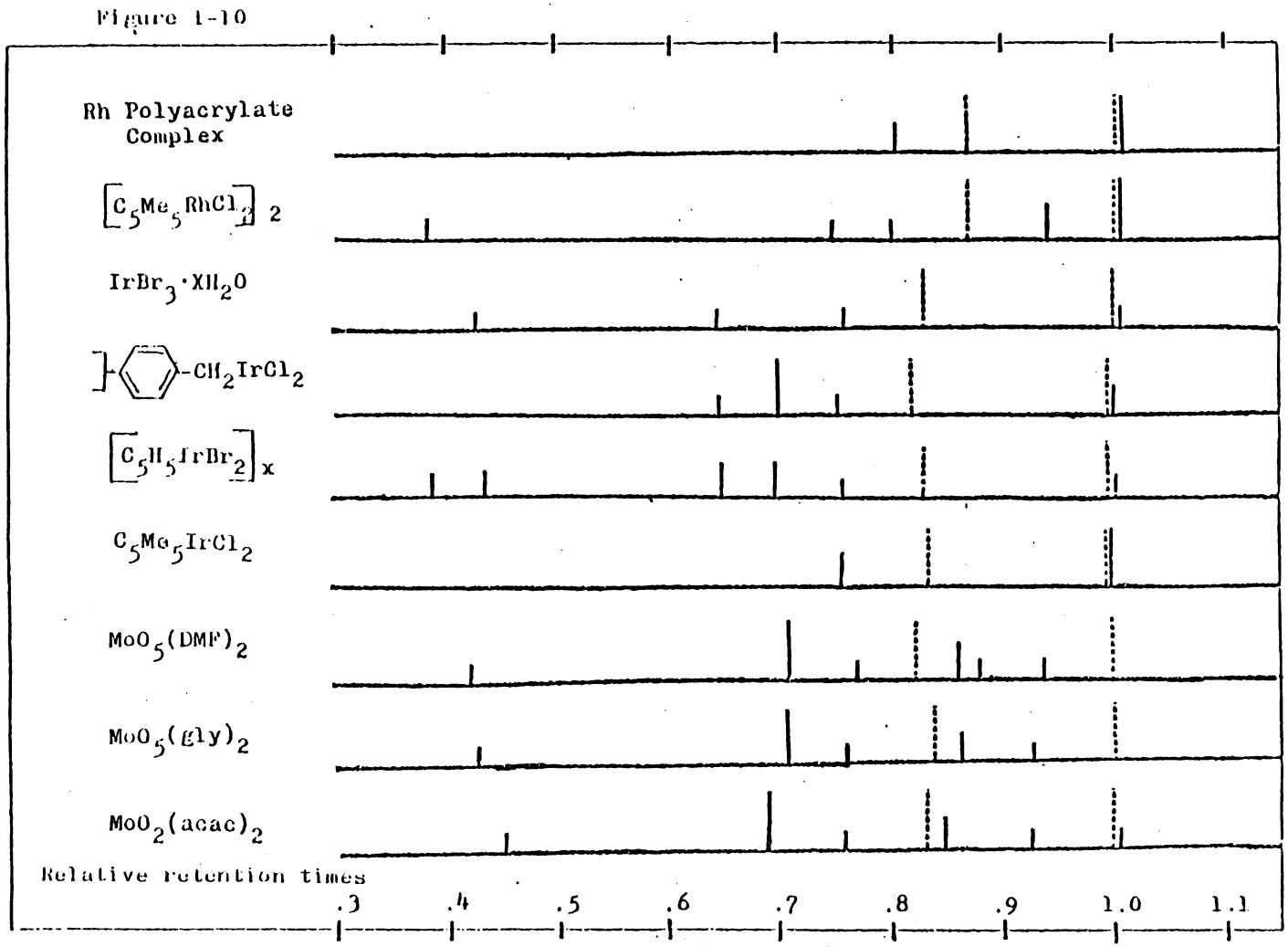
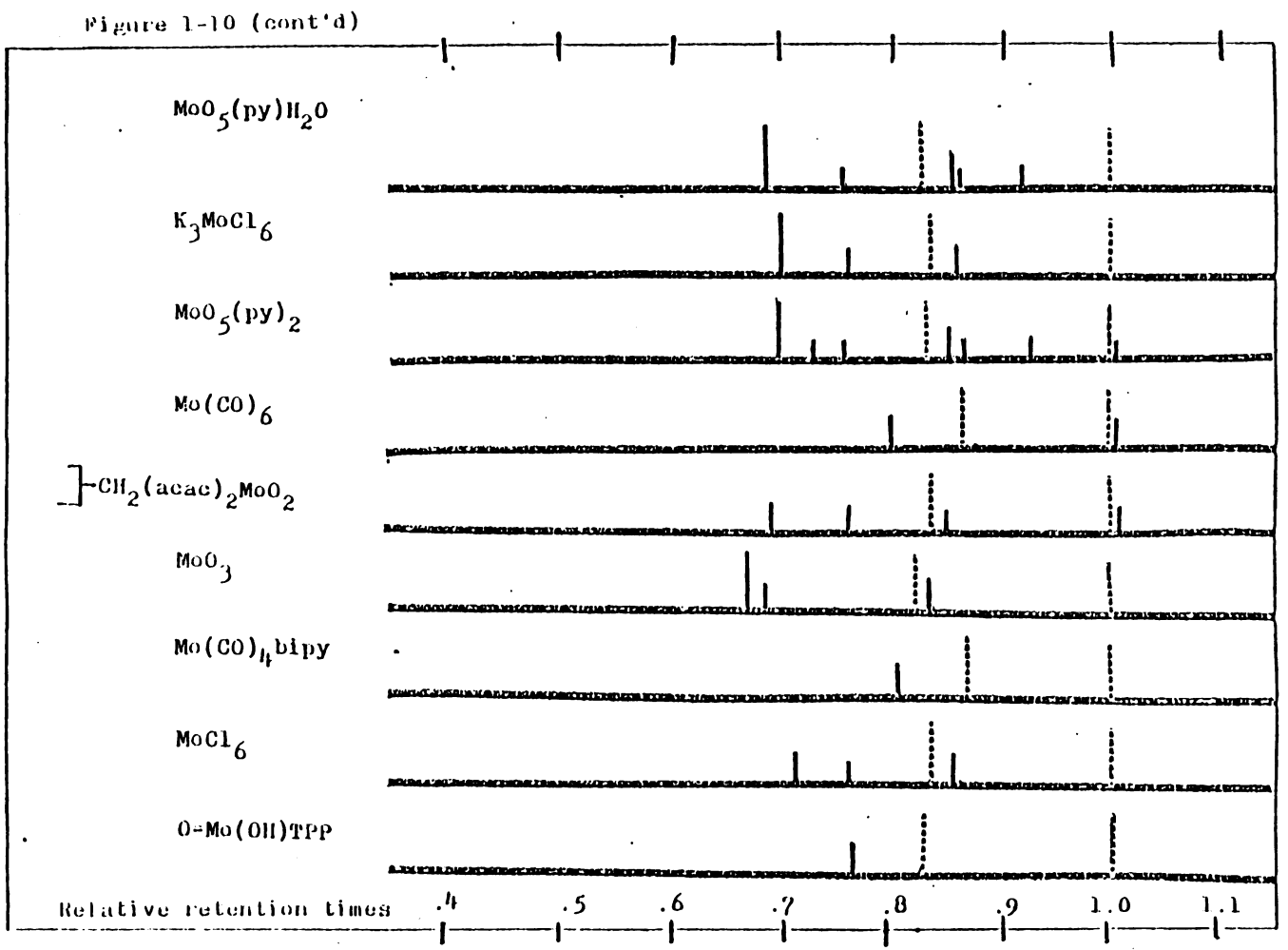

Rh Polyacrylate Complex
[C5Me5RhCl2]2
IrBr3·XH2O
-CH2IrCl2
[C5H5IrBr2]x
C5Me5IrCl2
MoO5(DMF)2
MoO5(gly)2
MoO2(acac)2
Relative retention times
.3
.4
.5
.6
.7
.8
.9
1.0
1.1

Figure 1-10 (cont'd)



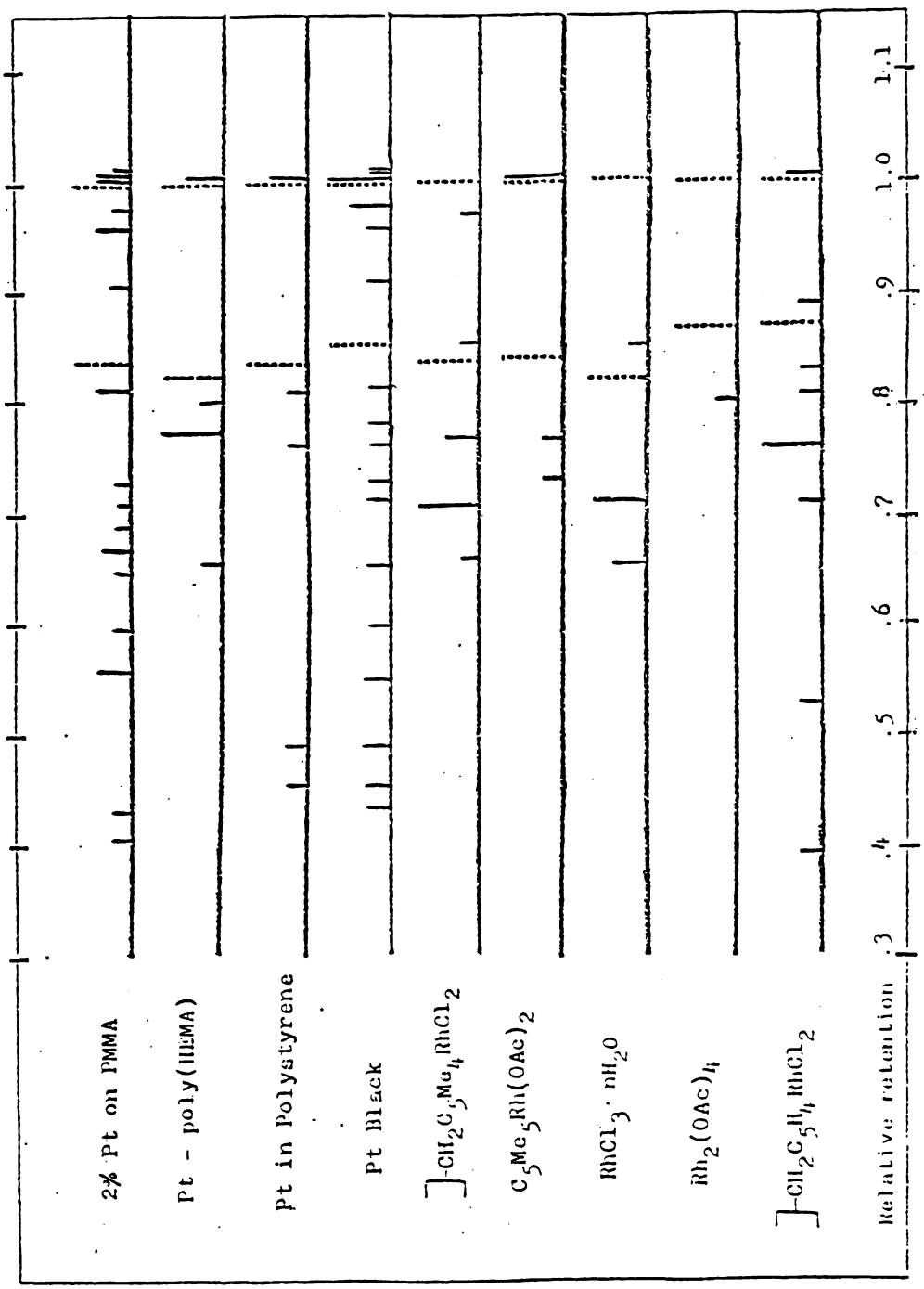
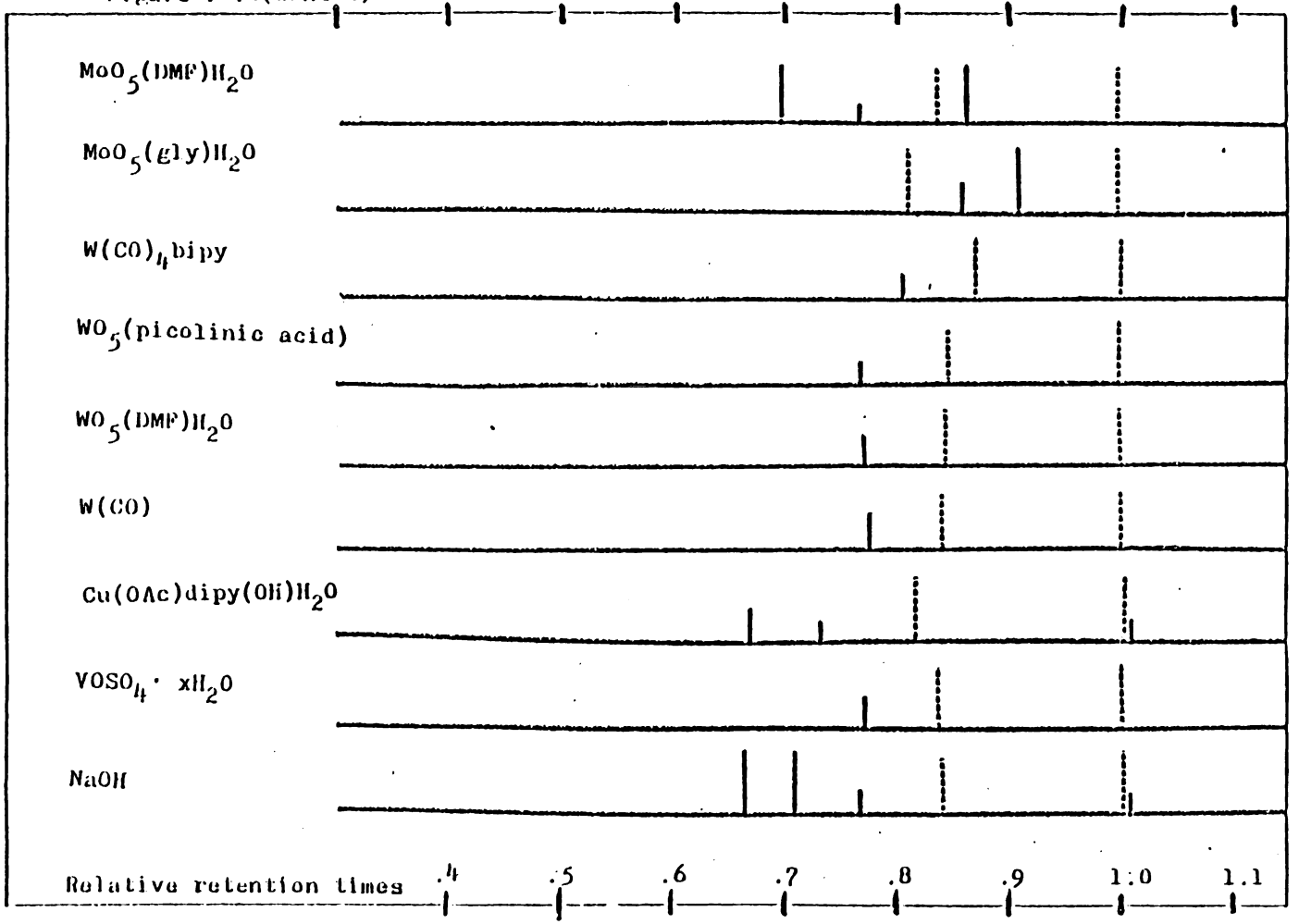



Figure 1-10 (cont'd)

Figure 1-10(cont'd)



analyzed platinum systems.

The variation in the major products in the iridium, rhodium and platinum systems also pose interesting mechanistic questions. Gluconic acid is believed to be the product with the longest retention time in the iridium and rhodium systems.

The data at this point is insufficient for further speculation. Future work, above all, must involve completion of the GC/MS analyses. Mechanistic studies from these data should follow immediately.

Further investigation into the effect of pH upon rates will also be needed. Finally, a more thorough screening of possible catalytic poisons in the blood should be made, along with determining the optimum polymer system for implantation. Biological screening, including toxicity studies and implantation work, although in the future, should be kept in mind as the ultimate goal.

# CHAPTER II: NEW α,ω-BIS LIGATING MONOMERS

# INTRODUCTION

The design of efficient polymer catalyst systems (hybrid catalysts) requires the development of a variety of methods and strategies for the production of such composites. Attempts to synthesize materials with high thermal stability and useful mechanical properties have become of increasing importance.

There are many possible methods of preparation for hybrid catalysts, but only one has been examined in any detail. This method, the first outlined schematically below, involves the synthesis of an insolubilized functionalized polymer to which the metal complex is attached. The major variations possible are shown in Figure 2-1.

Method 1. The majority of work in the field of supported catalysis by the Grubbs' laboratories and others have used this method in the functionalization of cross-linked polystyrene.[39]

Method 2. In this technique, the ligand is polymerized through an attached group to insolubilize the polymer. Each monomer unit has the capability of being a ligating site. These materials may also be utilized by copolymerization with a nonfunctionalized monomer for controlled loading of the catalyst.

