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SILYLATION OF CARBOHYDRATE SYRUPS

By

Mark Gorwitz

A Thesis submitted
in partial fulfillment of
the course requirements for
The Bachelor of Science Degree

Western Michigan University

Kalamazoo, Michigan

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TABLE OF CONTENTS

	<u>Page</u>
INTRODUCTION	1
Historical Background	2
Theoretical Background	2
Bonding Power	3
Bond Energies	3
Conjugative Effects	4
The Mechanism of Silylation	5
Reaction Kinetics	7
Stereochemistry of the Reaction	7
N Versus O Silylation	8
The Nature of X	8
The Influence of HY	9
Steric Effects	9
The Effect of Catalysts	10
PRESENTATION OF PROBLEM	11
EXPERIMENTAL	12
Chemicals	12
Equipment	12
Procedure	12
Results	13
DISCUSSION OF RESULTS	16
Table of Silylating Agents	18
REFERENCES	19

INTRODUCTION

Carbohydrates are usually difficult to analyze in solutions. Gas chromatography provides a suitable means for analysis. However most carbohydrate compounds are not volatile enough for use by this method.

Suitable derivatives are the aldol acetates and the silylated carbohydrates. Aldol acetates are difficult to prepare and require long time periods for their formation. Silylation is the most suitable means for preparing volatile derivatives. However most silyl compounds are water sensitive.

This paper discusses silylating agents, their reaction mechanisms and a solution to the problem of water sensitivity.

HISTORICAL BACKGROUND:

The earliest example of the use of silylation was the work of Sauer (1) who investigated the reaction of trimethylchlorosilane and pyridine with ethyl and methyl alcohols.

Hexamethyldisilizane was first used by Mjorne (2). He applied the use of this reagent to amines. Spier (3) later went on to use it for alcohols and phenols. He developed the hexamethyldisilizane-trimethylchlorosilane method of silylation. In this method the ammonia produced from the hexamethyldisilizane neutralizes the hydrogen chloride produced from the trimethylchlorosilane reaction.

The first silylated sugar was reported by Schwarz (4) in 1956. Earlier attempts at separation of silylated sugar by gas chromatography were made by Hedgley (5). These first early attempts were not successful.

In 1963 Sweeley (6) developed a simple method for the silylation of sugars. His method used hexamethyldisilizane and trimethylchlorosilane in pyridine. It was applied successfully to over one hundred sugar compounds.

Brobst and Lott (7) demonstrated that it is possible to silylate sugar syrups. Their method was to add hexamethyldisilizane to a mixture of the syrup and trifluoroacetic acid. This method was impractical due to the great amount of heat evolved during mixing.

Brittain (8) was the first person to investigate the use of N(trimethylsilyl)imidazole for wet sugars. These results were verified by Sennelo (9). He studied syrups containing 20% H₂O. Higher concentrations were not reported.

THEORETICAL BACKGROUND:

Properties of the trimethylsilyl group are responsible for the increased volatility of silylated carbohydrates. So its properties must be examined and considered in this context.

Silicon has a covalent radius of 1.17A (10). The silicon-carbon distance varies with the element attached to the fourth silicon bond. In trimethylchlorosilane it is 1.89A and in tetramethylsilane it is 1.93A. It has been determined that the C-Si-C bond angles are approximately tetrahedral. It has been found out (11) that the trimethylsilyl group has the same geometry as the t-butyl group, but is slightly larger. Because of its size, the trimethylsilyl group exerts steric effects. These will be discussed later.

BONDING POWER:

Silicon has available 3d orbitals for additional bonding unlike carbon. So one cannot discount the possibility that the 3d orbitals are involved in the tetravalent bonding of silicon.

BOND ENERGIES:

Silicon in comparison to carbon forms less stable bonds with the following elements: carbon and hydrogen; but more stable bonds to these elements: nitrogen, sulfur, oxygen and chlorine. Actual values vary with the method used. Hess (12) calculated the following values in Table I for the dissociation of $(\text{CH}_3)_3 \text{SiY}$.

Table I

Y	kcal/Mole \pm 10 Kcal
H	88
CH ₃	85
C ₂ H ₅	83
Si(CH ₃) ₃	86
OCH ₃	127
F	193
Cl	126
Br	86
N(C ₂ H ₅) ₂	131

These are of importance in considering cleavage of bonds in solution.

