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A Study of the Reactions in the
Zinc Chloride-Benzaldehyde-Glucose System

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A STUDY OF THE
REACTIONS IN THE ZINC CHLORIDE-BENZALDEHYDE-GLUCOSE
SYSTEM

A thesis submitted by

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INTRODUCTION

CHEMISTRY OF ACETALS

The work reported herein deals with the system usually used for the preparation of the benzylidene glucoses, namely the zinc chloride-benzaldehyde-glucose system. This section on the chemistry of acetals is included merely to acquaint the reader with some background on acetals, their preparation and reactions.

An ordinary acetal is formed as the result of reaction between an aldehyde molecule and two molecules of an alcohol with the elimination of a molecule of water. An intermediate compound in this process is the so-called "hemiacetal" which is the result of the addition of one molecule of the alcohol to the carbonyl double bond of the aldehyde. If the aldehyde is designated by RCHO and the alcohol by R'OH, the process of acetal formation can be represented as in Fig. 1.

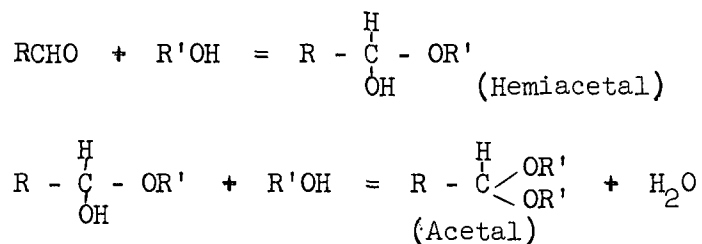


Figure 1. Process of Ordinary Acetal Formation

The chemistry of the cyclic acetals and ketals has been extensively reviewed by Barker and Bourne (1), so only certain highlights of the topic will be presented here. Cyclic acetals are formed as the result of reaction between an aldehyde and a polyhydric alcohol. The process of their formation, shown in Fig. 2, can be seen to closely parallel that of the ordinary acetals. The usual products contain

either five- or six-membered acetal rings. The condensation of an aldehyde with a polyhydric alcohol is reversible and is catalyzed by acidic substances such as concentrated sulfuric acid, hydrochloric and hydrobromic acids, zinc chloride and cupric sulfate (1). Since the reactions forming both cyclic and ordinary acetals are reversible and produce water, yields can be increased by subjecting the system to dehydrating conditions.

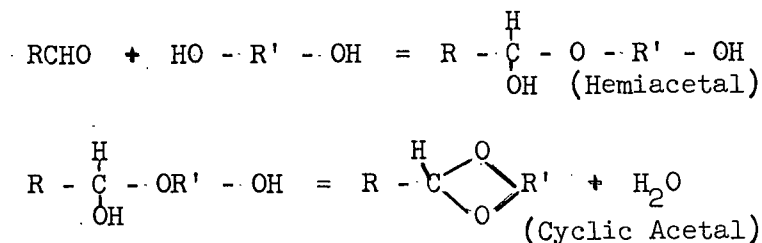


Figure 2. Process of Cyclic Acetal Formation

It has been shown that in some cases, the conditions used in the reaction (type of catalyst and temperature) will have an effect on the type of product or products obtained from the reaction. For instance, Haskins, Hann, and Hudson (2) found that they obtained a different isomer of dibenzylidene-1,6-dibenzoyl dulcitol when using zinc chloride as the catalyst than when using hydrogen chloride. Trister and Hibbert (3) found that by changing temperature in the preparation of acetals from glycerol they were able to change the relative amounts of five- and six-membered rings produced. They also found that, for glycerol, the five-membered rings predominated. Foster, Haines, and Lehmann (4) propose that the preponderance of five-membered rings in this case over the ordinarily more stable six-membered rings is due to hydrogen bonding between glycerol molecules. They consider that the formation of a six-membered acetal

ring from glycerol destroys two primary hydroxyl groups, whereas a five-membered ring destroys only one. They suggest that the greater tendency of primary hydroxyls to hydrogen bond counteracts the ordinary tendency of acetals to form six-membered rings. If this is the case, one would expect to find the energy difference between five- and six-membered acetal rings to be less than the energy of the hydrogen bond (about 5000 cal./mole).