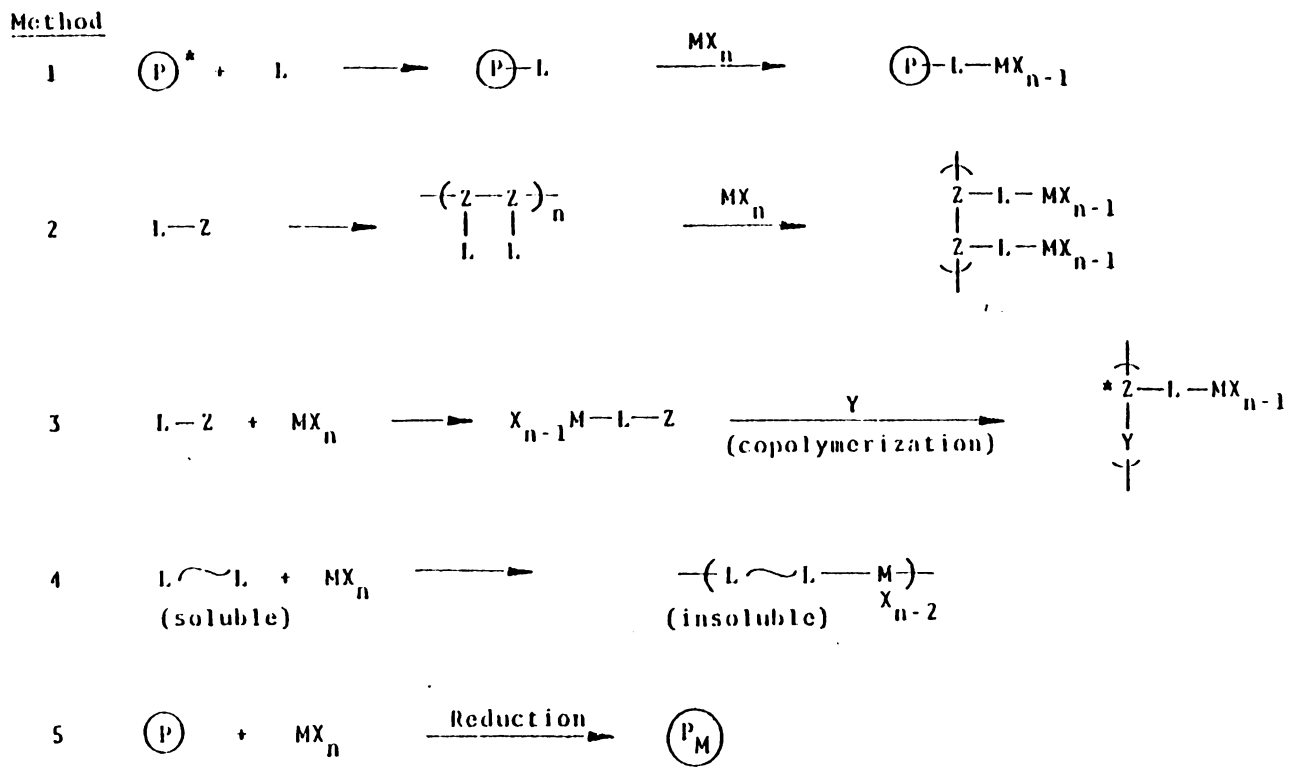

Method
1
2
3
4
5
(copolymerization)
(soluble)
(insoluble)
Reduction
* (P) = insoluble polymer
L = ligand
MX_n = metal complex
Z, Y = easily polymerized monomer groups

Figure 2-1.

Poly(vinylpyridine) has been used in most of the catalytic preparations which follow this classification. Gray in the United States[40] and Tsuchida and Nishide in Japan[41] have been responsible for this type of work. Their efforts resulted in new hydroformylation catalysts.

Other polymers which have been investigated by this method are those containing simple functional groups such as carbonyls, amines, amino acids, and ethylene diamine moieties.[41]

Method 3. This method has been the major approach to organometallic polymers. The technique involves the preparation of an organometallic monomer which is then polymerized

Examples of polymers prepared by this method are poly(vinylferrocene),[42] poly(vinylcynichrodine),[43] poly(vinylcyclopentadienyl) manganese tricarbonyl,[44] and the polyester of cobaltocenium-1,1'-dicarboxylic acid.[45] Very few investigations have been carried out with these materials. The requirement that the metal center be dormant during the polymerization is contradictory to the generally reactive nature of efficient catalyst systems. For this reason, it is unlikely that this method would result in a variety of useful hybrid catalysts.

Method 4. The preparation of bis-ligating monomers will be the subject of the majority of this chapter. Synthesizing $\alpha,\omega$-diligand monomers which will ultimately be polymerized through metal coordination should result in new and useful catalytic systems.[41] A variety of

polymer systems of this type which have already been developed are given in Table 2-1.

The advantages of these hybrid systems are numerous: 1) regular repeating structure in the polymer chain; 2) the ease of controlling molecular weight and solubility properties through variation in the monomer to metal ratio and by incorporating monofunctional ligands in the polymer mix; 3) the ease of solubilizing a polymer after it has undergone a reaction by the addition of monofunctionalized ligands (Figure 2-2); 4) ease of modifying bis-ligating monomers to vary the physical properties of the polymer; and 5) the possibility of forming films by evaporating excess non-complexed volatile ligand.[46]

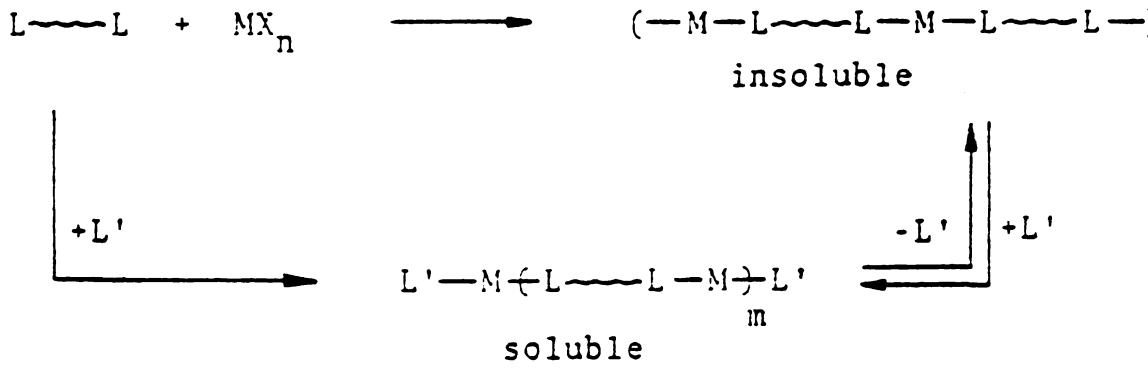
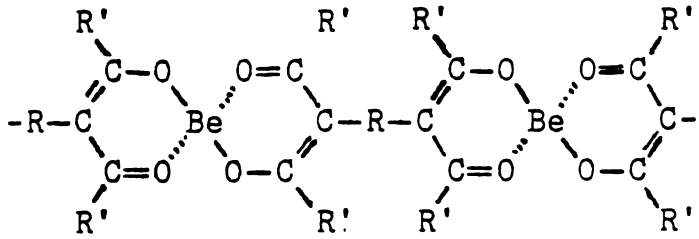
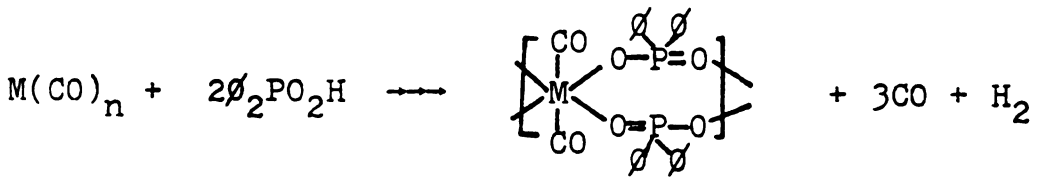



Figure 2-2. Solubilizing a coordination polymer system.

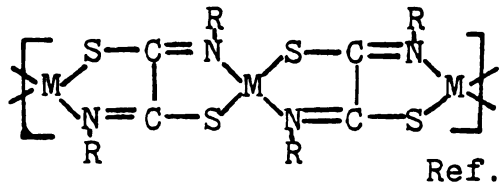
Table 2-1. Types of Coordination Polymers



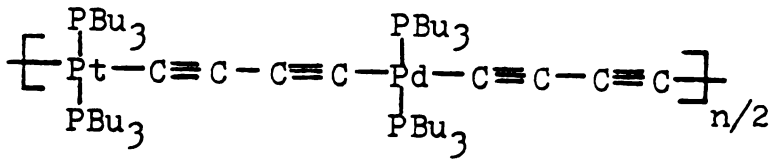
Ref. 47



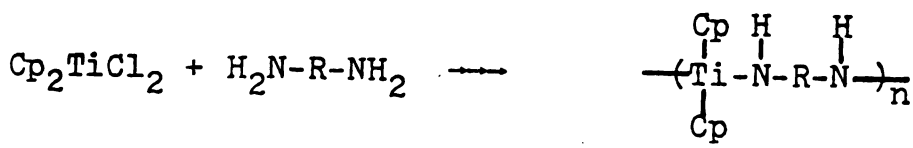
Ref. 48



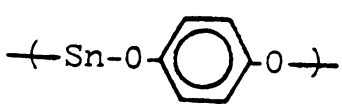
Ref. 49



Ref. 50



Ref. 51



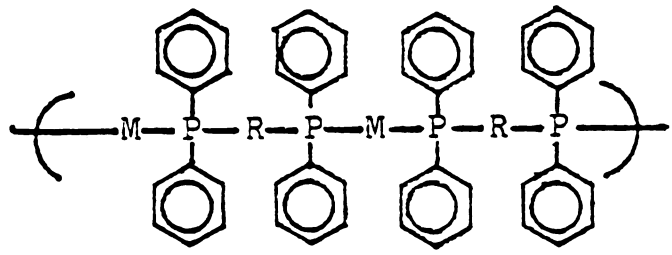
Ref. 52.

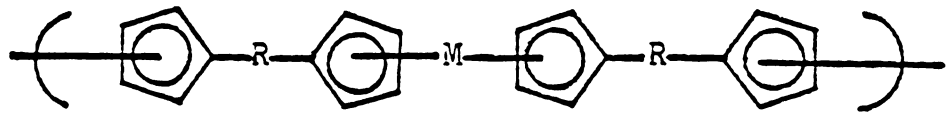
Method 5. The last method uses any functional group to trap finely divided metal. The metal is generated by the reduction of a transition metal salt.

The importance of polymer-metal systems is only now being fully realized. Applications are encompassing general catalysis,[53] electrode catalysis,[54] and such diverse uses as fungicides in fabrics.[55]

## DISCUSSION

This laboratory decided to concentrate its efforts on two types of ligand groups. The decision was based on several considerations: 1) stabilities; 2) ease of altering the polymer linkage through changes in the monomer unit; 3) possible electrochemical properties; and 4) possible catalytic properties. The bis-diphenylphospine monomers and bis-cyclopentadienyl monomers selected as the general synthetic targets are shown in Figure 2-3.




(R = alkyl or aryl)

Figure 2-3. General synthetic targets.

Synthetic work was begun on simple α,ω-bis(diphenylphosphine)n-alkanes (Figure 2-4). The dichloride was easily prepared in all cases attempted, for n = 4, 5, 10 and 12. Polymerization was only attempted for n = 12 which resulted in an intractable mass with a phosphorus to rhodium ratio of ca. 3:1.

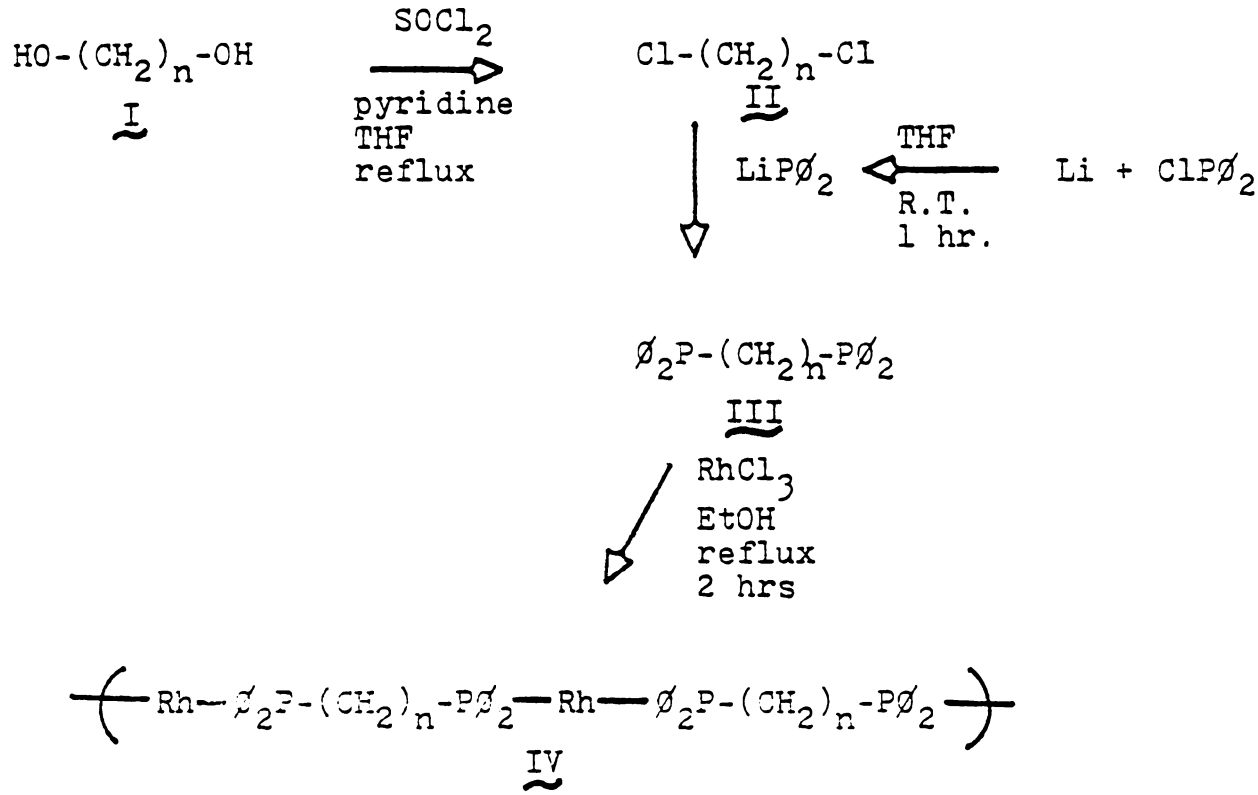



Figure 2-4. Synthesis of α,ω-bis(diphenylphosphine)n-alkane monomers.

1,4-bis(diphenylphosphine)benzene (Figure 2-5) and 4,4'-bis(diphenylphosphine)biphenyl (Figure 2-6) were also prepared using alternative methods already available in the literature.

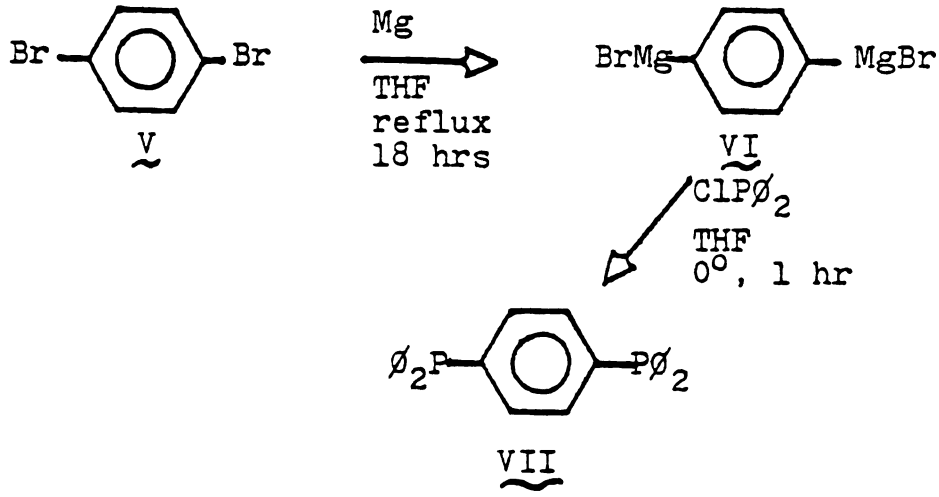



Figure 2-5. Synthesis of 1,4-bis(diphenylphosphine)benzene.

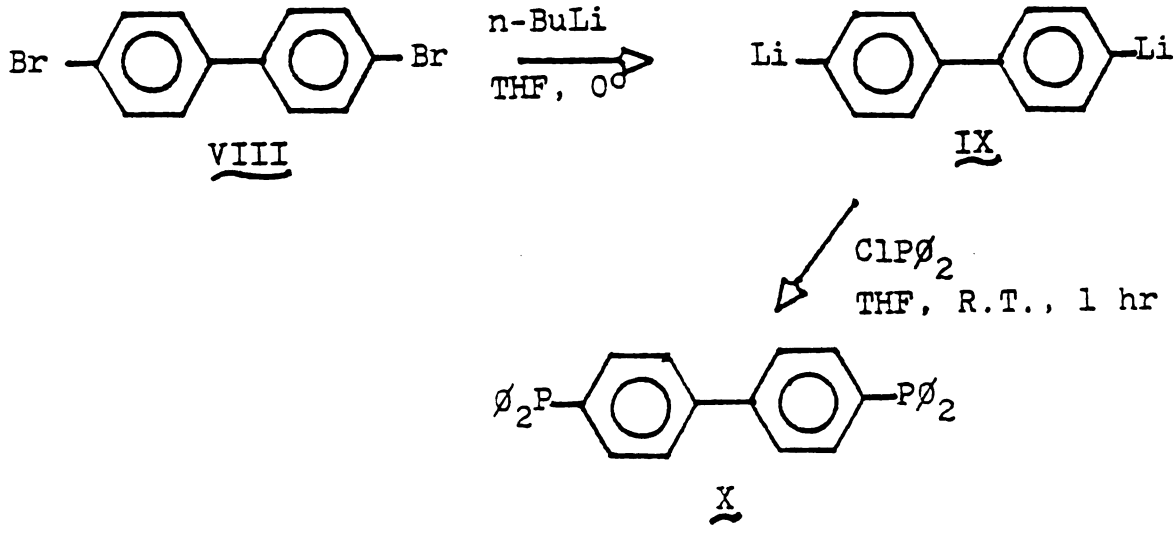



Figure 2-6. Synthesis of 4,4'-bis(diphenylphosphine)biphenyl.

Once the optimum polymerization conditions and analysis procedures have been defined, this series of compounds with various metals could have some very interesting catalytic properties.

The report by Grutzner et al. (Figure 2-7) gave impetus to a synthetic approach for α,ω-bis(cyclopentadienyl) moieties.