CONJUGATIVE EFFECTS:

Silanols are stronger acids than alcohols (13) but if one considers inductive effects alone, they should be weaker. This can be explained by considering that one of the unshared pair of electrons on the oxygen is shared by the silicon through its D orbitals. This is referred to as (P-d) bonding.

Assuming a bent Si-O-H bond, the (P-d) interaction can be pictured as in Figure 1.

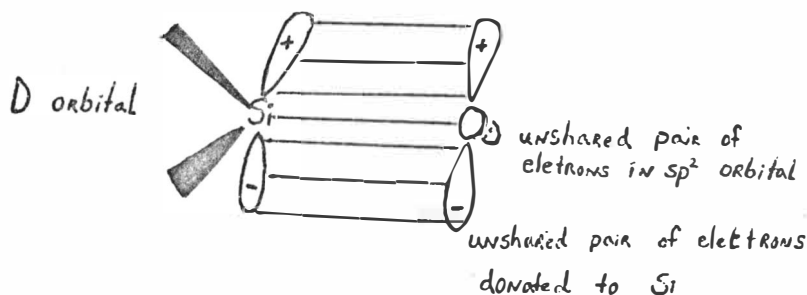


Figure 1.

More recently (14) it has been pointed out that the geometry of the molecule cannot be directly related to the absence or presence of (P-d) bonding. It has been suggested that an unshared pair of electrons in the SP^3 orbital can overlap with the d orbital enough for (P-d) bonding if the orientation is just right. The two d orbitals of silicon involved in bonding to two nitrogen atoms may have a node between them and therefore can be non transmitting.

The inability of silicon to transmit a conjugative effect at times may be explained by the fact that silicon is not as effective in competing for an unshared pair of electrons as another acceptor. Or possibly the involvement of one group with the d orbitals of silicon may prevent another from doing so.

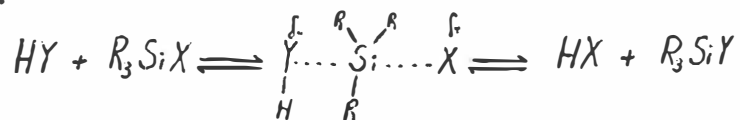
Since the t-butyl group was compared to the trimethylsilyl group, the following differences should be noted:

1. The trimethylsilyl group is larger and within itself less crowded but usually exerts a greater steric effect.
2. Bonds formed by the trimethylsilyl group are usually more thermodynamically stable.
3. The trimethylsilyl bonds are more polarizable and much more reactive.
4. There is less tendency for silyl free radicals or siliconium ions to form than for the corresponding carbanions.

The Mechanism of Silylation

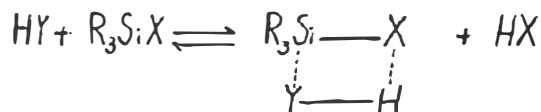
The majority of investigators believe that the silylation reaction is reversible. This is an important factor to consider when water is present. One wants a silylating agent that can react completely in the presence of water.

The mechanism is believed to proceed through bimolecular substitution at the silicon atom.

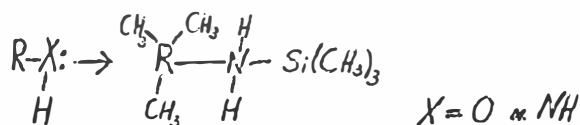


This is where Y is the nucleophilic component of the molecule being silylated and X is the group substituted in the silylating compound. Y is usually a stronger base than X and S_N2 or nucleophilic substitution is the probable mechanism.

Silylation may also proceed through a many center transition state. (15).



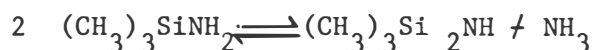
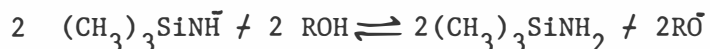
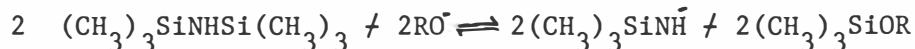
This type of mechanism can be used to explain the reaction of hexamethyldisilazane. The proposed intermediate was:



Protonation is important and was assumed to occur because a trace of trimethyl-

chlorosilane (an acid donor) catalyzed the reaction.

The mechanism for the reaction of hexamethyldisilizane (16) was given as follows:

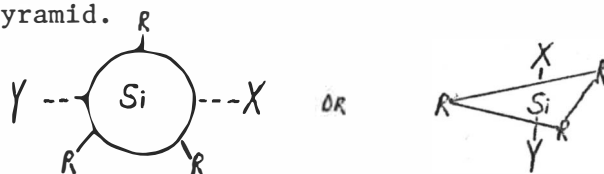


The rate limiting step of this reaction is believed to be the protonation of the silylation agent, followed by nucleophilic attack on the silicon atom.