The most outstanding chemical properties of acetals are their stability under alkaline conditions and their instability in aqueous acids. This makes them useful as blocking groups in protecting specific hydroxyls of polyhydric alcohols during such steps as acylation, sulfonation, methylation, benzylation and tritylation (1). Aqueous acids will hydrolyze the acetals, but the ease with which they do so is dependent upon (among other things), the size and position of the acetal ring and the type of acetal. Methylene acetals appear to be more resistant to hydrolysis than their higher homologues (1). Cyclic acetals containing fused five-membered rings such as 1,2-O-isopropylidene-D-glucopyranose (5) and 1,2-O-cyclohexylidene-D-glucopyranose (6) have been shown to be relatively resistant to acid hydrolysis. This was demonstrated by preparing the 1,2-substituted compounds by partial acid hydrolysis of the 1,2:5,6-diacetals. Mills (7) attributes this relative stability to steric effects -- particularly the decreased interaction of nonbonded groups.

PREPARATION OF THE BENZYLIDENE GLUCOSSES

4,6-O-BENZYLIDENE- α -D-GLUCOPYRANOSE

Two methods are used for the preparation of 4,6-O-benzylidene- α -D-glucopyranose, the structure of which is shown in Fig. 3. They are the method of Zervas (8) and the more recently developed method of Wood, Diehl, and Fletcher (9). For convenience, this compound will be subsequently referred to as 4,6-benzylidene glucose.

In the Zervas preparation, 130 g. of anhydrous dextrose and 100 g. of finely powdered zinc chloride were shaken for 24 hr. with 300 ml. of freshly distilled benzaldehyde. The thick liquid was then

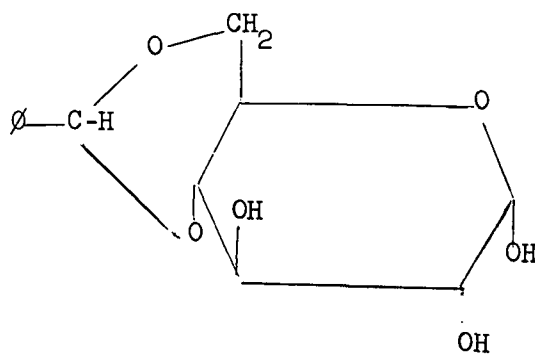


Figure 3. 4,6-O-Benzylidene- α -D-glucopyranose

mixed with 400 ml. of ice-cold water, whereupon crystallization took place. The mixture was filtered and the crystals were washed, first with cold water and then with petroleum ether. Zervas obtained between 60 and 70 g. of the crude product. (Sowden and Kuenne (10) report a crude yield of 17 g.) The crystals were recrystallized several times from ten times their weight of water to which ammonia

was added to make the solution alkaline. Zervas reported final yields of about 20 to 25 g. of 4,6-benzylidene glucose. This represents a yield of about 10 to 12% based on the original glucose.

In an attempt to increase the yield of 4,6-benzylidene glucose from this system, Wood, Diehl, and Fletcher (9) altered the proportions of reactants, the reaction time, and the method of processing the crude product. Their revised method consisted of shaking together 10 g. of powdered anhydrous D-glucose (which had been dried in vacuo at 60°C.), 40 g. of freshly fused and powdered zinc chloride, and 200 ml. of freshly distilled benzaldehyde. The shaking was continued for four hours at room temperature, after which the mixture was cooled and diluted with 250 ml. of cold water. After 0.5 hr. at 0°C. the resulting crystalline mass was filtered off and washed, first with cold water (2 x 25 ml.), and then with pentane (2 x 25 ml.).

The aqueous layer of the mother liquor and washings were extracted with ether (2 x 100 ml.). The ether extracts were added to the organic phase and the aqueous phase was filtered through 30 g. of Darco G-60 decolorizing carbon and discarded. The decolorizing carbon was washed with 100 ml. of water, heated with 100 ml. of dioxane, filtered off, and washed with 50 ml. more of warm dioxane. Concentration of the dioxane extracts in vacuo afforded a second batch of 4,6-benzylidene glucose.

The combined crops of 4,6-benzylidene glucose were recrystallized from dioxane-chloroform and then from ten times their weight

of water to which had been added 1 drop of aqueous ammonia per 10 ml. of water. The crystals were poured into the boiling water and the mixture was shaken for less than a minute, after which it was filtered through a very thin layer of decolorizing carbon. After filtration the solution was rapidly cooled to 0°C. This treatment yielded the pure 4,6-benzylidene glucose. (Yield = 42%).