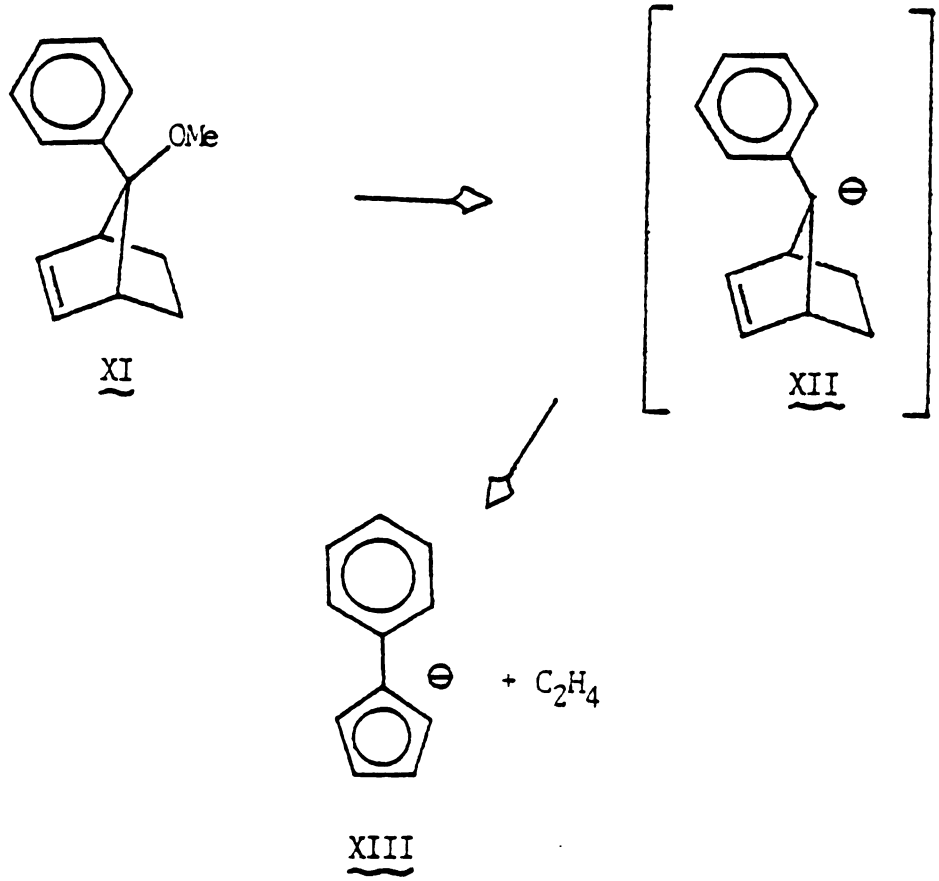
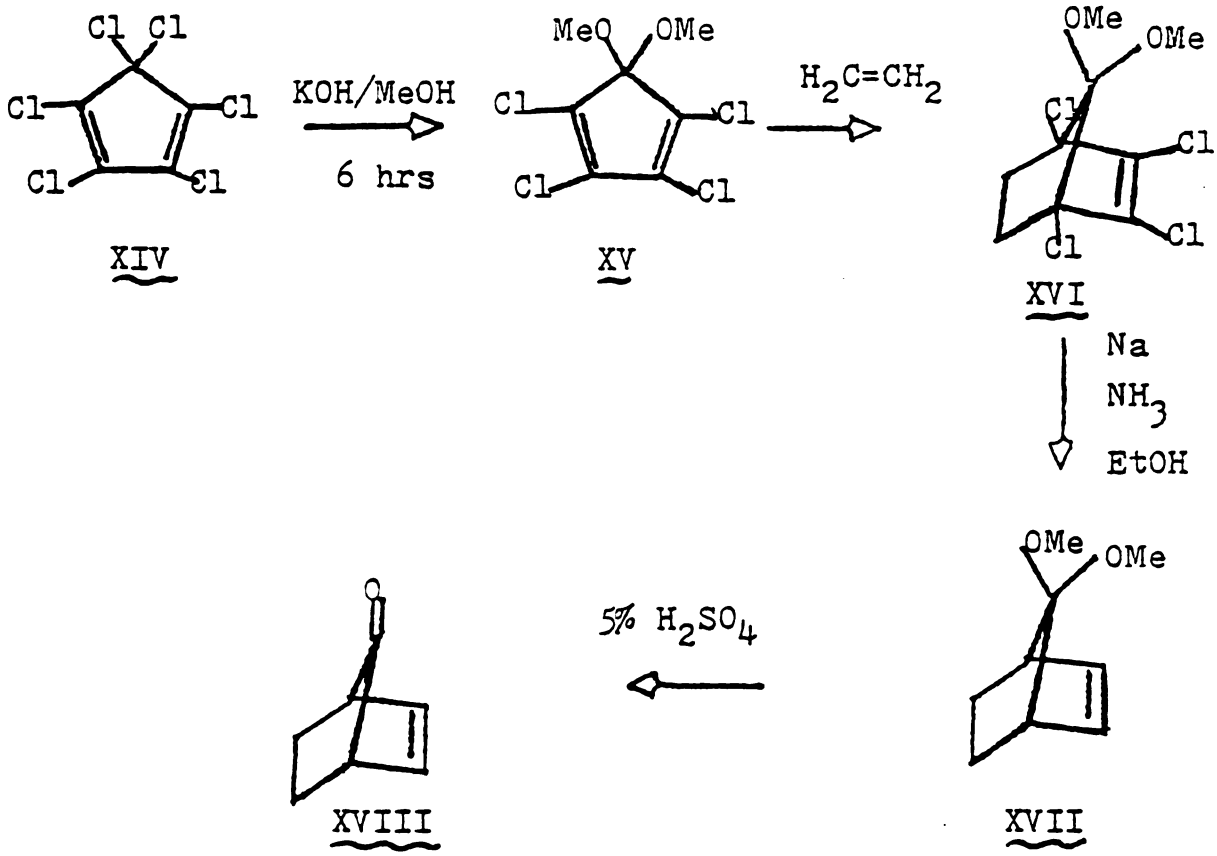



Figure 2-7. Generation of the cyclopentadienyl anion.[56]

After improvements on reported syntheses an overall yield of 55% of the ketone XVIII was obtained (Figure 2-8). The reaction of the ketone XVIII with the digrignard VI led to a clean reaction resulting in the diol XIX. Attempts to quench the reaction with methyl iodide did not result in

the diether XX and more strenuous procedures were not tried (Figure 2-9).




XIV XV XVI XVII XVIII

Figure 2-8. Synthesis of 2-Norbornen-7-one.

Three diastereomers are possible (Figure 2-10) and nuclear magnetic resonance does give an indication of their presence. Much discussion has been in the literature over the preferred mode of attack, syn versus anti. Phenyl magnesium reagents usually add selectively from the syn side whereas the corresponding phenyl lithium reagents give a higher percentage of the anti-addition product. Although gas liquid chromatographic analyses have been done with

phenyl addition products, no attempt was made to separate the mixtures. Generation of the dianion would result in loss of stereochemistry and precludes the need for isolation of each species.

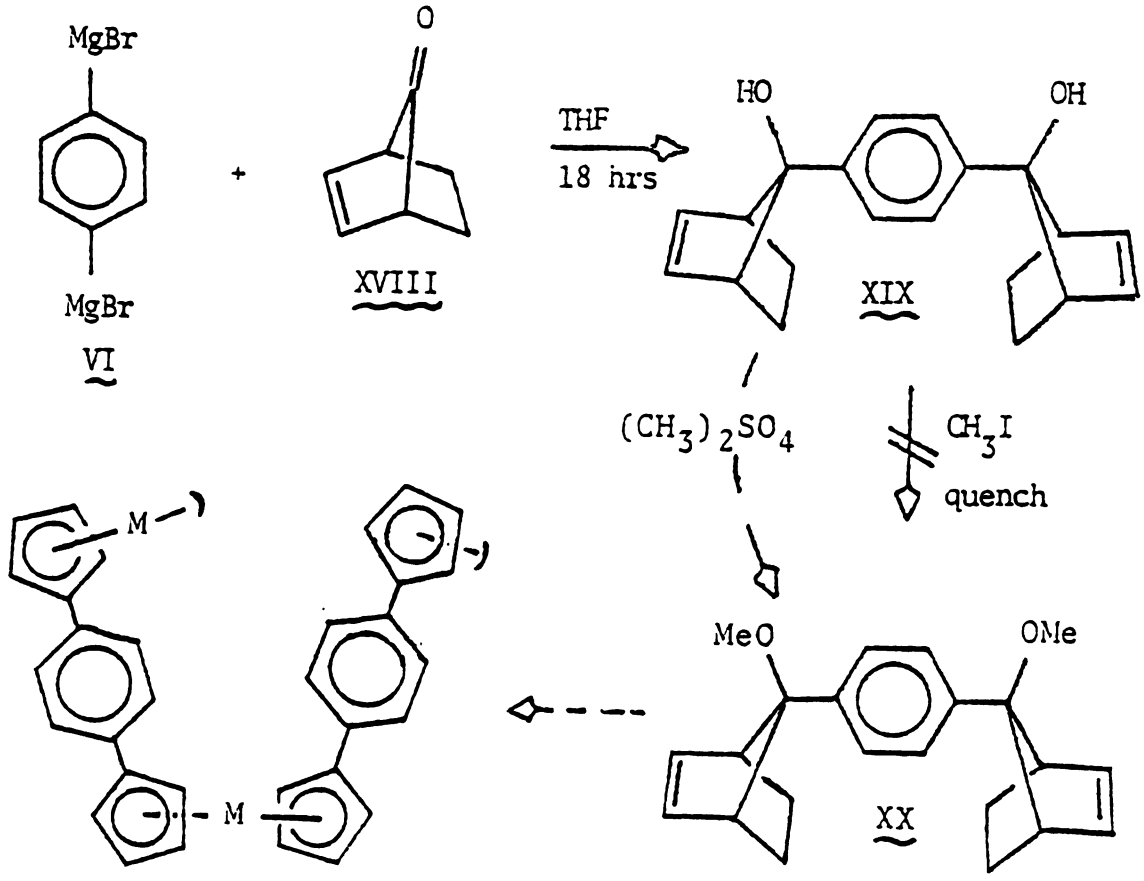
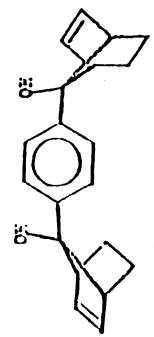


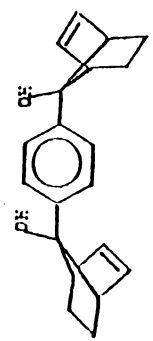

Figure 2-9. Synthesis of p-Phenylenebis(7-hydroxybicyclo(2.2.1)heptene) (XIX).

A tabulation of the nmr spectra does provoke some question as to the orientation observed in preference (Table 2-2). Since three configurations are possible, without separation and quantitation no assignments can be made. It is, however, interesting to see that in the dilithio-biphenyl case a ca. 50:50 ratio is observed with $H_1$ and $H_2$, along

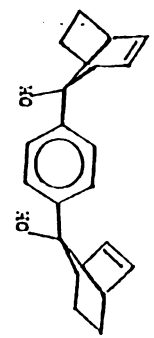
Figure 2-10. NMR of XIX.



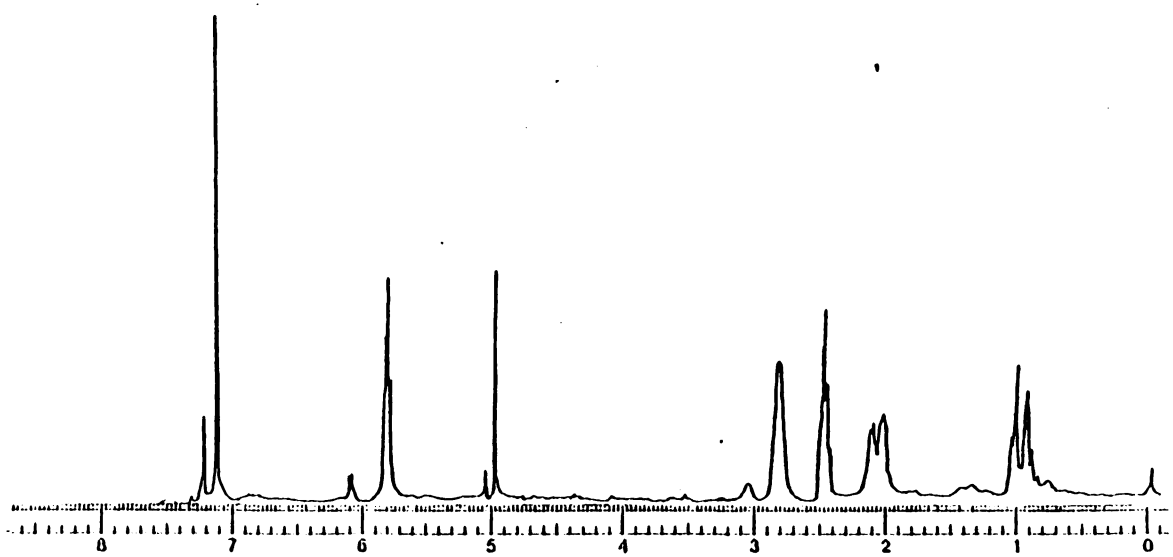
syn-syn



anti-syn



anti-anti

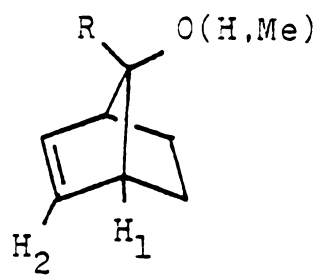


with the methoxy resonances, whereas there is a definite preference (ca. 3:1 with $H_1$, $H_2$ and $H_R$) in the product resulting from addition of the ketone XVIII to the di-grignard VI.

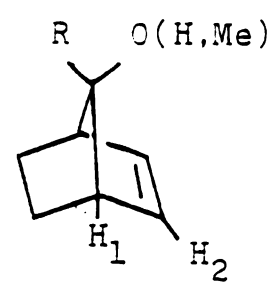
Table 2-2.

7-R-Norbornen-7-ols(1) and 7-R-Norbornen-7-syn-ols(2) (δ).[57]

| Compound R | -OMe | $H_1$ | $H_2$ | $H_R$ |
|---|---|---|---|---|
| $C_6H_5$(1) | | 2.85 | 5.82 | 7.20 |
| $C_6H_5$(2) | | 3.16 | 6.23 | 7.32 |
| $C_6H_4$(Major) (XIX) | | 2.86 | 5.85 | 7.13 |
| $C_6H_4$(Minor) | | 3.1 | 6.13 | 7.25 |
| $C_{12}H_8$ (XXI) | 2.79 | 3.12 | 6.02 | 7.33 |
| | 2.74 | 2.95 | 5.83 | |




(1)
anti-ol




(2)
syn-ol

Unlike the problems observed with quenching the grignard adduct with methyl iodide, the 4,4'dilithiobiphenyl adduct readily reacted to yield the dimethoxy compound XXI (Figure 2-11). Since the lithium phenyl reagents have been reported to react in higher yields this is the preferable method. However, attempts to make the 1,4-dilithiobenzene were of very low yield and therefore rejected in the synthesis of XX due to limited quantities of the ketone XVIII.

The generation of the anion XIII is in and of itself an interesting reaction. Unlike the normal retro-Diels Alder, which requires temperatures of 150° or more, the anion XII rapidly reverts to XIII within thirty minutes at room temperature. The ease of generating two such anions on the same molecule should present some interesting thermodynamic and kinetic questions.

In Figure 2-12, a rough analysis of the reaction energetics for anion XIII is given. Walsh and Wells[58] have established that the loss of ethylene from norbornene requires 42.5 Kcal/mol activation energy (extrapolated to 25°C) whereas the loss of ethylene from 7-phenylnorbornenide ion has an activation energy of less than 23 Kcal/mol. Several synthetic examples relying on this principle are given in Reference 59.