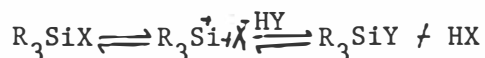
The mechanism of the substitution stage at the silicon atom has been studied and these versions were discussed:

1. The first case involved inversion of the optical configuration at the silicon atom. In this case the X group is replaced by Y via a bimolecular substitution. The transition state assumes the form of a trigonal bipyramid.



2. In this case (17) the optical configuration at the silicon atom is retained. The reaction is also considered bimolecular, but the shape of the transition state is different. It is either a tetragonal pyramid or trigonal bipyramid in which case the relative positions of X and Y are not the same as above.

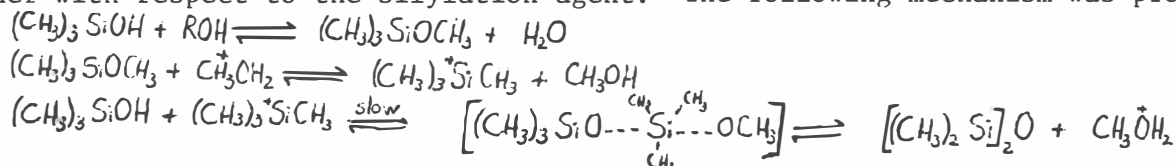
3. This involves the loss of optical activity. This involves the formation of a planar siliconium cation.



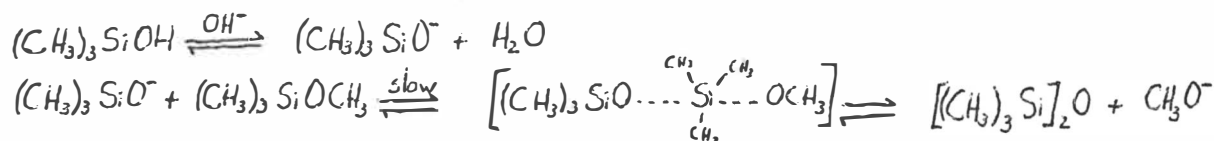
REACTION KINETICS:

It has already been stated that in many cases the rate determining step in the silylation reaction is nucleophilic substitution at the silicon atom.

Grubb (18) established that silylation proceeds with participation of the solvent and is acid- or base-catalyzed. The reaction was proposed to be of first order with respect to the silylation agent. The following mechanism was proposed:

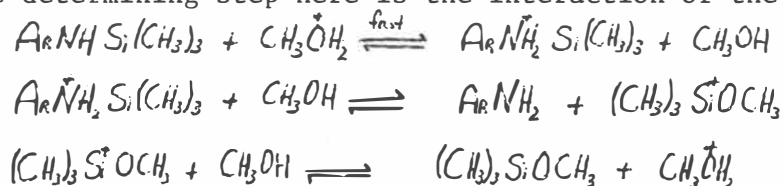


Base catalyst (19) gives the following mechanism:

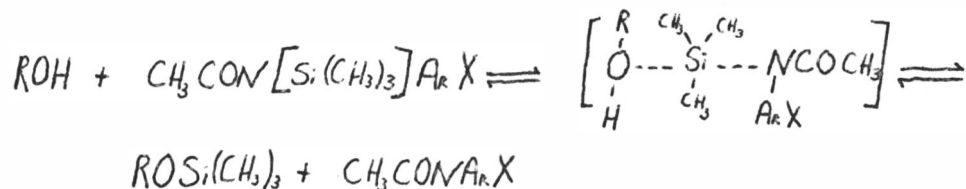


The kinetics for the reaction of silylamines (20) were also determined.

The rate determining step here is the interaction of the silylamine with ROH.



The kinetics of the silylamides were studied by Klebe (21). He believed that the rate determining step is the bimolecular substitution at the silicon atom.



Stereochemistry of the Reaction

Silylation as a rule (22) seems to process with almost complete inversion at

the configuration of the R_3Si^- fragment. The silylating agents interact in both neutral and protonated forms. Protonated forms being more acceptable. The silylated compound can thus react as either an anion or a neutral molecule.