1,2:4,6-DI-O-BENZYLIDENE- α -D-GLUCOPYRANOSE

Wood, Diehl, and Fletcher (9) prepared and characterized 1,2:4,6-di-O-benzylidene- α -D-glucopyranose (see Fig. 4) as a by-product of their preparation of 4,6-benzylidene glucose previously discussed. This compound will be subsequently referred to as 1,2:4,6-dibenzylidene glucose. They concentrated the combined organic phase and ether extracts in vacuo at 60°C. The residual sirup gave, from 15 ml. of absolute alcohol at -5°C., a crystalline product, which when recrystallized from methanol was 1,2:4,6-dibenzylidene glucose. The final yield was about 6%.

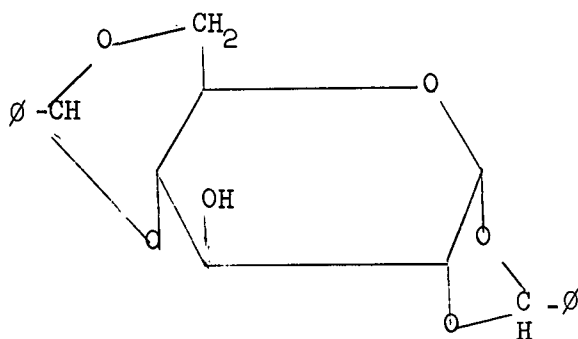


Figure 4. 1,2:4,6-Di-O-benzylidene- α -D-glucopyranose

An interesting sidelight to this preparation was the fact that by decreasing the amount of zinc chloride in the original mixture by

75%, the yield of the dibenzylidene derivative was increased to 11% and the yield of the 4,6-benzylidene glucose was decreased to 17%.

1,2-O-BENZYLIDENE-D-GLUCOFURANOSE

Sowden and Kuenne (10) prepared and characterized 1,2-O-benzylidene-D-glucofuranose (see Fig. 5) as a by-product of the Zervas procedure for preparing 4,6-benzylidene glucose. They took the liquid phase after filtering off the crude 4,6-benzylidene glucose and cooled it to -20°C . whereupon, with shaking, a crystalline precipitate formed. The precipitate was filtered from the solution and washed with ether and ice-water (yield = 10.9 g.). This material was recrystallized from water and then from ethanol to give pure 1,2-benzylidene glucose.

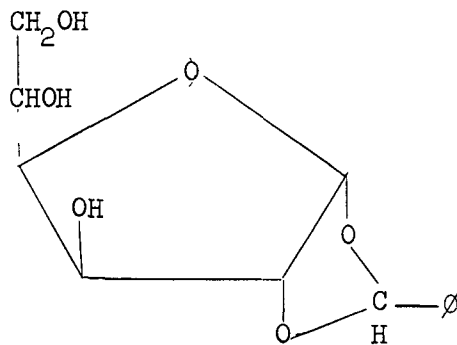


Figure 5. 1,2-O-Benzylidene-D-glucofuranose

PRESENTATION OF THE PROBLEM

It can be seen that since the three preparations just presented contain virtually all that was known about the zinc chloride-benzaldehyde-glucose system, little of a fundamental nature regarding the system was understood. There was little basis for comparison of the results of the separate workers since they used different conditions of reaction time, concentrations, and methods of isolation. No information was available on the yields of the compounds as functions of time and no conclusions could be drawn regarding the function of zinc chloride in the system.

With the above in mind, the goals of this research were set to be as follows:

- (1) An analytical procedure was to be developed which would give reliable data on the concentration of glucose and its derivatives in the system.
- (2) The analytical procedure would then be used to study the equilibria and kinetics of the reactions found to take place in the system.
- (3) An attempt would be made to discover the function of zinc chloride in the system.

For the purpose of simplifying the experimental work and also the analysis of the data, the concentration of zinc chloride was to be kept below its saturation value in benzaldehyde at room temperature (about 0.54 molar). Only those reactions which took place in the liquid phase would be studied.