Future work in this area is easily defined. First a comprehensive series of $\alpha,\omega$-bis(diphenylphosphine) monomers should be completed. The preparation of catalytic systems as coordination polymers with a wide variety of physical

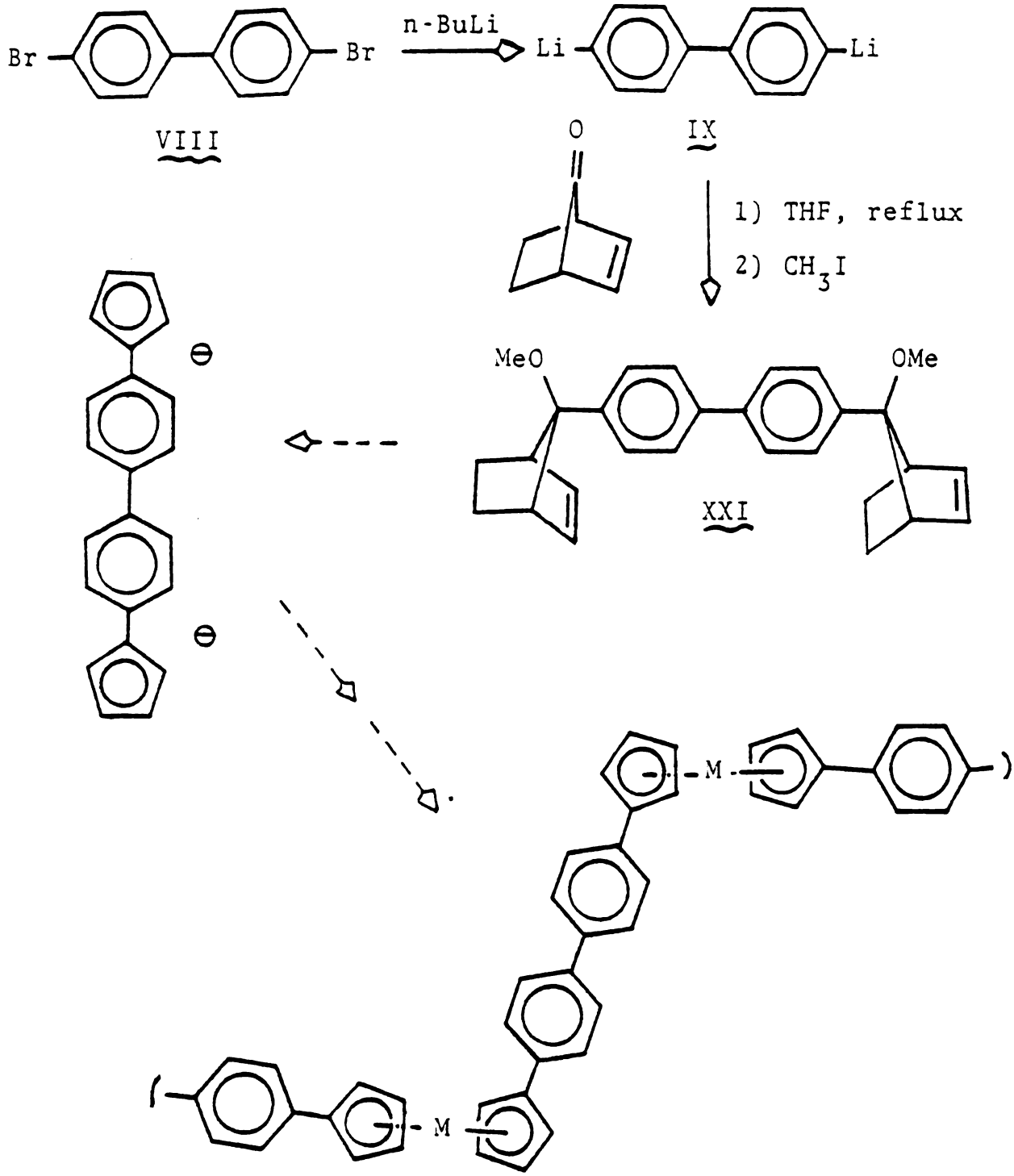
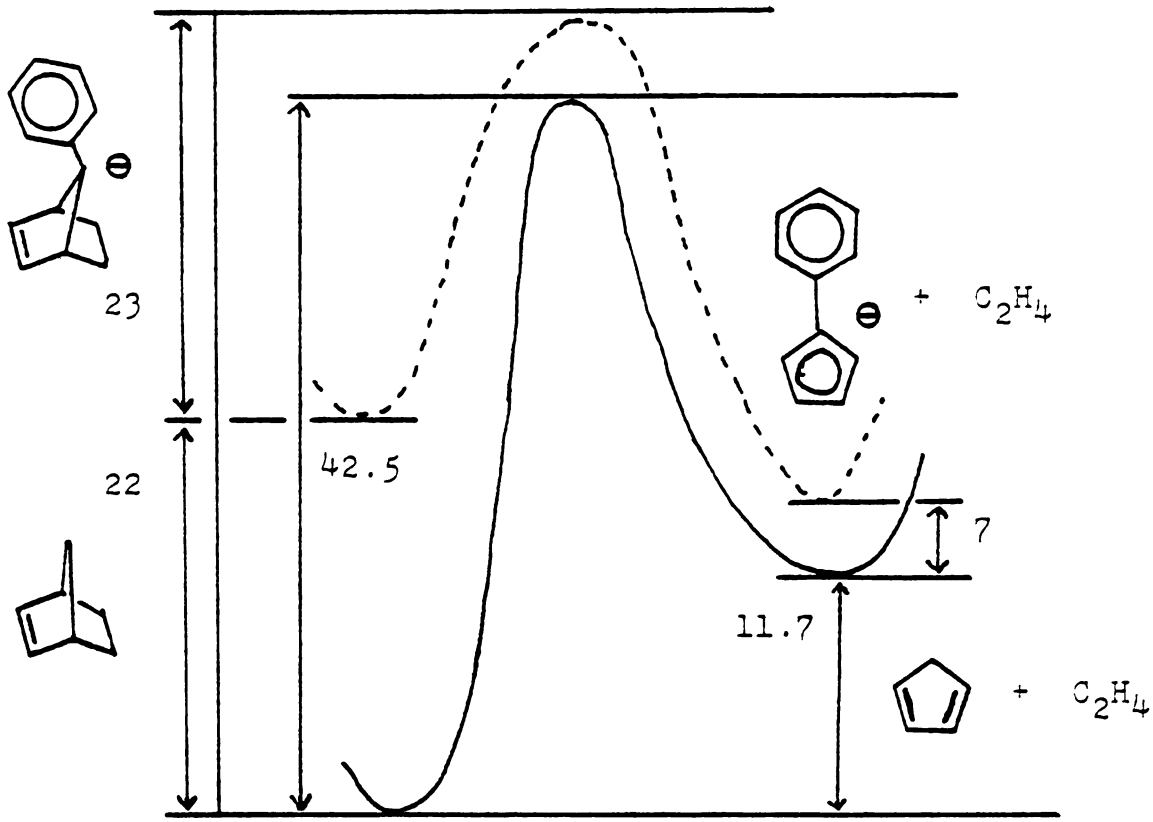



Figure 2-11.

properties and active metals would then be feasible.

Secondly, methylation of XIX and generation of α,ω-bis(cyclopentyldienyl) anions should be attempted. The expected polymerization with incorporated metal ions holds significant promise in both catalysis and electrochemistry due to the dispersed electron density. Separation of the anion-benzene moiety by various alkyl and aryl chains opens the way to another series of interesting polymer metal systems.




Energies in kcal/mole

Figure 2-12. Reaction energetics for anion XIII.[60]

# EXPERIMENTAL

General. Nuclear magnetic resonance spectra were recorded on the California Institute of Technology Varian EM-390 spectrometer.

Infrared spectra were recorded on the Beckman IR 4210 in Professor D. A. Evans' labs.

Mass spectra and analyses were obtained by the Caltech analytical lab unless otherwise noted.

Dry diethyl ether was Mallinkrodt absolute ether and was distilled under argon from the sodium benzophenone ketyl. MCB tetrahydrofuran was dried and distilled in a similar fashion.

Butyllithium was purchased from Alfa as ca. 1.5N solution in hexane.

Specific Preparations.

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (XV).

Following the procedure developed by Gassman and Marshall[60] 500 gm hexachlorocyclopentadiene (1.86 mol, M.C.B.) in 800 ml methanol was placed in a 5 liter 3-neck flask equipped with an addition funnel, overhead stirrer and reflux column. 240 gm potassium hydroxide (3.6 mol) in 1200 ml methanol was added dropwise over a period of

four hours. After addition began, the reaction flask was cooled in an ice bath until completion. The mixture was then stirred for an additional two hours at room temperature. The mixture was then poured over 4 l crushed ice. Extraction was carried out with three 300 ml portions of dichloromethane. Combined extracts were dried over magnesium sulfate overnight at 4°C. Concentration of the organic layer with a rotary evaporator resulted in a yellow oil. Distillation yielded 388 gm, 80% of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene, bp 80-85°/0.8 mm (reported 79-84°/0.6 mm[60]). NMR (90 MHz, δ, $CDCl_3$): 3.33 (s, 6H).

7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo(2.2.1)hept-2-ene (XVI).

A one liter glass lined high pressure Parr bomb apparatus containing 300 gm (1.14 mol) of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene was charged with 1400 psi ethylene (Matheson) and held at 150° for two days with agitation. Distillation of the yellowish-orange oil resulted in 319 gm, 95% XVI, bp 95°/0.8 mm (reported 70-75°/0.15 mm[60]). NMR (90 MHz, δ, $CCl_4$): 3.48 (s, 3H); 3.53 (s, 3H); 2.28 (q, 2h); 1.72 (q, 2H).

7,7-Dimethoxybicyclo(2.2.1)heptene (XVII).

65.89 gm sodium metal (2.37 mol) was added as small chunks to 1.5 l liquid ammonia in an insulated three liter flask equipped with mechanical stirring by glass blade and rod (under the reaction conditions teflon is destroyed). 52 ml absolute ethanol (1.43 mol) and 96 gm (.36 mol) XVI

were degassed with argon for several hours before being added dropwise over a four hour period. Stirring continued for another four hours after the addition was completed. This was followed by cautious quenching with aqueous saturated ammonium chloride solution. This mixture was then extracted with three 150 ml portions of dichloromethane. The combined extracts were then washed with 100 ml portions of saturated sodium chloride (2X) and distilled water (2X). The organic layer was combined and dried over anhydrous magnesium sulfate. After filtration and concentration with a rotary evaporator, XVII was distilled under reduced pressure at 25°C/ 0.03 mm in an 80% yield, 44.7 gm (reported 56-68°/17 mm[60]). NMR (90 MHz, δ, $CDCl_3$): 5.97 (t, 2H); 3.0 (s, 3H); 3.1 (s, 3H; 2.63 (m, 2H); 1.76 (m, 2H); 0.867 (m, 2H).

Bicyclo(2.2.1)heptene-7-one (2-Norbornen-7-one) (XVIII).

Adapting the procedure of Gassman and Pape,[61] 40 gm (.26 mol) XVII is combined with 80 ml 5% aqueous sulfuric acid and stirred magnetically in a 250 ml stoppered Erlenmeyer flask for 20 hours. Three extractions with 20 ml diethyl ether were followed by washing of the combined extracts with saturated sodium chloride (2X), 10% sodium carbonate (4X), and saturated sodium chloride (2X). The combined ether extracts were then dried over magnesium sulfate overnight at 4°C. Using a rotary evaporator, ca. 75% of the diethyl ether is removed. Vacuum transfer of the ketone at room temperature (0.1 mm) results in a 90% yield, 25.3 gm of XVIII. NMR (90 MHz, δ, $CDCl_3$): 6.4 (t, 2H);

2.67 (m, 2H); 1.69 (m, 2H); 1.13 (m, 2H). Special note: if all traces of acid are not removed, upon distillation an unidentified product is obtained. NMR (90 MHz, δ, $CCl_4$): 7.62 (s). IR (KBr, μm): 7.1, 7.4, 8.5, 9.3. mp 43°C.

An alternative method of preparing the ketone has been reported by Bly and Bly[62] and Story.[63] This method was also used but the above procedure was found to be more suitable for larger scale production.

1,4-Di(bromomagnesium)benzene (VI).

In a 100 ml Schlenck tube fitted with a reflux condenser and under argon flow was placed 10 gm 1,4-dibromobenzene (.042 mol), 2.5 gm oven dried magnesium turnings (.104 mol) 50 ml dry tetrahydrofuran and a crystal of iodine. The mixture was heated at reflux with magnetic stirring overnight. After cooling, the white precipitate was filtered off using inert techniques and washed with ten ml portions of dry tetrahydrofuran until all yellow coloration was removed from the crystals. The crystals were then separated from any unreacted magnesium and dried in vacuo overnight. Analysis was accomplished by quenching a known amount of the dried crystals and quantitating the amount of benzene produced using glc.

Lithium diphenyl phosphide.

In a 250 ml flask equipped with magnetic stirrer, reflux column and addition funnel was placed 1.4 gm lithium ribbon (0.2 mol) pounded flat and cut into ½ inch lengths in 85 ml

dry tetrahydrofuran. 8.02 gm chlorodiphenylphosphine (.036 mol, 9.86 ml) was dissolved in ca. 15 ml dry THF and added dropwise over a period of 15 minutes at 0°C. Resulting solution color is dark red. The solution is stirred at room temperature for at least one hour prior to use.

p-Phenylenebis(7-hydroxybicyclo(2.2.1)heptene) (XIX).

Ketone XVIII, 0.8 ml (0.0062 mol), was added via syringe to 0.74 gm (0.003 mol) di(bromomagnesium)benzene stirring under argon with 6 ml dry tetrahydrofuran in a septum capped round bottom flask. The solution was stirred with gentle warming overnight. The reaction was quenched with 5% hydrochloric acid. Extraction was accomplished with three 10 ml portions of diethyl ether. Combined extracts were dried over anhydrous sodium carbonate after the normal aqueous washing procedure. The solvent was then distilled off. Recrystallization from methanol resulted in 0.79 gm, 90% XIX. NMR (90 MHz, δ, DMSO-$d_6$): Major isomer, 7.13 (s, 4H); 5.85 (t, 4H), 5.02 (s, 2H), 2.86 (m, 4H), 2.1 (m, 4H), 1.02 (m, 4H); Minor isomer, 7.25 (s), 6.13 (t), 5.1 (s), 3.1 (m) (last two resonances not resolved or in baseline noise). Precise mass calculated for $^{12}C_{20}{}^{1}H_{22}{}^{16}O_2$ 294.162, obtained 294.164. Attempts to methylate the hydroxyl groups by quenching with methyl iodide were unsuccessful.

4,4'-Biphenylenebis(7-methoxybicyclo(2.2.1)heptene(XXI).

5 ml n-butyl lithium in hexane (1.58N) was added via syringe to 1.2 gm (.0039 mol) 4,4'-dibromobiphenyl in 5 ml dry THF under argon. The mixture was stirred at -78°C for ca. 10 minutes. The temperature of the solution was raised to 0°C over a period of thirty minutes. The solution was then returned to -78°C at which time 1 ml (.0077 mol) bicyclo(2.2.1)heptene-7-one was added via syringe. Solution temperature was raised to ambient where it was allowed to stir for twelve hours.

Two ml (.032 mol) methyl iodide was added via syringe and the solution was taken to reflux for another twelve hours. The clear orange solution was quenched with aqueous ammonium chloride and extracted with ether. The combined extracts were then washed in the usual manner and dried over anhydrous sodium carbonate. Solvent was removed by distillation. Recrystallization from methanol and drying in vacuo resulted in .79 gm, 69% yield of XXI. NMR (90 MHz, δ, $CCl_4$): 7.33 (m, 8H); 6.02 (t, 2H); 5.83 (t, 2H); 3.12 (br s, 2H); 2.95 (br s, 2H), 2.79 (s, 3H), 2.74 (s, 3H); 2.07 (m, 2H); 1.5 (m, 2H), 1.0 (m, 4H). Precise mass, calculated for $^{12}C_{28}{}^{1}H_{30}{}^{16}O_2$ 398.224, obtained 398.226. No attempt was made to resolve isomers.

1,12-dichlorododecane (II).

In a 250 ml three neck flask equipped with an addition funnel and reflux column was placed 44 gm (.22 mol) 1,12-dihydroxydodecane in 40 ml dry THF. 30 ml dry pyridine

(freshly distilled from barium oxide) was added over 10 minutes at 0°C. 40 ml of thionyl chloride (freshly distilled from quinoline) in 50 ml THF was added dropwise over one hour at ambient temperature. The solution was then allowed to reflux for twelve hours.

Upon slow cooling to room temperature, water was added until all solid material was dissolved. The solution was washed three times with 20 ml portions of diethyl ether. Combined extracts were dried over anhydrous magnesium sulfate. Removal of solvent with a rotary evaporator after filtration yielded crystals. Recrystallization from a 50:50 $CHCl_3$:MeOH mixture yielded 38.24 gm, 70% II. NMR (90 MHz, δ, $CCl_4$): 3.53 (t, 4H), 1.83 (m, 4H), 1.26 (m, 16H).

1,12-bis(diphenylphosphine)dodecane (III).

1 gm of 1,12-dichlorododecane (.0042 mol) in 15 ml dry THF was added dropwise over one hour at room temperature to a two fold molar excess of the lithium diphenyl phosphide solution previously described. The products from this exothermic reaction were allowed to stir at room temperature for six hours and then were heated to just under reflux temperature for twelve hours. 40 ml 5% aqueous ammonium chloride was added slowly to quench the reaction. Three 20 ml portions of diethyl ether were used to extract. Extracts were combined and dried over sodium sulfate. After filtration and rotary evaporation yellow crystals were obtained. The crystals were washed repeatedly with methanol until white crystals were obtained. After drying in vacuo over-

night, 0.87 gm, 54% III was recovered. NMR (90 MHz, δ, $CCl_4$): 7.25 (m, 20H); 2.0 (m, 4h); 1.4 (m, 4H); 1.2 (s, 16H). MS: $M^+$, m/e 538.

p-Phenylenebis(diphenylphosphine) (VII).

Following the procedure reported by Baldwin and Cheng[64] 0.62 gm (0.98 mmol) 1,4-di(bromomagnesium)benzene in 5 ml THF was cooled to -10°C. Chlorodiphenylphosphine, 0.44 gm (1.96 mmol), was added via syringe. The mixture was stirred at room temperature under argon for one hour. The mixture was then quenched with distilled water and extracted with three 10 ml portions of diethyl ether. After the usual washing procedure of the combined extracts and drying over anhydrous magnesium sulfate, the solvent was removed on a rotary evaporator. Recrystallization from methanol yielded 0.153 gm, 35%.

4,4'-Biphenylenebis(diphenylphosphine) (X).

Following the procedure published by Baldwin and Cheng[64] with slight modifications, 1.032 gm (0.003 mol) 4,4'-dibrombiphenyl in 6 ml dry THF was cooled to -78° before 5 ml of 1.58 N n-butyllithium was added via syringe. The solution was warmed to 0°C over a period of thirty minutes then recooled to -78°C. 1.66 gm (0.075 mol) neat chlorodiphenylphosphine was added via syringe and the reaction mixture was then warmed to room temperature and stirred vigourously for one hour in the same septum capped round bottom. The insoluble product was then filtered off and washed several

times with water. Recrystallization from 50:50 MeOH:THF yielded 0.8 gm, 50% X.

Polymer-like material from $RhCl_3$ and 1,12-(diphenylphosphine)-dodecane.