N Versus O Silylation

O- Silylation involving amides usually occurs first, with a rapid shift to the more thermodynamically stable N-trimethylsilyl form. O and N silylation forms do not exist together. Simple amides were found to give N-substituted forms by reason of a group capable of giving resonance stabilization to the O-substituted form (23). Either a mixture of isomers or the O-silylated form may result from silylation.

The Nature of X

The rate of silylation depends on the properties of the substituent X as the group to be eliminated. Silylation reagents are characterized by good leaving groups. Important factors are (24): low basicity, ability to stabilize a negative charge in the transition state and little or no (P-d) bonding with silicon. X should be a weaker base than Y. It is desirable that X should be capable of delocalizing the negative charge arising on it during the transition state (24).

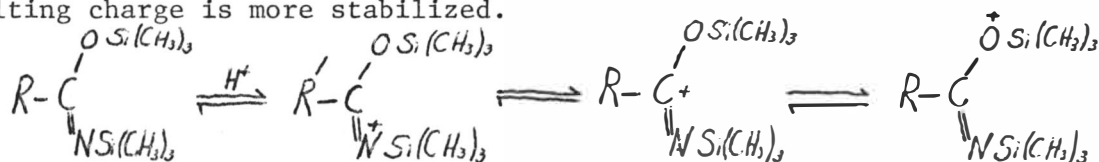
The weaker the (P-d) interaction between the silicon atom and the group X, the greater the ease of nucleophilic attack on the silicon atom and the dissociation of the Si-X bond. In many cases the ease or rate of the silylation reaction depends on the ease of protonation of the silylating agent. The following derivatives are arranged in order of their silylating ability.



Silylamines are less effective donors than silylated ureas or amides. Bis(trimethylsilyl) amides are usually the best silylating agents.

The reason for this being that introduction of the carbonyl group at the nitrogen atom linked to the silicon atom weakens the (P-d) interaction between them and facilitates nucleophilic attack on the silicon atom. The introduction of a second trimethylsilyl group further weakens the double-bond character of the linkage between the silicon atom and the group X to be substituted. There is also an increase of the capacity of the group X being eliminated for the delocalization of the negative charge due to the carbonyl group.

Amides are more easily protonated than amines or ureas. This is because the resulting charge is more stabilized.



Thus amides are excellent silylating agents. They were given first consideration in the experimental section.

The Influence of HY

The silylation mechanism can also be affected by the substance being silylated. If HY has pronounced nucleophilic properties, then silylation is encouraged. If HY is acidic in nature, this tends to lead to a many centered transition state. When this is so, the rate determining step becomes the protonation of the silylating agent. Hydroxy compounds (25) are more easily silylated than compounds with a N-H bond. The possible reason for this being, hydroxy compounds can easily protonate the silylating agent, and they themselves are easily deprotonated. The anion RO- being more nucleophilic than N-H helps account for this.

Steric Effects

Usually the rate and mechanism of the silylation is determined by steric effects associated with the silylating agent or compound being silylated. Branched compounds (25) are silylated with more difficulty than straight chain compounds.

A study (26) of the rate of hydrolysis of various silanes showed that bulky

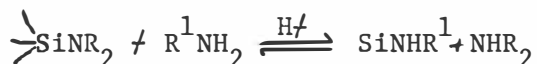
substituents at the silicon atom retard the reaction. The same effects are probably responsible for their increased resistance to hydrolysis.

The Effect of Catalysts

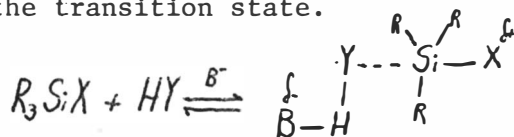
Acid catalysts help increase the rate of protonation of the silylating agent.

This in turn weakens the (P-d) interaction between the silicon atom and the group X.

Proton donating compounds help catalyze the attainment of equilibrium.



Bases also catalyze the reaction. Their role may be reduced to bonding the proton from HY in the transition state.



Bases can also help the dissociation of HY.

Pyridine deserves mention here also. The formation of an intermediate pyridine-trimethylchlorosilane complex has been assumed (26). This was especially noted in the case of carbohydrates.

PRESENTATION OF PROBLEM

It is known already that silylation is an effective means of preparing volatile carbohydrate derivatives for gas chromatography. N-(trimethylsilyl) imidazole (27) has already been demonstrated to silylate carbohydrates in 20% water syrups. No one has tried higher concentrations of water. So, my experiments will touch on that problem.

The problem then becomes: Will N-(trimethylsilyl) imidazole silylate carbohydrates at 30%, 40% and 50% water concentrations as effectively as at 20% concentration?