RESULTS AND DISCUSSION

ANALYTICAL PROCEDURE

GENERAL DESCRIPTION

The method which was developed for the analysis of the reaction mixtures entailed separating the various components by paper chromatography, eluting them from the paper, and determining their amount by a color reaction. An adaptation of the anthrone color reaction (11,12) was used for the benzylidene glucoses and the Forest Products Laboratory modification (13) of the Somogyi (14) color reaction was used for determining glucose. A detailed description of the step-by-step procedures is given under "Experimental Procedures."

DEVELOPMENT OF THE PROCEDURE

Chromatography

Two chromatographic solvents were found which would separate the glucose and the glucose-containing components of the system. The first consisted of 20 parts ethanol to 1 part water (by volume). This proved slightly inferior to a water-saturated isobutanol solvent, so the latter was used almost exclusively. The R_f values of the pure compounds in the isobutanol solvent are given in Table I. The values were observed qualitatively to vary some with temperature, but separation of the compounds remained good.

TABLE I

 R_f VALUES OF COMPOUNDS IN WATER-SATURATED ISOBUTANOL

Compound	R_f
D-glucose	0.06
4,6-benzylidene glucose	0.71
1,2-benzylidene glucose	0.80
1,2:4,6-dibenzylidene glucose	0.94

It was found that p-anisidine spray reagent which was acidified by the addition of chloroacetic acid detected the presence of all of the compounds listed in Table I except 1,2-benzylidene glucose. This latter compound was detected with a permanganate-periodate spray reagent.

The physical layout of the chromatograms and the preparation of the chromatographic paper (Whatman No.1) were standardized in order to give more nearly reproducible results. It was found that material would elute from untreated paper which would cause the results of the color reaction to be high. Prewashing of the sheets with methanol reduced, but did not completely remove this effect. The apparent glucose content of a 2 by 3 inch piece of the chromatographic paper was reduced from about 0.32 μ moles to about 0.05 μ moles with the prewashing treatment. This elution blank was still of sufficient magnitude and variability that it had to be accounted for in each determination. In order to accomplish this the individual chromatograms were arranged and spotted as shown in Fig. 6.