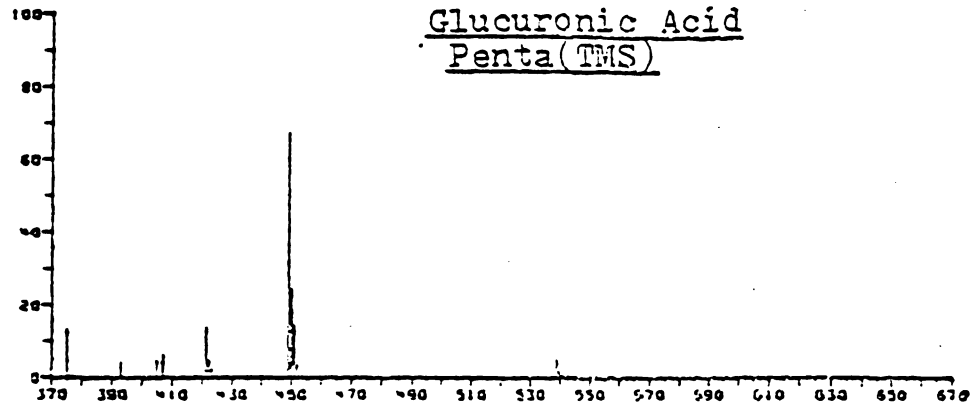
Two gm 1,12-bis(diphenylphosphine)dodecane in 30 ml absolute ethanol was placed in a 100 ml round bottom flask with a reflux condenser under argon flow. Rhodium trichloride, 0.258 gm (0.0012 mol) in 10 ml absolute ethanol was added dropwise over ten minutes to the refluxing phosphine solution. A yellow intractable material began to adhere to the sides of the flask. After several hours at reflux the ethanolic solution was decanted off. Upon contact with air the yellow material began to turn orangish-red. Washing with benzene caused the material to become transparent. It was not soluble in any solvents tried. Analysis for rhodium and phosphorus obtained from Schwarzkopf Microanalytical Lab was 6.20% and 6.11% respectively.

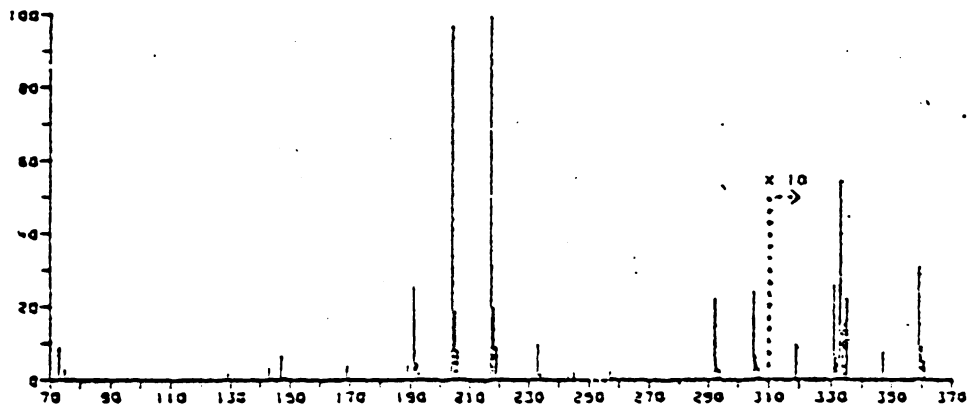
Appendix 1. Collected Mass Spectra and Associated Reference Spectra.

Collected Mass Spectra were run by personnel in Dr. C. Sweeley's laboratories.

64

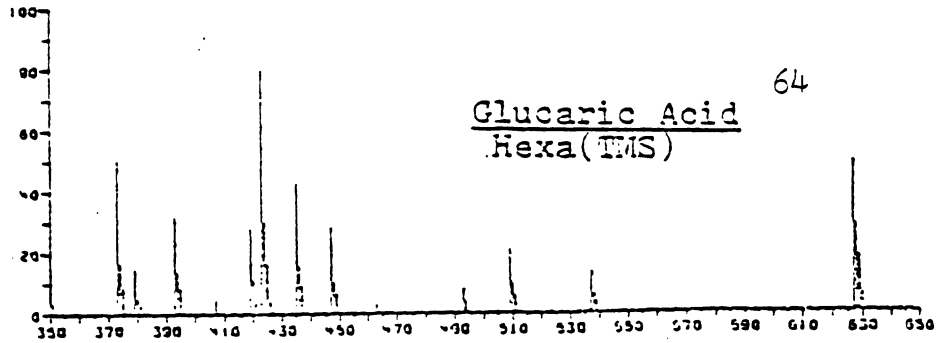
## Glucuronic Acid
## Penta(TMS)

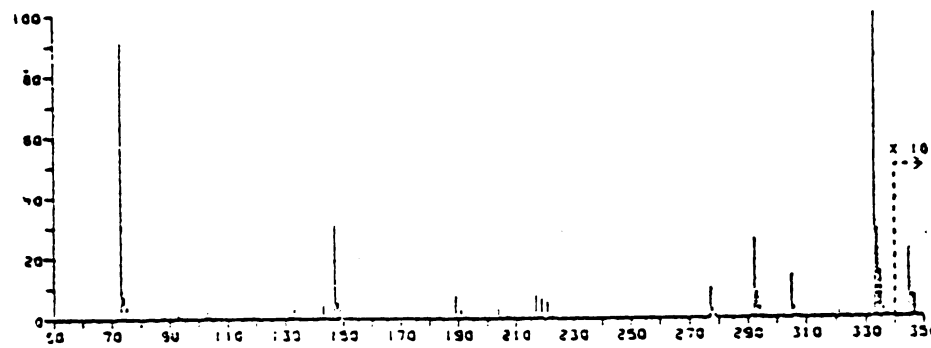




64

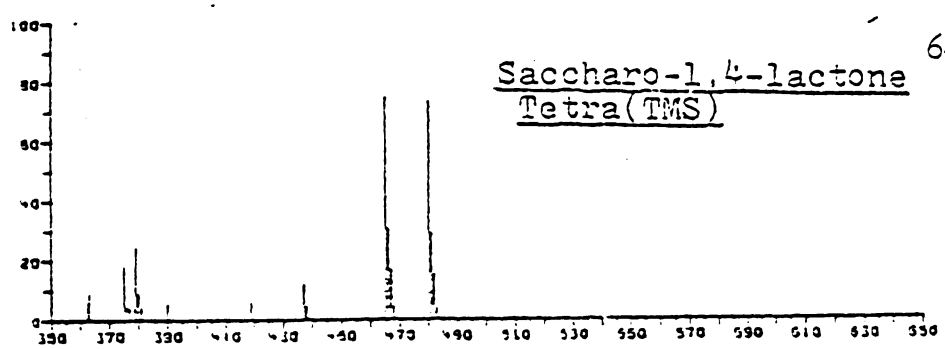
Glucaric Acid
Hexa(TMS)

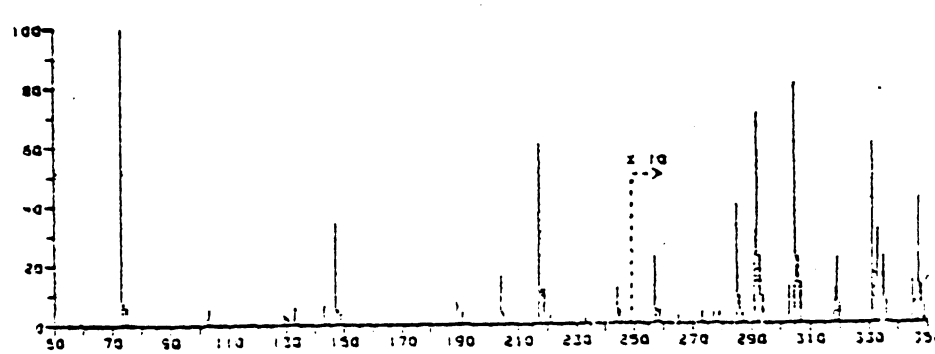





64

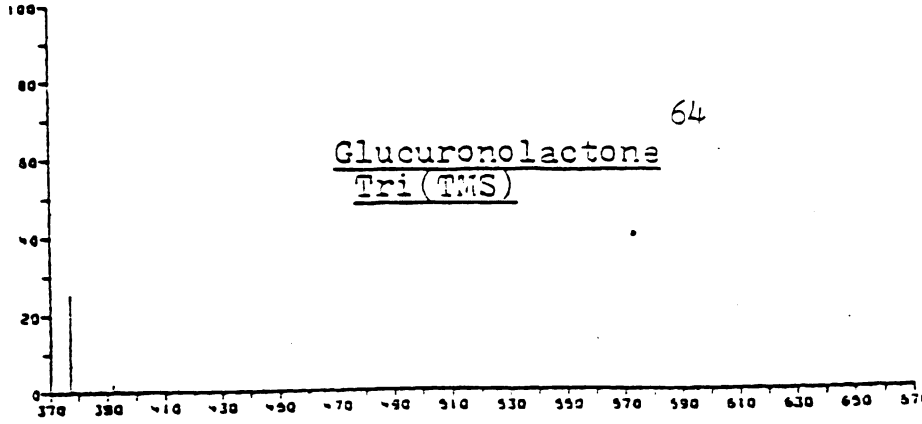
Saccharo-1,4-lactone
Tetra(TMS)

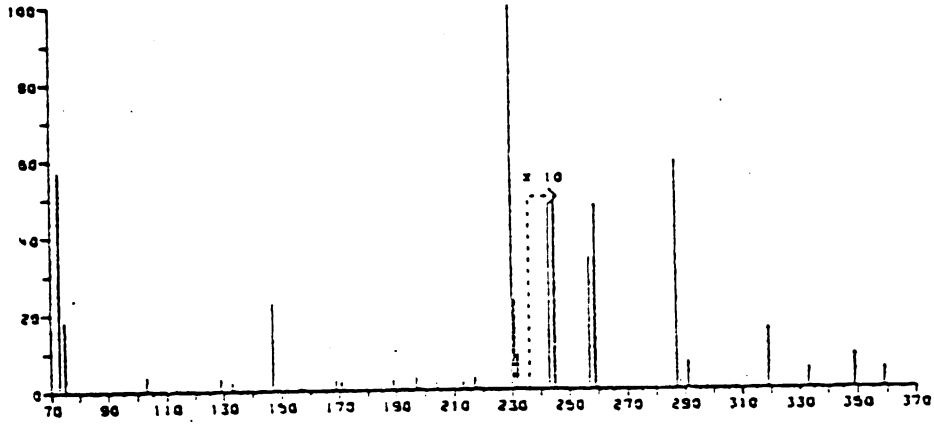




64

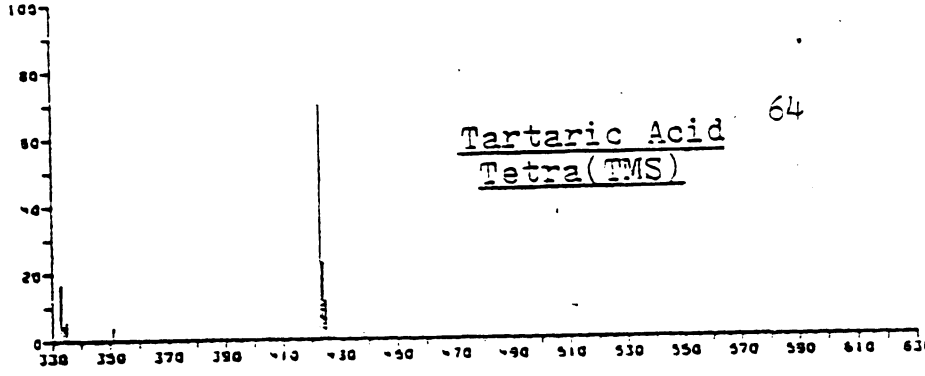
Glucuronolactone
Tri(TMS)

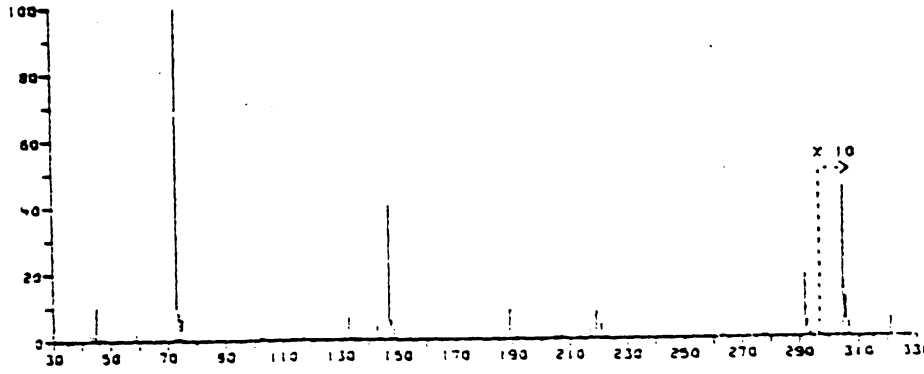





64

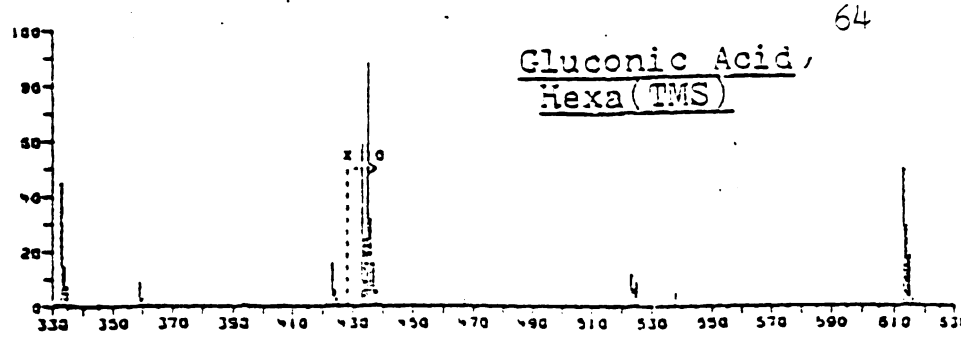
Tartaric Acid
Tetra(TMS)

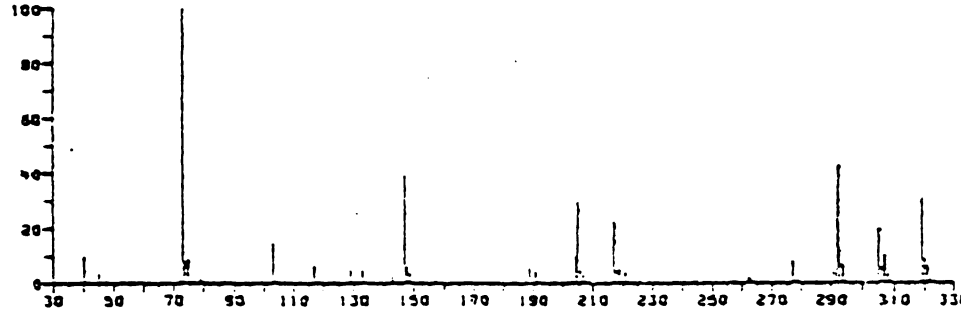




64

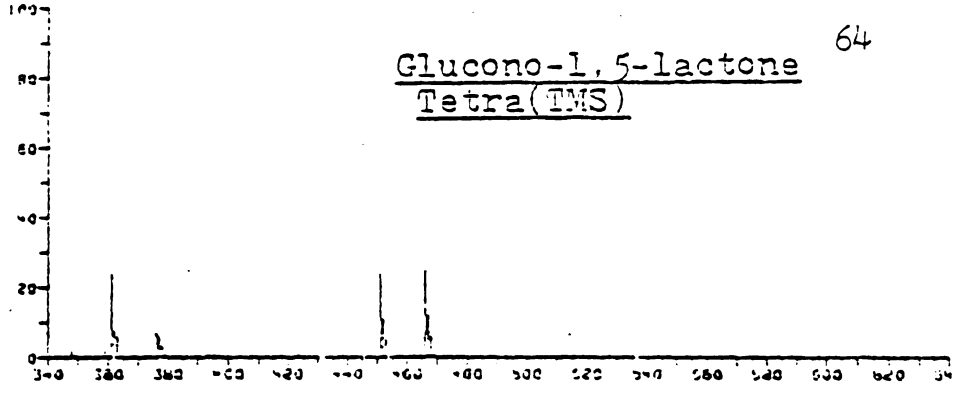
Gluconic Acid,
Hexa(TMS)

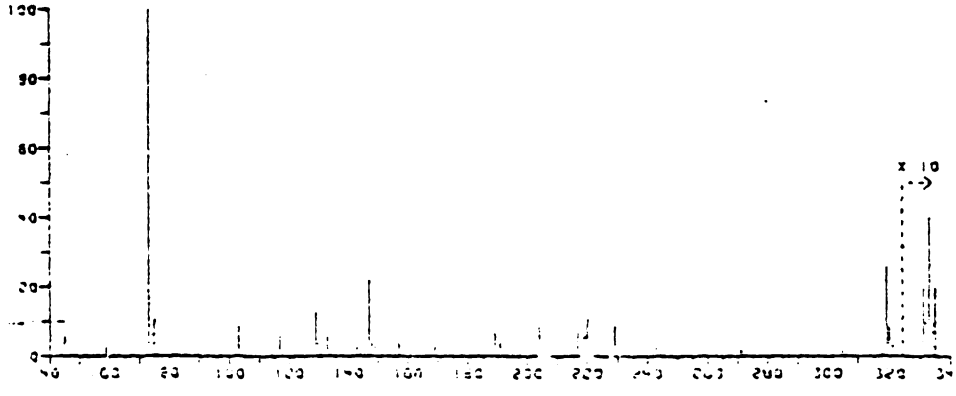




64

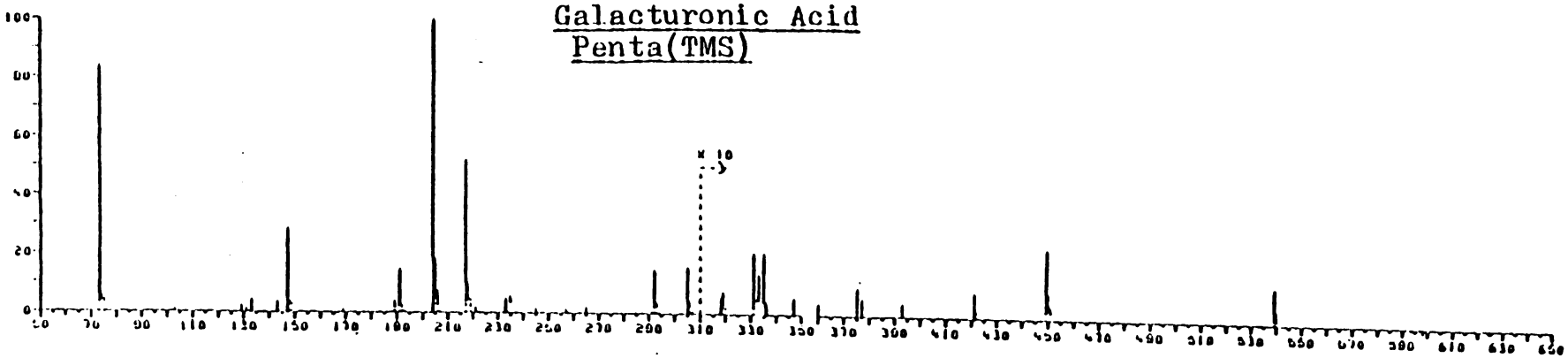
Glucono-1,5-lactone
Tetra(TMS)