The reasons for employing this reagent have already been discussed in the theoretical section.

EXPERIMENTAL

I employed a standard silylation method as developed by Sennello (28) in their work on N(trimethylsilyl) imidazole. Four-six runs at each water concentration were done, and a final comparison was done. This involved comparing N(trimethylsilyl) imidazole to the standard silylating agents hexamethyldisilazane and Bis-(trimethylsilyl) acetamide.

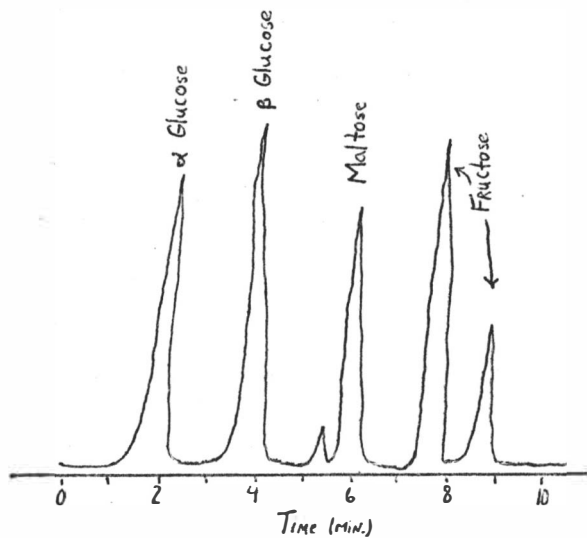
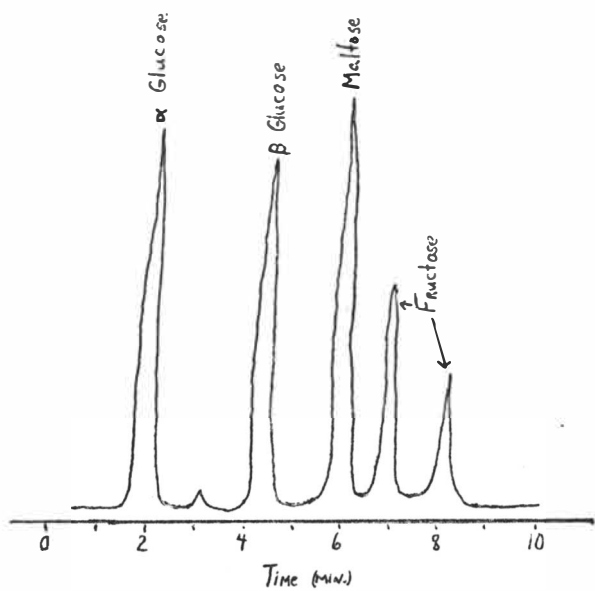
Chemicals: All chemicals were purchased and used as obtained from Aldrich Chemical Company, Milwaukee, Wisconsin. My sugar mixture was equal parts maltose, glucose and fructose.

Equipment: The gas chromatograph used for this work was a Varian Model 1800 equipped with hydrogen flame detectors. The column was a stainless steel coil and was packed with 5% OV-101 on 80-100 mesh Gas-Chrom Q. The temperatures were: oven, 205°C; detector, 205°C; and flame heater, 235°C. The flow rates were: nitrogen, 29m/min.; hydrogen, 31m/min. and air, 300ml/min. All injections were made with a micro syringe.