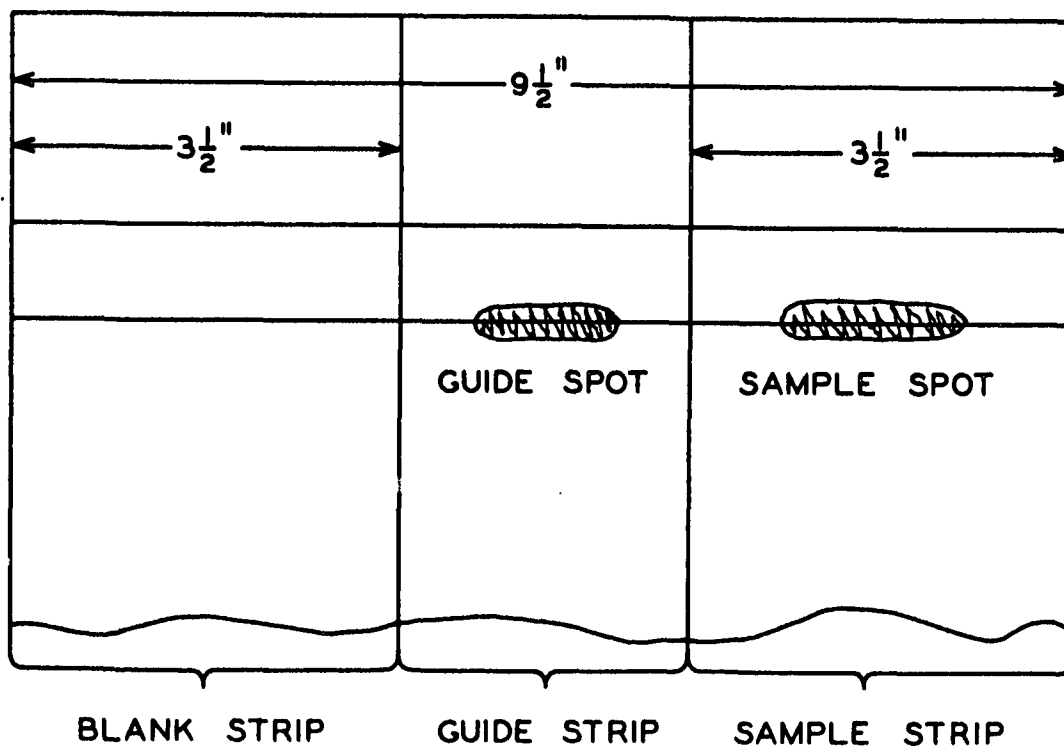


Figure 6. Layout of Chromatograms

Each marked and prewashed sheet was spotted with a sample of the liquid phase of the reaction mixture at the places indicated. The sheet was developed with the isobutanol-water solvent and the guide strip was sprayed with the suitable spray reagent in order to locate the spots and to give a visual indication of their relative sizes. The spot-containing areas were cut from the sample strip and their corresponding areas cut from the blank strip. Thus, the hope was that the blank tab, having received identical treatment throughout as the sample tab, would contain the same amount of "blank" material. In the subsequently described procedures for elution and color reactions, the sample-containing tabs and their corresponding blank tabs were treated identically.

Elution and Sample Treatment

The method used for elution was that of Saeman, Moore, Mitchell, and Millet (13), in which the material is washed from the paper tab into a capillary pipet. The advantage of this technique is that a constant volume of eluting solvent is used for each tab, thereby assuring that each pair of sample and blank tabs receives the same treatment. Methanol was used to elute the benzylidene glucose and the pipets were 1 ml.; water was used to elute glucose and the pipets were $3/8$ ml.

The eluted glucose spots were not subjected to any further treatment prior to their analysis. The samples of the benzylidene glucoses were diluted to 10 ml. with methanol and a suitable fraction of this was pipetted into a test tube and dried under a stream of warm air. It was this dried aliquot which was analyzed.

Color Reactions

It was found that although glucose could be determined using the anthrone procedure, better results could be obtained using the Forest Products method (13) which uses the alkaline reagent of Somogyi (14). The reason for this is that the highly acidic medium utilized in the anthrone reaction is more sensitive to the elution blank than an alkaline medium and since the quantities of glucose encountered were small, the reported result was a small difference between two larger numbers. This difficulty was somewhat diminished by using the alkaline system.

The concentrations of 4,6-benzylidene glucose and 1,2:4,6-di-benzylidene glucose which were encountered were larger than the concentrations of glucose and could be determined quite readily using a modification of the published procedures (11,12) involving the anthrone color reaction. The procedure adopted for their determination involved adding 10 ml. of a freshly prepared 0.2% solution of anthrone in a sulfuric acid-water mixture (760 ml. sulfuric acid + 240 ml. water) to 1 ml. of a methanol solution of the benzylidene glucose. The resulting solution was heated for 15 min. at 90°C. to develop the green color. The absorbance was measured at 620 m μ . on a Beckman D. U. spectrophotometer.

It was found that small amounts of zinc chloride and benzoic acid did not interfere with the determination.

VERIFICATION OF THE PROCEDURE:

The chromatographic separation was subjected to the following test to determine if any reactions were taking place on the chromatographic sheet which would alter the concentrations of the components of the reaction mixture. A series of chromatograms was prepared on which were spotted samples of the pure benzylidene glucoses. Over these spots were spotted amounts of zinc chloride (from a 0.2M solution in benzaldehyde) varying from a mole-to-mole ratio of 1:1 to 20:1 (zinc chloride: benzylidene glucose). The sheets were then developed in the chromatographic solvent, dried and sprayed. In no case did any spot appear which was not originally spotted, thus indicating that no reactions were occurring. Also, chromatograms of

reaction mixtures showed none of the streaking which would have been expected had there been reaction occurring on the sheet.

The anthrone determination was calibrated for 4,6-benzylidene glucose, 1,2:4,6-dibenzylidene glucose, and also for glucose. The calibration curve (Fig. 7) for the anthrone determination is the same for all three compounds if their amounts are expressed on a molar basis. On Fig. 7, the quantity $(\underline{A}-\underline{A}_0)$ is the difference between the absorbances of the sample and a blank. A possible reason for the three compounds reacting similarly is that the strongly acidic conditions of the determination hydrolyze off the benzylidene groups, leaving the glucose free to participate in the color reaction. The maximum experimental deviation from the line is equivalent to about 0.02 μ moles.