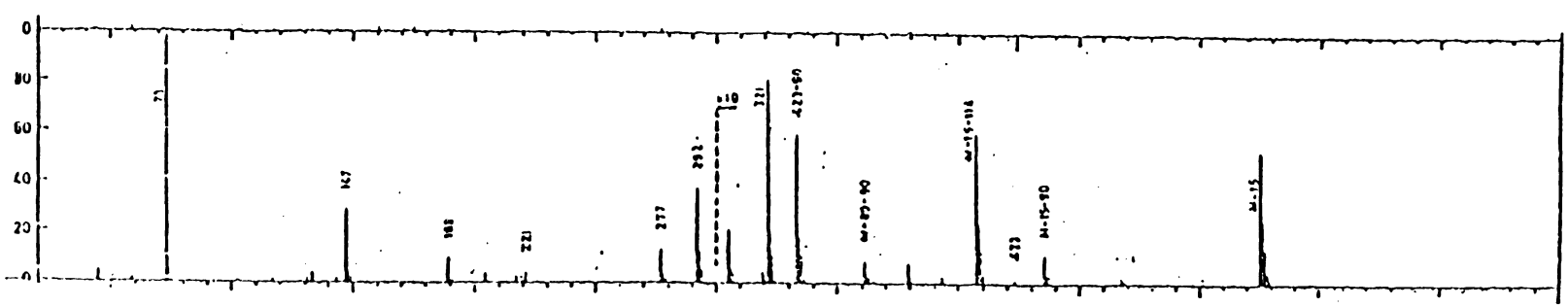
64

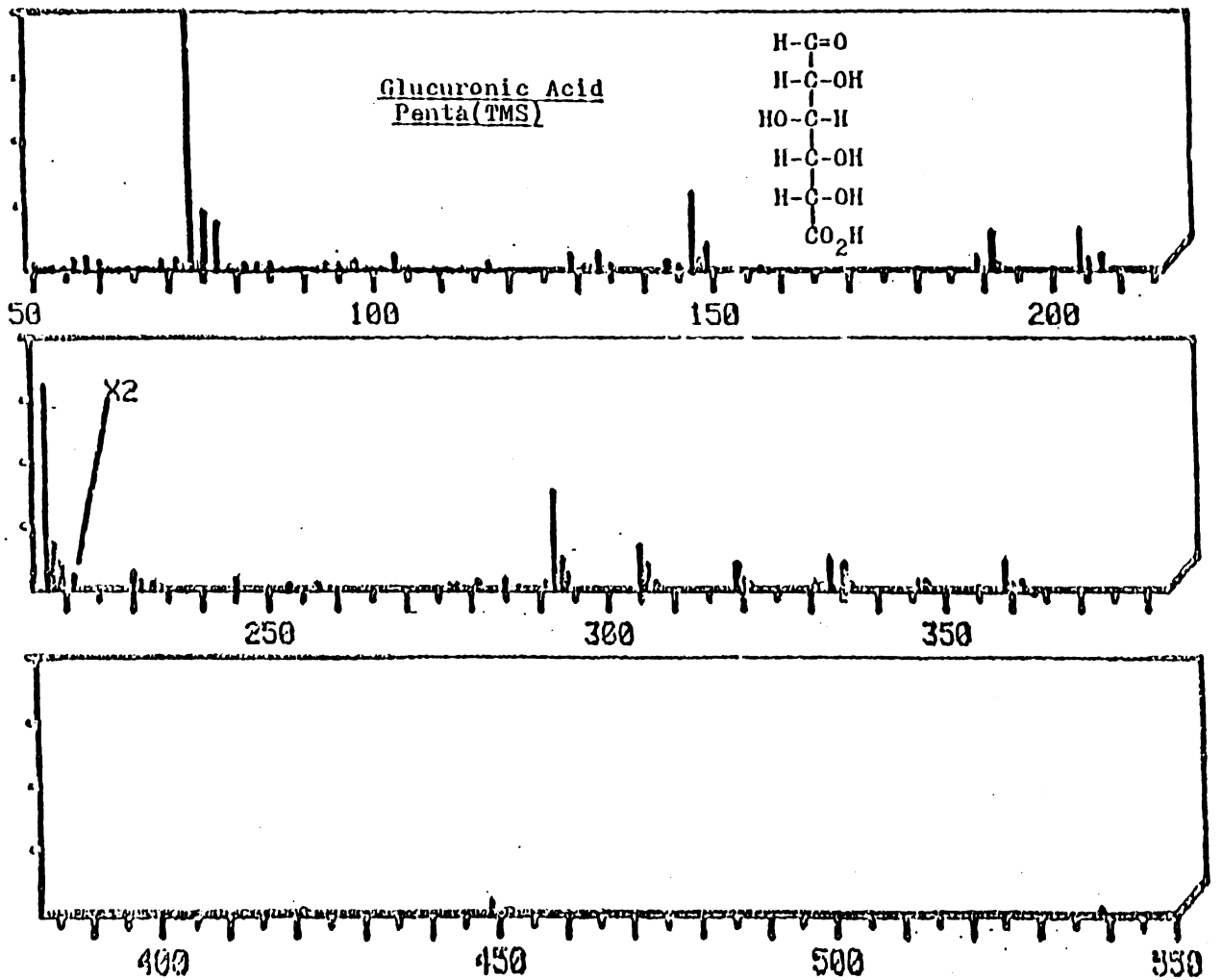
## Galacturonic Acid
## Penta(TMS)

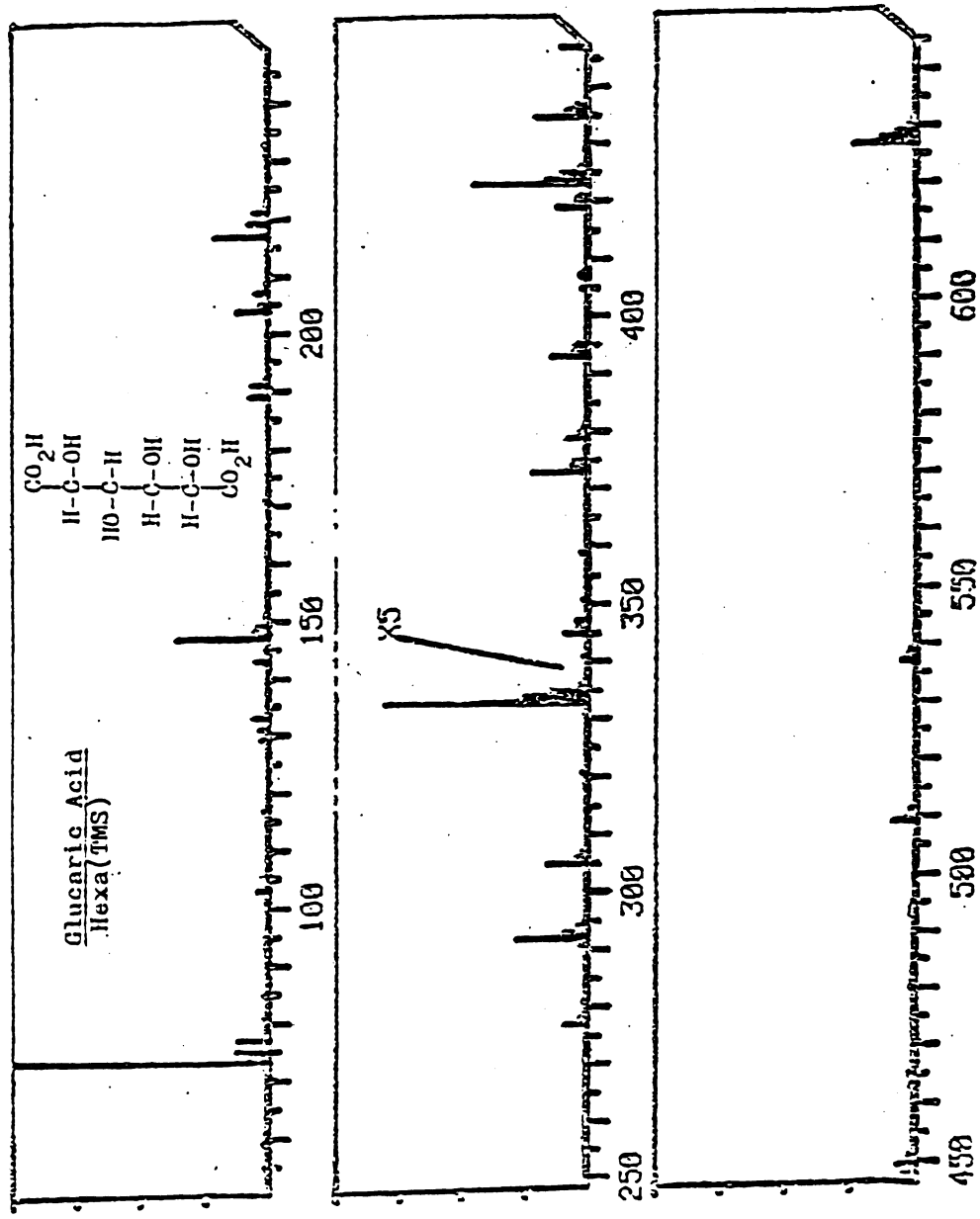


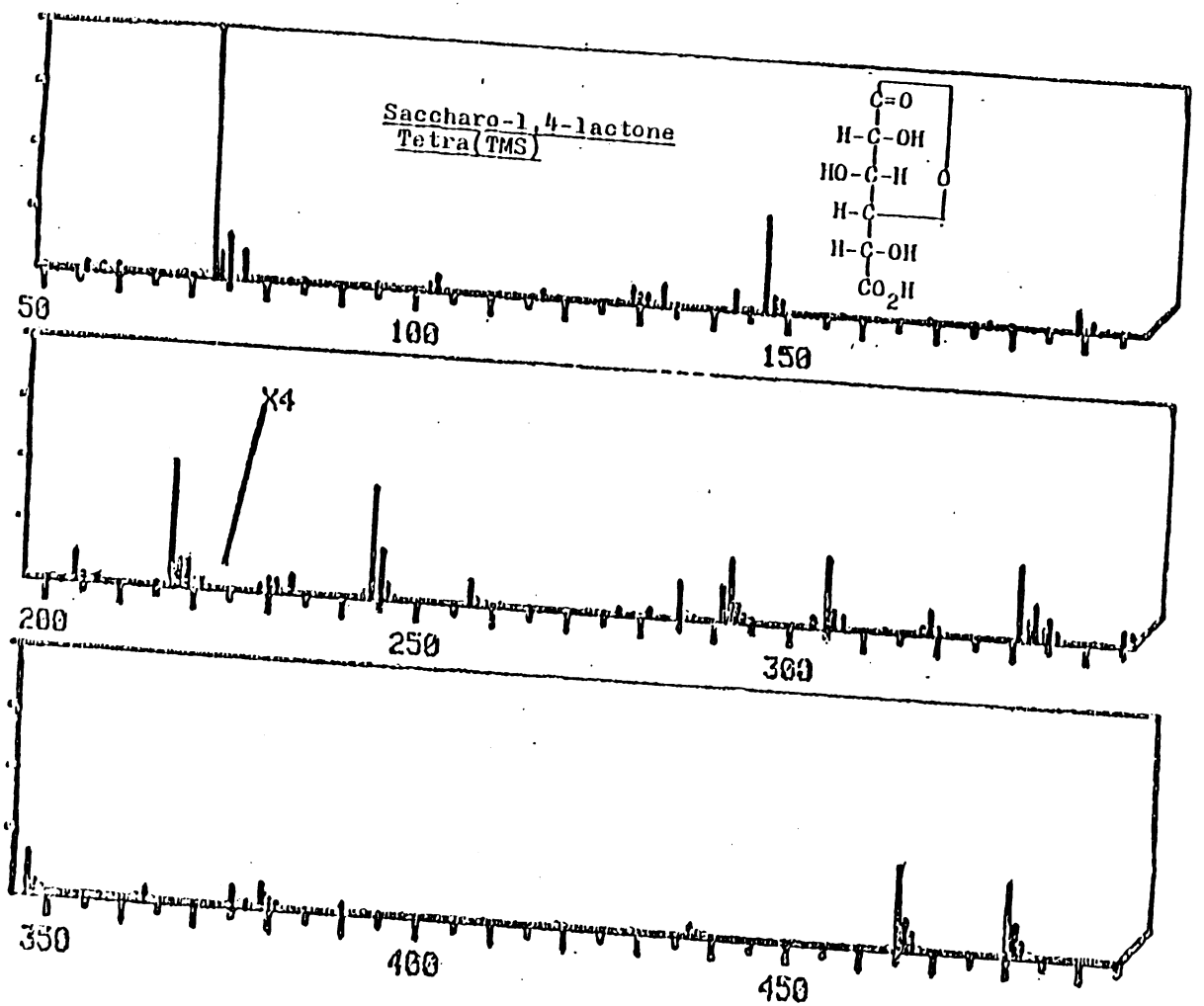
65

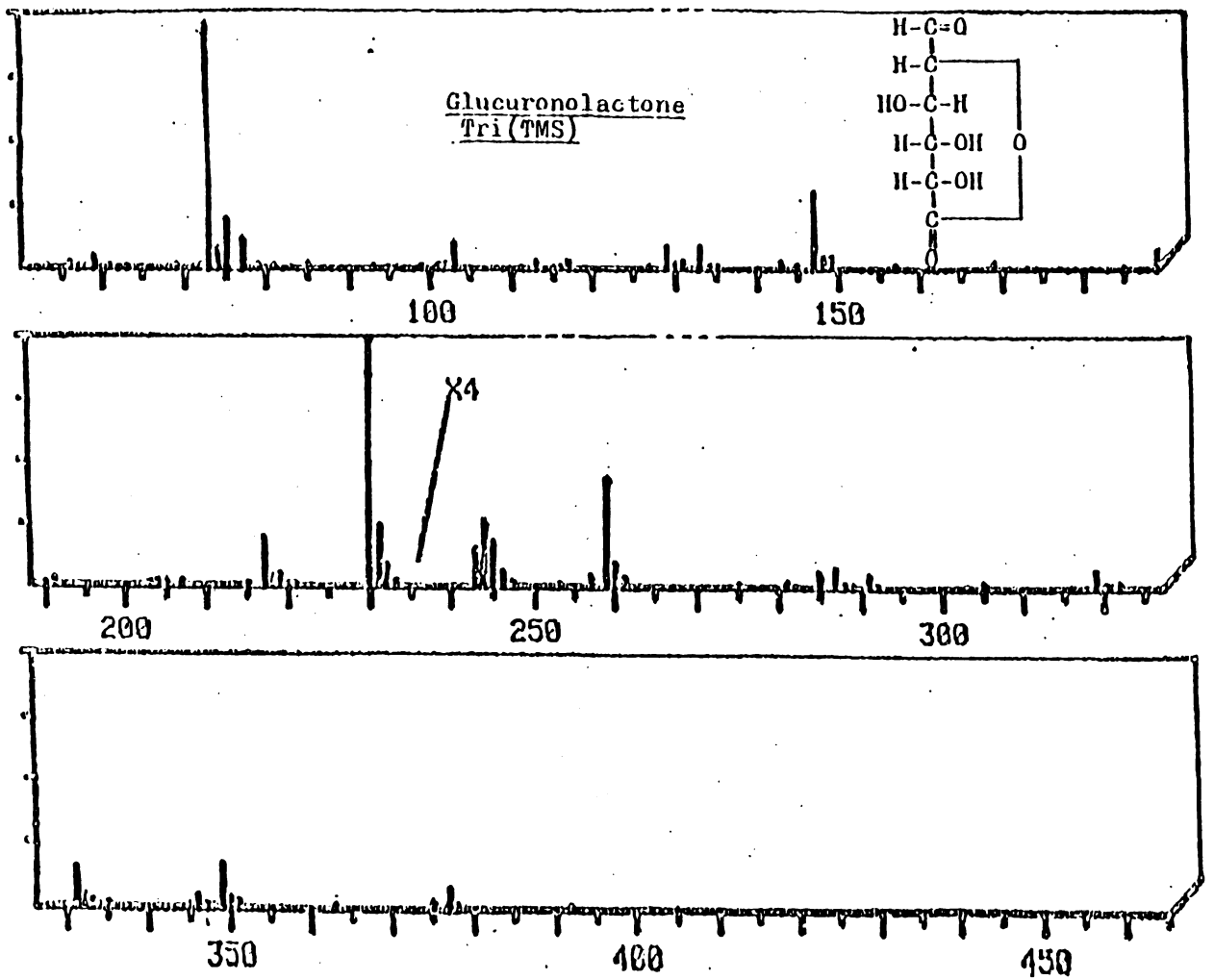
## Arabinaric Acid
## Penta(TMS)