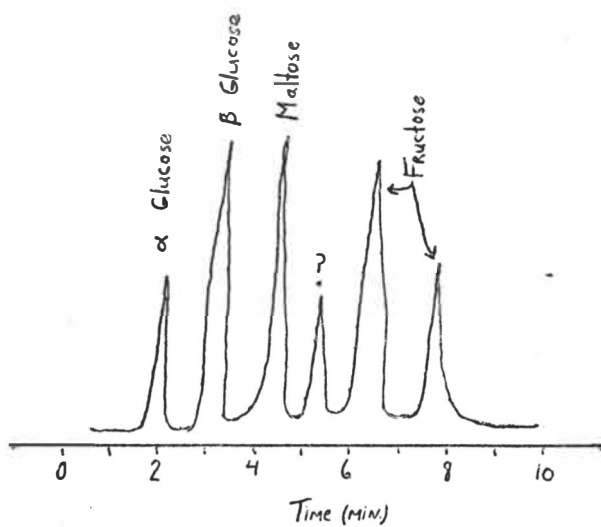
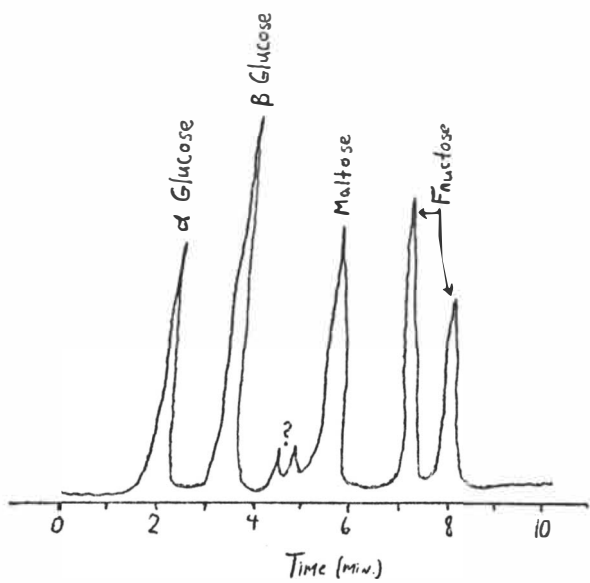
Procedure: Silylation was performed as follows: four volumes of pyridine were mixed with one volume each of trimethylchlorosilane and N(trimethylsilyl) imidazole. Two ml. of the silylating mixture was added with 100 mg. of the sugar mixture, the vial capped and then shaker briefly to ensure mixing. Then it was allowed to sit for 20 minutes before injection into the gas chromatograph.

Thirty, forty and fifty percent water syrups were used. Finally the N(trimethylsilyl) imidazole was compared against a standard mixture of hexamethyldisilazane-trimethylchlorosilane (1:1 mixture).

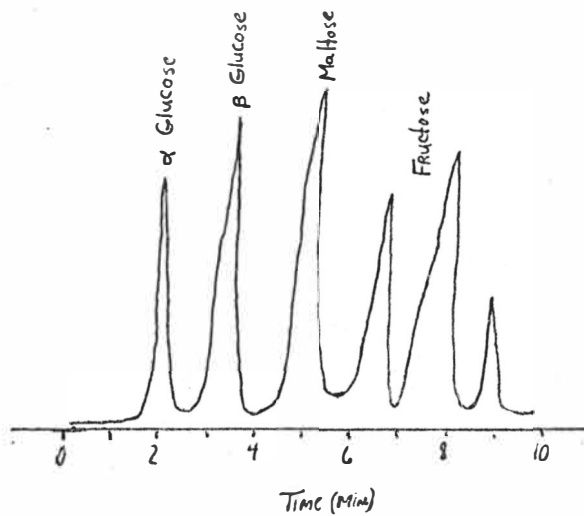
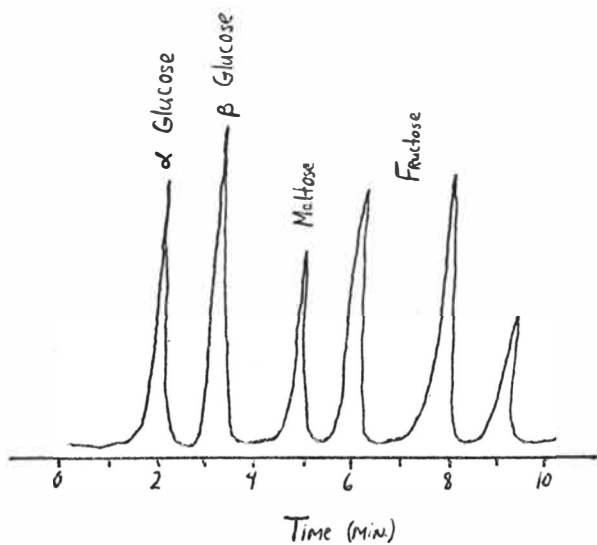
Results: The results of two runs at each level and one of the final comparisons are drawn out. A copy of the graph for each level is also included.