The over-all accuracy of the analytical procedure was estimated by spotting known amounts of the pure compounds, chromatographing them, and subjecting them to the operations of elution and determination. The results are given in Table II.

The maximum error in Table II is 0.05 μ moles. Most of the determinations made in this study were made on 10 or 20 λ of solution. An error in the determination of 0.05 μ moles for any one spot would correspond to an error in its reported molar concentration of 0.005 or 0.0025 for the 10 and 20 λ spots, respectively. It was found in actual use that this expected precision was not always attained. Table VIII, Appendix II shows that the worst scatter encountered in

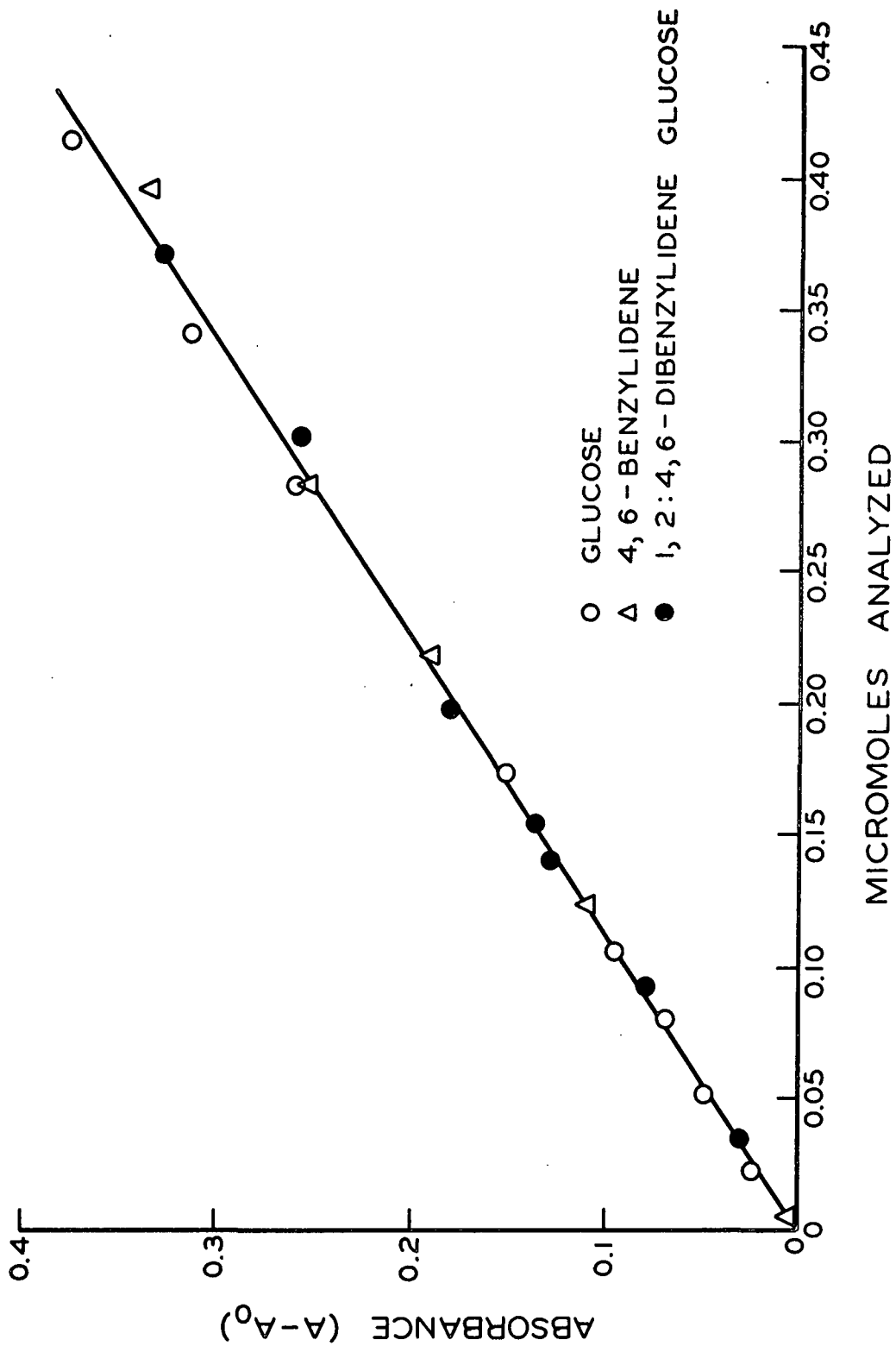


Figure 7. Calibration Curve for Anthrone Reaction

TABLE II

ACCURACY OF THE OVER-ALL ANALYTICAL PROCEDURE

Compound	Added, μmoles	Found, μmoles	Error, μmoles
Glucose	0.39	0.34	-0.05
Glucose	0.10	0.10	0.00
Glucose	0.20	0.20	0.00
4,6-Benzylidene glucose	0.40	0.36	-0.04
4,6-Benzylidene glucose	0.10	0.08	-0.02
4,6-Benzylidene glucose	0.20	0.18	-0.02
1,2:4,6-Dibenzylidene glucose	0.41	0.38	-0.03
1,2:4,6-Dibenzylidene glucose	0.10	0.10	0.00
1,2:4,6-Dibenzylidene glucose	0.20	0.20	0.00

any of the determinations was accompanied by $\pm 0.077M$ 95% confidence limits.

Since the chromatographic separation did not alter the composition of the reaction products and the over-all process was capable of the accuracy mentioned it was concluded that this comprised a valid procedure for studying the zinc chloride-benzaldehyde-glucose system.

STUDIES OF THE REACTION SYSTEM

ROLE OF 1,2-O-BENZYLIDENE GLUCOSE

It was found that 1,2-benzylidene glucose does not participate to a measurable extent in the equilibria of the system under the conditions of this work (liquid phase at 30°C.). This was suggested by

the inability to find any 1,2-benzylidene glucose by chromatographing the reaction solutions and demonstrated by the fact that this same material is unstable in zinc chloride-benzaldehyde solutions. A sample of 1,2-benzylidene glucose (0.021 g.) was dissolved in 1 ml. of a 0.4M solution of zinc chloride in benzaldehyde. Chromatograms of a sample of this solution taken one-half hour after the addition of the 1,2-benzylidene glucose showed no spots corresponding to this compound, but did show spots corresponding to 1,2:4,6-dibenzylidene glucose. The permanganate-periodate spray reagent was capable of detecting 0.2 μ moles of 1,2-benzylidene glucose on a chromatogram. The largest sample size used was 40 λ , which means that the concentration of this compound must have been less than 0.005M to remain undetected.