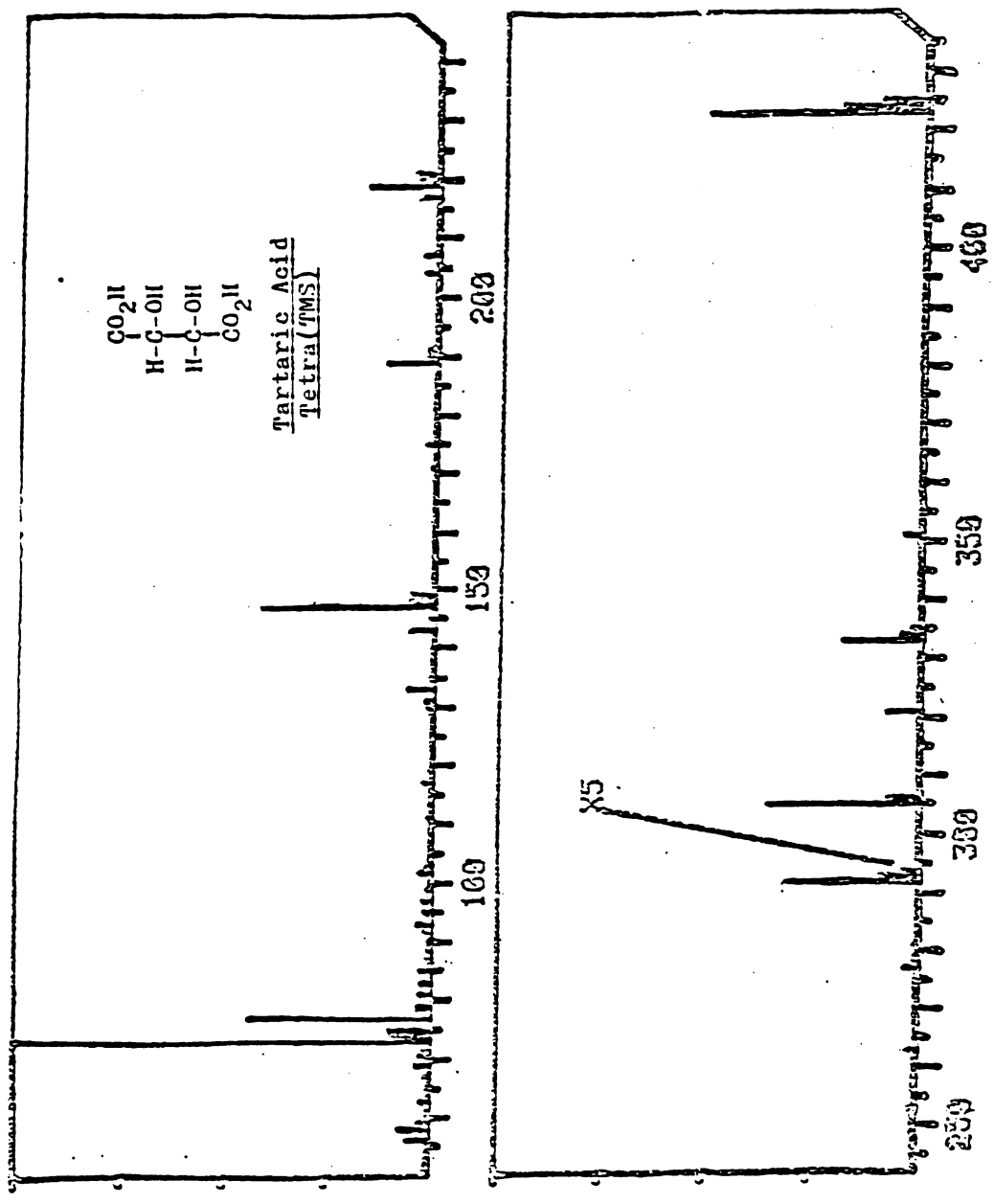


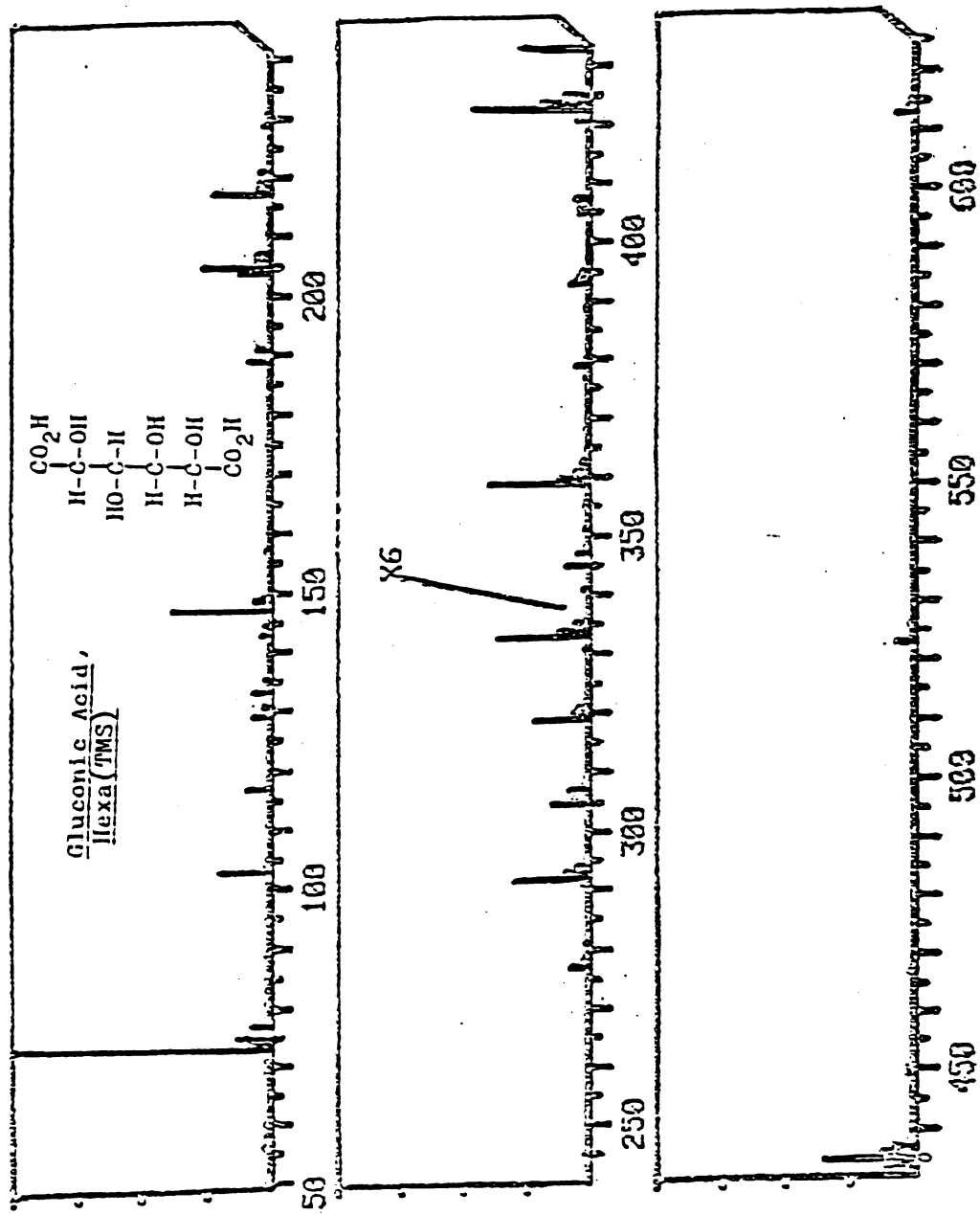

Glucuronic Acid
Penta(TMS)
H-C=O
H-C-OH
HO-C-H
H-C-OH
H-C-OH
CO2H
50
100
150
200
X2
250
300
350
400
450
500
550

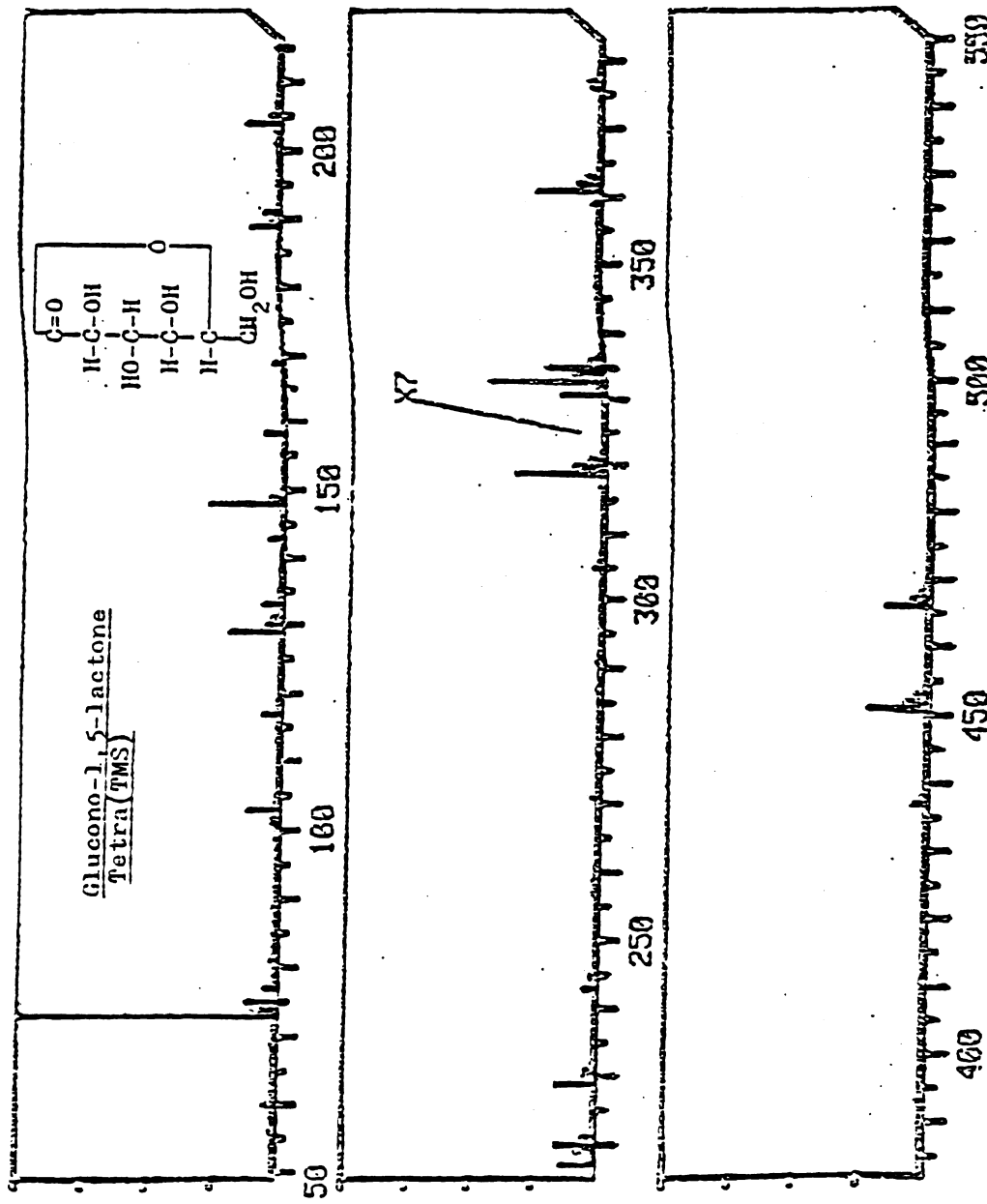

Glucaric Acid
Hexa(TMS)
CO2H
H-C-OH
HO-C-H
H-C-OH
H-C-OH
CO2H
X5
100
150
200
250
300
350
400
450
500
550
600

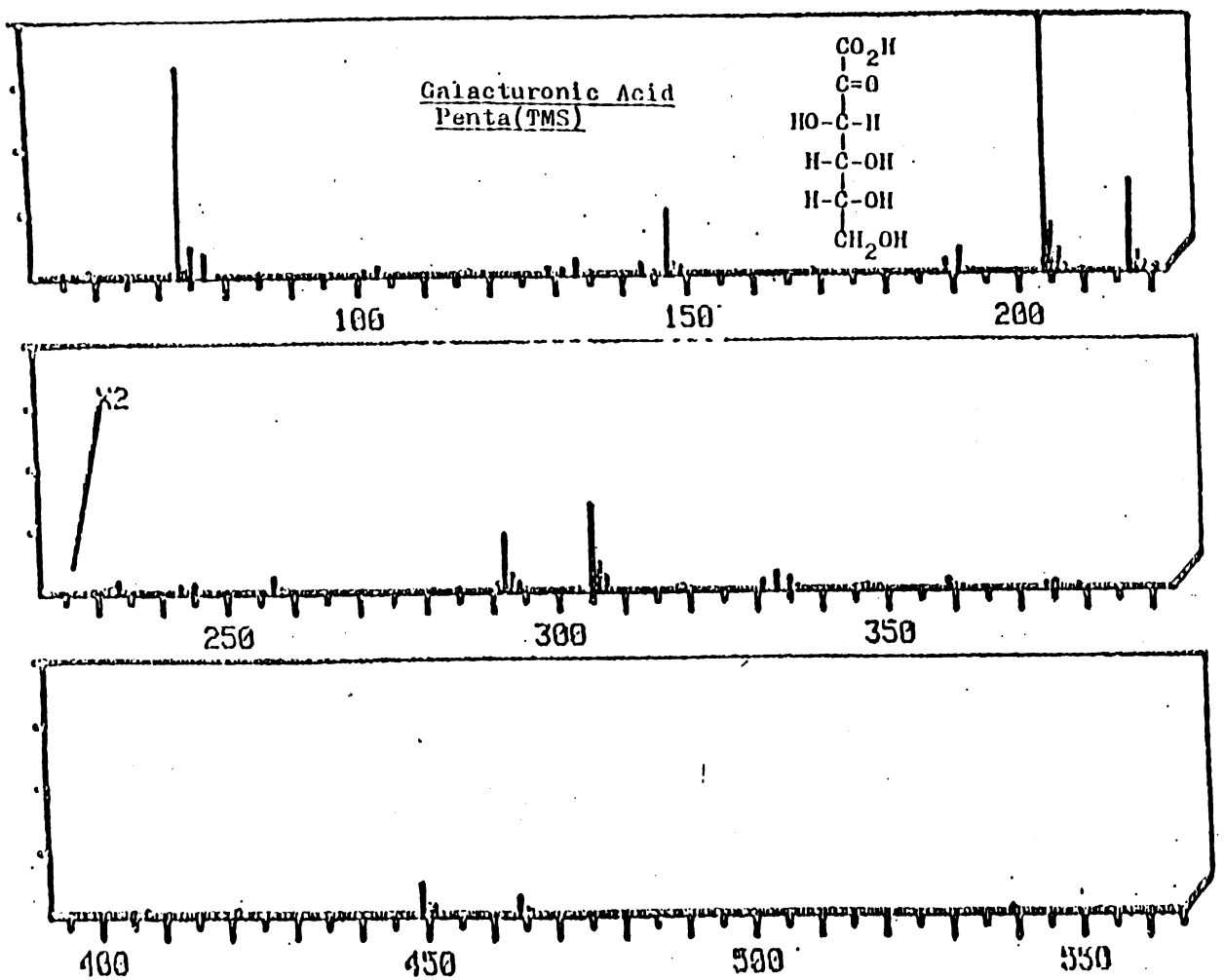

Saccharo-1,4-lactone
Tetra(TMS)
C=O
H-C-OH
HO-C-H
H-C
H-C-OH
CO2H
O
50
100
150
X4
200
250
300
350
400
450

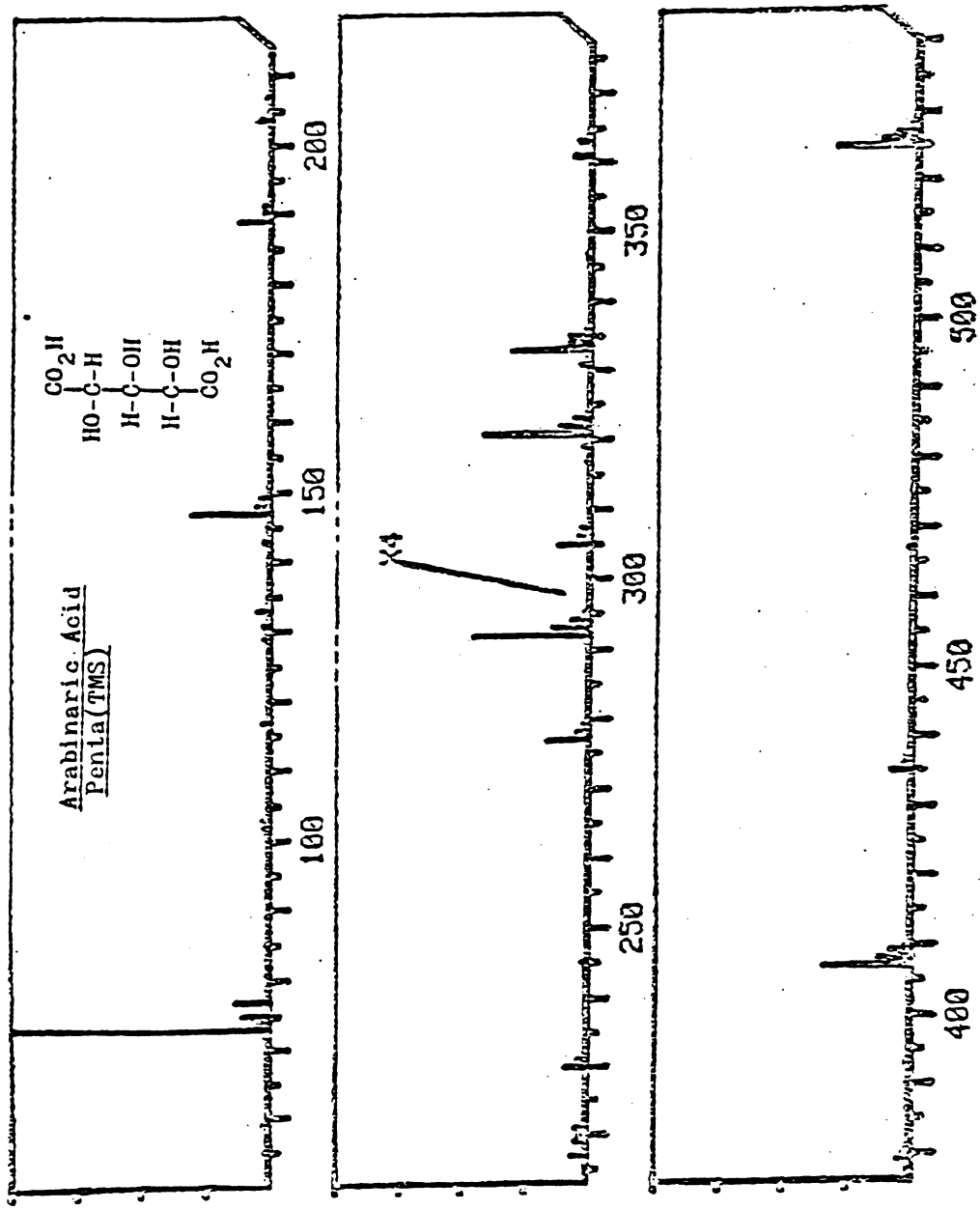

Glucuronolactone
Tri(TMS)
H-C=O
H-C
HO-C-H
H-C-OH
H-C-OH
C
O
O
100
150
X4
200
250
300
350
400
450


Tartaric Acid
Tetra(TMS)
CO2H
H-C-OH
HO-C-OH
CO2H
100
150
200
250
300
350
400
X5


Gluconic Acid,
Hexa(TMS)
CO2H
H-C-OH
HO-C-H
H-C-OH
H-C-OH
CO2H
X6
50
100
150
200
250
300
350
400
450
500
550
600


Gluconо-1,5-lactone
Tetra(TMS)
C=O
H-C-OH
HO-C-H
H-C-OH
H-C
CH2OH
O
X7
50
100
150
200
250
300
350
400
450
500


Galacturonic Acid
Penta(TMS)
CO2H
C=O
HO-C-H
H-C-OH
H-C-OH
CH2OH
100
150
200
X2
250
300
350
400
450
500
550


Arabinaric Acid
Penta(TMS)
CO2H
HO-C-H
H-C-OH
H-C-OH
CO2H
100
150
200
250
300
350
400
450
500

Appendix 2. Tabulation of Relative Retention Times of Glucose Oxidation Products (based on β-D-glucose).