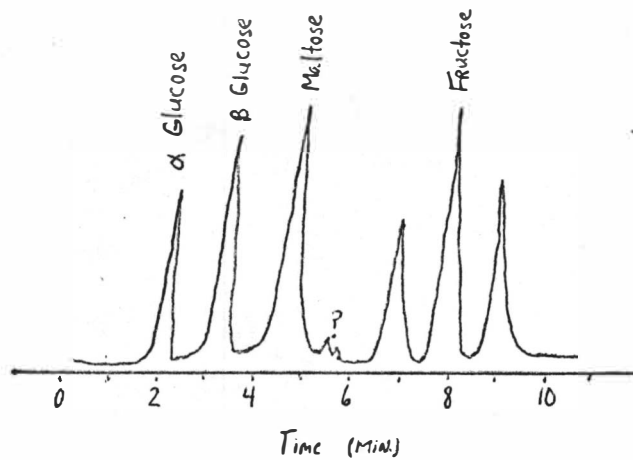
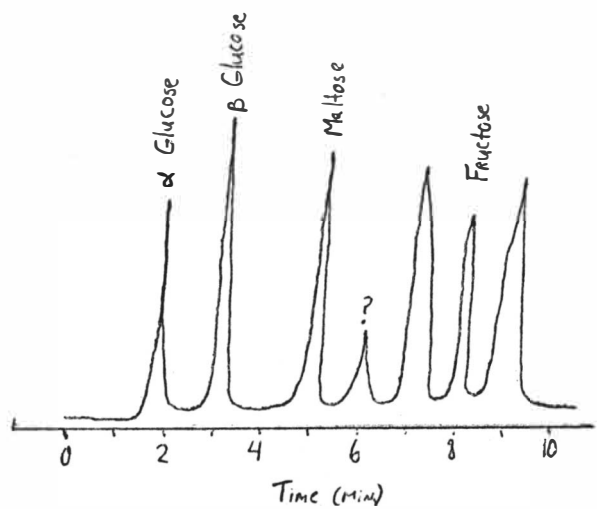
30% Water
Figure I.



40% Water
Figure II

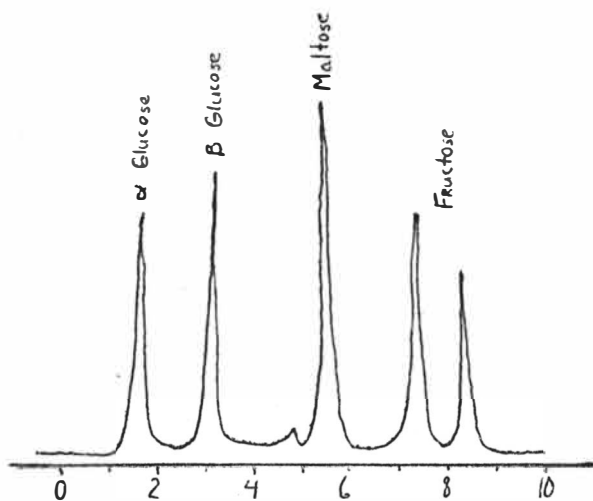


50% Water
Figure III

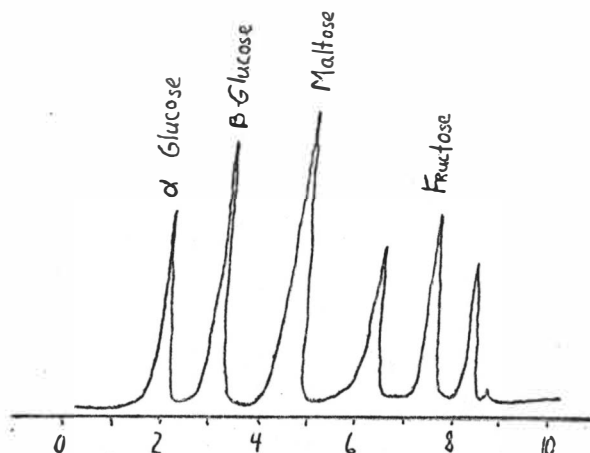


N(trimethylsilyl) imidazole
Alone
Figure IV

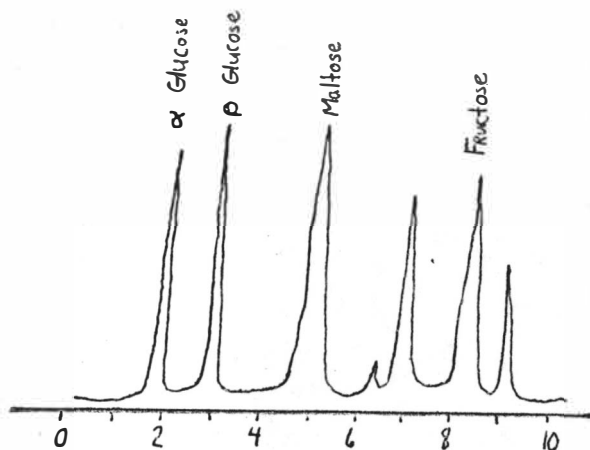
COMPARISON RUN



N(trimethylsilyl) imidazole
Figure V



Hexamethyldisililane
Figure VI



Bis(trimethylsilyl) acetamide
Figure VII

DISCUSSION OF RESULTS

Each set of graphs will now be examined separately. Then a final comparison will be made at the end of this section.