It is felt that failure to find 1,2-benzylidene glucose in the reaction solution is not contradictory to the findings of Sowden and Kuenne (10). It could be that the conditions of reaction used by them were in some way favorable for the formation of this compound. Such a case would not seem unreasonable in light of the fact that cases are known where changing the reaction conditions for acetal formation changes the nature of the products (2,3). Another possibility is that their 1,2-benzylidene glucose was a product, not of the system, but of the system from which it was isolated. The liquid phase from which they finally isolated the compound had water added to it. This water, along with the zinc chloride present could constitute the conditions of a mild hydrolysis; conditions under which

fused five-membered rings are relatively stable (5-7). This relative stability toward hydrolysis was confirmed in this work by the fact that 1,2-benzylidene glucose would not react with the acidified p-anisidine spray reagent, but the 1,2:4,6-dibenzylidene glucose would. If the 1,2-benzylidene glucofuranose is a hydrolysis product of 1,2:4,6-dibenzylidene glucopyranose, the hydrolysis must be accompanied by a change of the ring structure from a pyranose to a furanose form.

KINETIC STUDIES

The results of the kinetic studies done on the system are shown in Fig. 8 and 9. The tabulated data are listed in Appendix I. The glucose used in these reactions was all from the same sample which had been ground to pass a 170-mesh screen. In both figures, the rapid initial increase of 4,6-benzylidene glucose concentration and its subsequent levelling off and decrease, coupled with the ever-increasing concentration of 1,2:4,6-dibenzylidene glucose indicate that the reactions which produce these compounds are consecutive. That is, glucose reacts to give 4,6-benzylidene glucose which subsequently reacts to yield 1,2:4,6-dibenzylidene glucose. This would appear to be a reasonable sequence of events because the six-membered acetal ring on the 4,6-benzylidene glucose is sterically more easily formed than is the five-membered acetal ring at the one and two positions. This can be visualized from the perspective formula of 4,6-benzylidene glucose (Fig. 10) as given by Ferrier and Overend (15) and by Foster, Haines, Homer, Lehmann, and Thomas (16).