Key: M-major, m-minor, md-intermediate
*-glucose.

# Appendix 2.

## Relative Retention Times

| $MoO_5(py)H_2O$ | |
|---|---|
| .695 | M |
| .757 | m |
| .828* | M |
| .863 | md |
| .866 | m |
| .923 | m |
| 1.00* | M |

| $MoO_5(DMF)_2$ | |
|---|---|
| .45 | m |
| .707 | M |
| .771 | m |
| .825* | M |
| .861 | md |
| .878 | m |
| .936 | m |
| 1.00* | M |

| $K_3MoCl_6$ | |
|---|---|
| .701 | M |
| .766 | m |
| .838* | M |
| .86 | md |
| 1.00* | M |

| $MoO_5(gly)_2$ | |
|---|---|
| .439 | m |
| .707 | M |
| .765 | m |
| .842* | M |
| .861 | md |
| .937 | m |
| 1.00* | M |

| $MoO_5(py)_2$ | |
|---|---|
| .69 | M |
| .728 | m |
| .759 | m |
| .835* | M |
| .851 | md |
| .87 | m |
| 1.00* | M |
| 1.03 | m |

| $MoO_2(acac)_2$ | |
|---|---|
| .451 | m |
| .687 | M |
| .755 | m |
| .830* | M |
| .849 | md |
| .928 | m |
| 1.00* | M |
| 1.03 | m |

| $Mo(CO)_6$ | |
|---|---|
| .805 | m |
| .871* | M |
| 1.00* | M |
| 1.03 | m |

| $Mo(CO)_4bipy$ | |
|---|---|
| .807 | m |
| .837* | M |
| 1.00* | M |

$O{=}Mo(OH)TPP$

.769 m
.837* M
1.00* M

$MoO_3$

.692 md
.760 m
.836* M
.851 m
1.00* M
1.03 m

$MoO_5(gly)H_2O$

.817 M
.856 md
.910 M
1.00* M

$MoCl_6$

.718 md
.763 m
.845* M
.865 md
1.00* M

$MoO_5DMF(H_2O)$

.702 M
.768 m
.840* M
.862 M
1.00 M

$\}CH_2(acac)_2MoO_2$

.692 md
.760 m
.836* M
.851 m
1.00* M
1.03 m

$W(CO)_4bipy$

.805 md
.871* M
1.00* M

$WO_5$(picolinic acid)

.769 md
.845* M
1.00* M

$WO_5DMF$

.769 md
.845* M
1.00* M

$W(CO)_6$

.774 md
.840* M
1.00* M

$Cu(OAc)dipy(OH)H_2O$

.668 md
.738 m
.821* M
1.00* M
1.01 m

$VOSO_4 \cdot xH_2O$

.771 md
.84* M
1.00* M

NaOH

.664 M
.713 M
.770 md
.84* M
1.00* m

$Rh_2(OAc)_4$

.801 m
.868* M
1.00* M

$\}CH_2C_5H_4RhCl_2$

.386 m
.529 m
.715 m
.768 M
.812 m
.826 m
.871* M
.886 m
1.00* M
1.03 md

Rh polyacrylate

.803 md
.868* M
1.00* M
1.03 M

$C_5Me_5RhCl_2$ 2

.384 m
.746 m
.801 m
.867* M
.936 md
1.00* M
1.03 M

$\}CH_2C_5Me_4RhCl_2$

.661 m
.708 M
.770 md
.839* M
.857 m
.974 m
1.00* M

$C_5Me_5Rh(OAc)_2$

| | |
|---|---|
| .734 | m |
| .766 | m |
| .839* | M |
| 1.00* | M |
| 1.03 | M |

$RhCl_3$

| | |
|---|---|
| .655 | md |
| .711 | M |
| .818* | M |
| .855 | m |
| 1.00* | M |

$C_5Me_5IrCl_2$

| | |
|---|---|
| .759 | md |
| .838* | M |
| 1.00* | M |
| 1.03 | M |

$]-CH_2IrCl_2$

| | |
|---|---|
| .645 | md |
| .698 | M |
| .753 | m |
| .822* | M |
| 1.00* | M |
| 1.01 | md |

$IrBr_3 \cdot 4H_2O$

| | |
|---|---|
| .298 | m |
| .388 | m |
| .430 | m |
| .649 | m |
| .758 | m |
| .833* | M |
| 1.00* | M |
| 1.03 | m |

$C_5H_5IrBr_2$ x

| | |
|---|---|
| .288 | m |
| .388 | m |
| .430 | m |
| .649 | md |
| .701 | md |
| .758 | m |
| .833* | M |
| 1.00* | M |
| 1.03 | m |

Pt on PMMA

| | |
|---|---|
| .407 | m |
| .43 | m |
| .559 | md |
| .596 | m |
| .648 | m |
| .667 | md |
| .693 | m |
| .711 | m |
| .73 | m |
| .815 | md |
| .837* | M |
| .907 | m |
| .922 | md |
| .959 | md |
| .978 | m |
| 1.00* | M |
| 1.03 | md |
| 1.04 | md |
| 1.08 | m |

Pt in poly(HEMA)

| | |
|---|---|
| .654 | m |
| .774 | M |
| .801 | m |
| .822* | M |
| 1.00* | M |
| 1.02 | md |

Pt on polystyrene

| | |
|---|---|
| .454 | m |
| .488 | m |
| .760 | m |
| .813 | m |
| .832* | M |
| 1.00* | M |
| 1.03 | md |

Pt black

| | |
|---|---|
| .429 | m |
| .455 | m |
| .489 | m |
| .548 | m |
| .597 | m |
| .652 | m |
| .712 | m |
| .731 | m |
| .764 | m |
| .783 | m |
| .813 | m |
| .847* | M |
| .914 | m |
| .962 | m |
| .978 | md |
| 1.00* | M |
| 1.03 | M |
| 1.05 | md |
| 1.08 | md |

# Appendix 3.

## Definitions.

PMMA- polymethylmethacrylate
]- - polystyrene backbone
OAc - acetate
DMF - dimethylformamide
gly - glycine
acac- acetylacetonate
py - pyridinium
bipy- bipyridyl
TPP - tetraphenylphorphyrin

# REFERENCES


1. Ebers Papyrus from Notkins, A. L., Scientific American, 241, 62 (1979).

2. Banting, F. G. and Best, C. H. (1921) from Notkins, A. L., ibid.

3. Latest available statistics from the American Diabetes Association.

4. Trivelli, L. A., et al., N. Engl. J. Med., 284, 353 (1971); Charache, S., Clin. Haematol., 3, 357 (1974); Reaven, G., et al., California Medicine, 100, 1 (1964); Reaven, G., et al., Metab. Clin. Exp., 27,235 (1978); Bonar, J. R., Diabetes: A Clinical Guide, Med. Exam. Pub. Co., Inc. (1977).

5. Notkins, A. L., ibid.

6. Nerup, J. and McDevitt, H. O. from Notkins, A. L., ibid.

7. Bunn, H. F., Gabbay, K. H., and Gallup, P. M., Science, 200, 21 (1973).

8. Arturson, G., et al., Scan. J. Clin. Lab. Invest., 34, 19 (1974).

9. Spiro, R. G., Diabetologia, 12, 7 (1976).

10. Keiding, N. R., Root, H. E., Marble, A., J. Am. Med. Soc., 150, 964 (1952); Rossini, A. N., Arch. Surg., 3, 229 (1976); Onloff, M. J., Lee, S., Charters, A. C., Grambort, D. E., Ann. Surg., 182, 198 (1975); Weil, R., Nozawa, M., Koos, M., Weber, C., Surg. Forum, 25, 386 (1974); Mauer, S. M., Sutherland, D. E. R., Diabetes, 23, 748 (1974); Pirart, J., Diabetes Care, 1, 168 (1978).

11. Spiro, R. G., ibid.

12. Gilman, H., Organic Chemistry, Vol II, 1415 (1938), Braunworth and Co., Inc.

13. This work was performed in Dr. B. Rosenburg's laboratories by Gary Smith.

14. deWilt, H. J., Ind. Eng. Chem. Prod. Res. Develop., 11, 370 (1972).

15. Eaborn, C., Walton, D. R. M., Thomas, B. S., Chem. Ind. (london), 827 (1967).

16. Lonngren, J., Pilotti, A., Acta. Chem. Scan., 25, 3 (1971); Neeman, M., et al., Tet.,6, 36 (1959); Hakomori, J., J. Biochem., 55, 205 (1964); Svensson, S., et al., Angew. Chem., Int. Ed., 9, 610 (1970); Sandford, P. A., Biochem., 5, (1966); Svensson, S., et al., Acta. Chem. Scand., 21, 1801 (1967); McInnes, A. M., Ball, D. H., Cooper, F. P., Bishop, C. T., J. Chromatog., 1, 556, (1958).

17. Jones, H. G., Jones, J. N., Perry, M. B., Can. J. Chem., 40, 1559 (1962); Bishop, C. T., Cooper, F. P., Murray, R. K., Can. J. Chem., 41, 2245 (1963); Perry, M. B., Can. J. Biochem., 42, 451 (1964).

18. Vilkas, M., Hiu-I-Jan, Boussac, G., Bonnard, M. C., Tet. Lett., 1441 (1966), Tamura, Z., Imanari, T., Chem. Pharm. Bull., 15, 246 (1967); Tamura, Z., Imanari, T., Arakawa, Y., Chem. Pharm. Bull, 17,1967 (1969).

19. Supona, W. R., Kruppa, R. F., Henley, R. S., J. Amer. Oil Chem Soc., 44, 74 (1967).

20. Dutton, G. C., Adv. in Carbo. Chem., 28, 11 (1971).

21. Bentley, R. E., Sweeley, C. C., et al., Biochemical and Biophysical Research Commun., 11, (1963); Sweeley, C. C., Bentley, R., Makita, M., J. Am. Chem. Soc., 85, 2497 (1963); Perry, M. B., Hulyalkar, R. K., Can. J. Biochem., 43, 573 (1965).

22. Sjostrom, E., Haglund, P., Jansson, J., Acta. Chem. Scand., 20, 1718 (1966).

23. Shapira, J., Nature, 222, 792 (1969).; Baine, R. A., Elbein, A. D., Biochemistry, 10, 2547 (1971).

24. Bethge, P. O., Holmstrom, C., Juslin, S., Svensk. Papperstidn, 69, 60 (1966). Zinkel, D. F., Lathrop, M. B., Zank, J., J. Gas Chromatogr., 6, 158 (1968). Shyluk, J. P., et al., J. Gas Chromatorg., 6, 158 (1968). Rowland, M., et al., Anal. Biochem., 20, 463 (1967).

25. Martinez, M., Nurok, D., Zlatkis, A., Anal. Chem., 50, 1226 (1969).

26. Sweeley, C. C., et al., Carb. Res., 5, 373 (1967).

27. Sweeley, C. C., Bentley, R., Makita, M., Wells, W. W., J. Am. Chem. Soc., 85, 2497 (1963).

28. Ed., Yancey, J. A., Analabs-Guide to Stationary Phases For Gas Chromatography., Pub.-Analabs, Inc. (1977). Ed., Heftman, E., Chromatography, 3rd ed., Van Nostrand Reinhold Co, (1975).

29. Bishop, C. T., Adv. in Carbo. Chem., 19, 95 (1964).

30. Verhaar, L. A., deWilt, H. G. J., J. Chrom., 11, 168 (1969).

31. Petersson, G., Org. Mass Spec., 6, 577 (1972).

32. Petersson, G., ibid.

33. Kochetkov, N. K., Chizhov, O. S., Adv. in Carbo. Chem. 21, 39 (1966).

34. Finn, P. A., Reed, R. I., Nature, Lond., 184, 1866 (1959).

35. Kochetkov, N. K., Wulfson, N. S., Chizhov, O. S., Zolotarev, B. M., Tet., 19, 2209 (1963).

36. Petersson, G., ibid.

37. Kochetkov, N. K., ibid (1963). Kochetkov, N. K., Chizhov, O. S., Tet., 21, 55 (1965).

38. Petersson, G., Acta. Chem. Scand., 21, 1251 (1967).; Choy, Y. M. et al., J. of Chrom., 72, 13 (1972). DeJongh, D. C., Sweeley, C. C., et al., J. Am. Chem. Soc., 91, 1728 (1969).; Kochetkov, N. K., Chizhov., O. S., ibid. (1966).

39. Grubbs, R. H., Chemtech, 512 (1977) and references therein.

40. Gupta, A., Rembaum, A., Gray, H. B., Volkesen, W., 172nd National ACS Meetin, San Francisco, 1975.

41. Tsuchida, E., Nishide, H., Adv. in Polymer Sci., 24, 1 (1977).

42. George, M. H., Hays, G. F., J. Polymer Sci. Chem. Ed., 14, 475 (1976).

43. Pittman, C. U., Rounsefell, T. D., Macromolecules, 9, 936 (1976).

44. Pittman, C. U., et al., "Organometallic Polymers," Carraher, Pittman and Sheats, Eds., Academic Press, 1978, p. 67.

45. Pittman, C. U., et al., Macromolecules, 4, 360 (1971).

46. Brit. Patent #131,374 (C. A. 70, 4984S (1968).

47. Wilking, J. P., U. S. Patent # 2,659,711 (1953).

48. Podall, Iapalucci, T. L., Polymer Letters, 1, 457 (1963).

49. Jensen, D. A., Z. Anorg. Allgem. Chem., 252, 227 (1944).

50. Sonogashira, K., Kataoka, S., et al., J. Organomet. Chem., 160, 319 (1978).

51. Carraher, C. E., J. Poly. Sci,, 16, 2965 (1978).

52. Carraher, C. E., Macromol., 2, 306 (1969).

53. Matsuda, H., J. App. Poly. Sci., 22, 2093 (1978) and references therein; Tsuchida, E., Nishide, H., Adv. in Poly. Sci., 24, 1 (1977) and references therein; Carraher, C. E., Jorgensen, S., J. Poly. Sci., 16, 2965 (1978) and references therein.

54. Diaz, A., J. Am Chem. Soc., 99, 5838 (1977); Miller, L. L., J. Am. Chem. Soc., 100, 3223 (1978); J. Am. Chem. Soc., 97, 3549 (1975); Murray, R. W., Moses, P.R., J. Am. Chem. Soc., 98, 7433 (1976); Anson, F. C., et al., Anal. Chem., 49, 1589 (1977); J. Electroanal. Chem., 88, 289 (1978); Kuwana, T., J. Electroanal. Chem., 88, 285, (1978); Bard, A. J., Merz, A., J. Am. Chem. Soc. 100, 3222 (1978).

55. Gertner, D., Frankel, M., Wagner, D., Zilkha, A., Israeli Patent #23,197 (1969).

56. Bowman, E. S., Hughes, G. B., Grutzner, J. B., J. Am. Chem. Soc., 98,8273 (1976).

57. Clark, F. R. S., Warkentin, J., Can. J. of Chem., 49, 2223 (1971).

58. Walsh, R., Wells, J. M., J. Chem. Soc., Perkin Trans., 2, 52 (1972); J. Chem. Thermodyn., 7, 149 (1975).

59. Ireland, R. E. et al., J. Am. Chem. Soc., 98, 2868 (1976). Franzus, B., et al., J. Am. Chem. Soc., 98, 1241 (1976).

59. Evans, D. A., J. Am. Chem. Soc., 97, 4765 (1975).

60. Gassman, P. G., Marshall, J. L., Org. Syn, Coll. Vol 5, 425 (1973).

61. Gassman, P. G., Pape, L., Org. Syn, Coll. Vol 5, 91 (1973).

62. Bly, R. K., Bly, R. S., J. Org. Chem., 28, 3165 (1963).

63. Story, P. R., J. Org. Chem., 26, 287 (1961).

64. USAEC Office of Information Services-Technical Information, Oak Ridge Tenn., TID-26553, parts 1, 2, and 3. "Mass Spectra of Compounds of Biological Interest."

65. Petersson, G., Org. Mass. Spec., 6, 577 (1972).

66. Verchise, J. F., Fleury, M. B., J. Less Common Metals, 54, 135 (1977).

67. The diabetes project was initiated by Dr. Barnett Rosenburg, Biophysics Department, Michigan State University. The collaboration between Dr. R. H. Grubbs and Dr. B. Rosenburg was established after initial investigations with Pt black were completed in the laboratories of the latter.