For the 30% H₂O level using N(trimethylsilyl)imidazole as the silylating agent the following results were noted. α and β anomers of glucose both appear. These can partly be explained by considering the slightly acid nature of N(trimethylsilyl)imidazole. It is acid enough to cause the formation of those anomers. On further examination, one sees only two peaks present for fructose. This was a pleasant surprise, for fructose usually gives rise to at least three or possibly four peaks. However, a fairly strong acid has to be present for this to occur. Thus the only slightly acidic nature of N(trimethylsilyl)imidazole circumvents this.

At the 40% H₂O level the following results were noted. Again, both α and β glucose anomers are present. But one also notes the appearance of a few unexplained peaks. These come to early in the one graph to be fructose anomers. They could possibly be other ring isomers of glucose. Looking now at the fructose peaks, you can see one small additional peak. This can possibly be explained by the fact the additional water present caused increased hydrolysis of the silylating agent and led to the generation of additional acid species.

Continuing on to the 50% H₂O level, all the peaks are easily identified. Both α and β glucose anomers are present. However, when looking at the fructose section, you can see multiple peaks. These are possibly accounted for by the explanation in the preceding paragraph.

Coming to the last step of graphs, these were run at 40% H₂O concentration. N(trimethylsilyl)imidazole gave the best results. As usual α and β glucose were present. But only two peaks were observed for fructose.

Hexamethyldisilazane gave multiple peaks for fructose. This can be explained

by the highly acidic nature of this silylating agent combined with trimethylchlorosilane.

Bis(trimethylsilyl) acetamide also gave multiple peaks for fructose plus one unidentified peak.

Conclusion: Anomer formation appears to be the major problem associated with silylation. However, this can be overcome by using N(trimethylsilyl) imidazole along with a small amount of trimethylchlorosilane. The amount of water present is also important; best results were obtained in the 30-40% range. At higher water levels too much hydrolysis and generation of acidic species can occur.

Recommendations: As it was shown that the addition of trimethylchlorosilane cuts down on anomer formation, the concentration giving best results should be further investigated. Also the rate of hydrolysis could be monitored and followed to determine an optimum time for sample useage.

Silylating Agents

Agent	X or Leaving Group	Water Stability
<p>Hexamethyldisilazane</p> $\begin{array}{c} \text{CH}_3 \qquad \text{CH}_3 \\ \qquad \\ \text{CH}_3-\text{Si}-\text{NH}-\text{Si}-\text{CH}_3 \\ \qquad \\ \text{CH}_3 \qquad \text{CH}_3 \end{array}$	<p><i>NH, forms NH₃</i></p>	<p>Extremely Water Sensitive (25)</p>
<p>Trimethyl Chlorosilane</p> $\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{Si}-\text{Cl} \\ \\ \text{CH}_3 \end{array}$	<p><i>Cl, forms HCl</i></p>	<p>Extremely Water Sensitive (25)</p>
<p>N(trimethylsilyl) imidazole</p> $\begin{array}{c} \text{CH}_3 \\ \\ \text{N}=\text{CH} \\ \qquad \\ \text{CH}=\text{CH} \quad \text{N}-\text{Si}-\text{CH}_3 \\ \qquad \qquad \\ \qquad \qquad \text{CH}_3 \end{array}$	$\begin{array}{c} \text{N}=\text{CH} \\ \qquad \\ \text{CH}=\text{CH} \quad \text{N}- \end{array}$	<p>Water Stable (9)</p>
<p>N,O Bis(trimethylsilyl) acetamide</p> $\begin{array}{c} \text{O Si(CH}_3)_3 \\ \\ \text{CH}_3-\text{C} \\ \qquad \qquad \backslash \\ \qquad \qquad \text{N Si(CH}_3)_3 \end{array}$	$\begin{array}{c} \text{O}- \\ \\ \text{CH}_3-\text{C} \\ \qquad \qquad \backslash \\ \qquad \qquad \text{N}- \end{array}$	<p>Sensitive (25)</p>

Table II

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