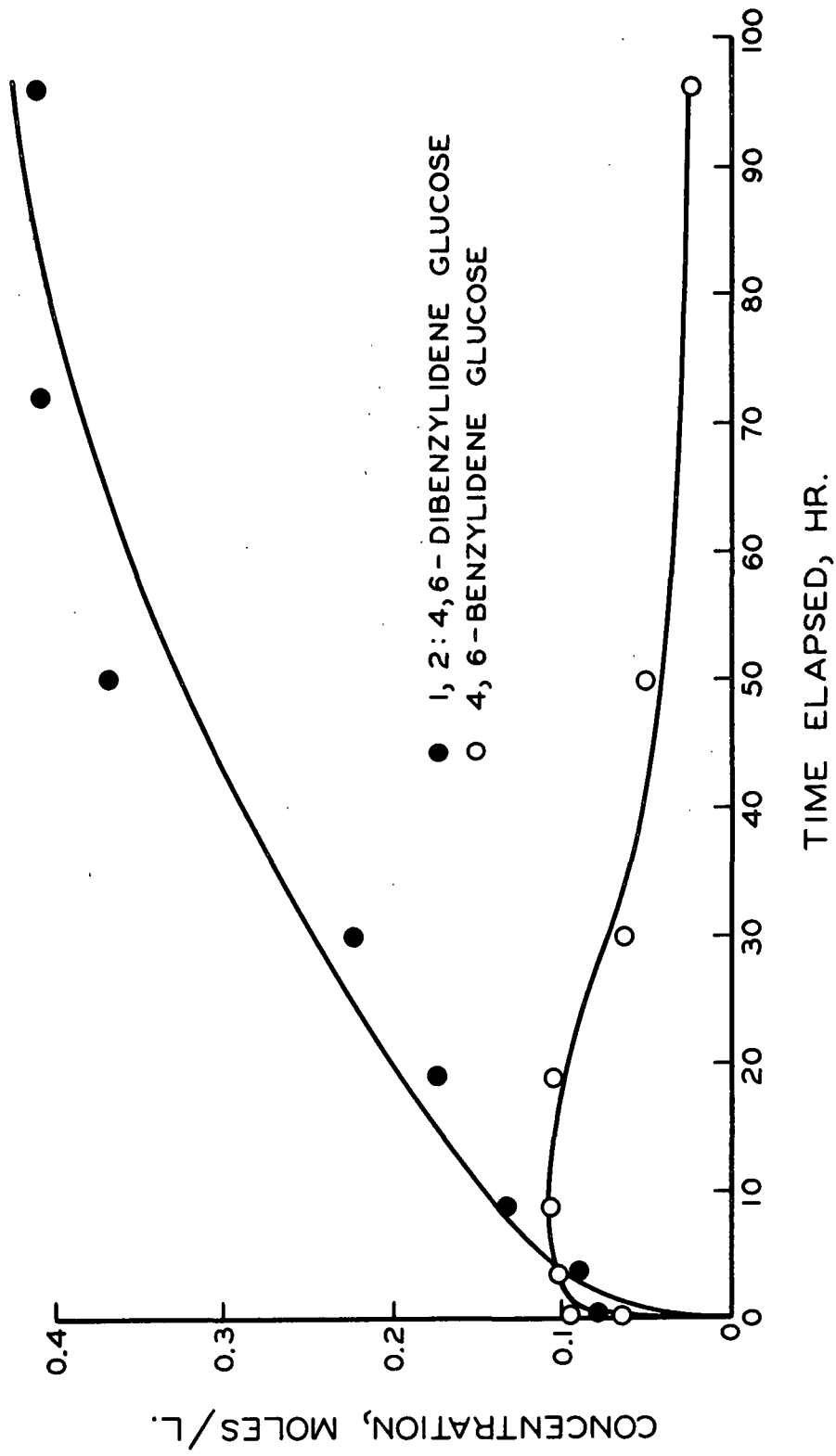


Figure 8. Kinetic Study I: 0.408M ZnCl_2 and 0.408M Glucose (30°C.)

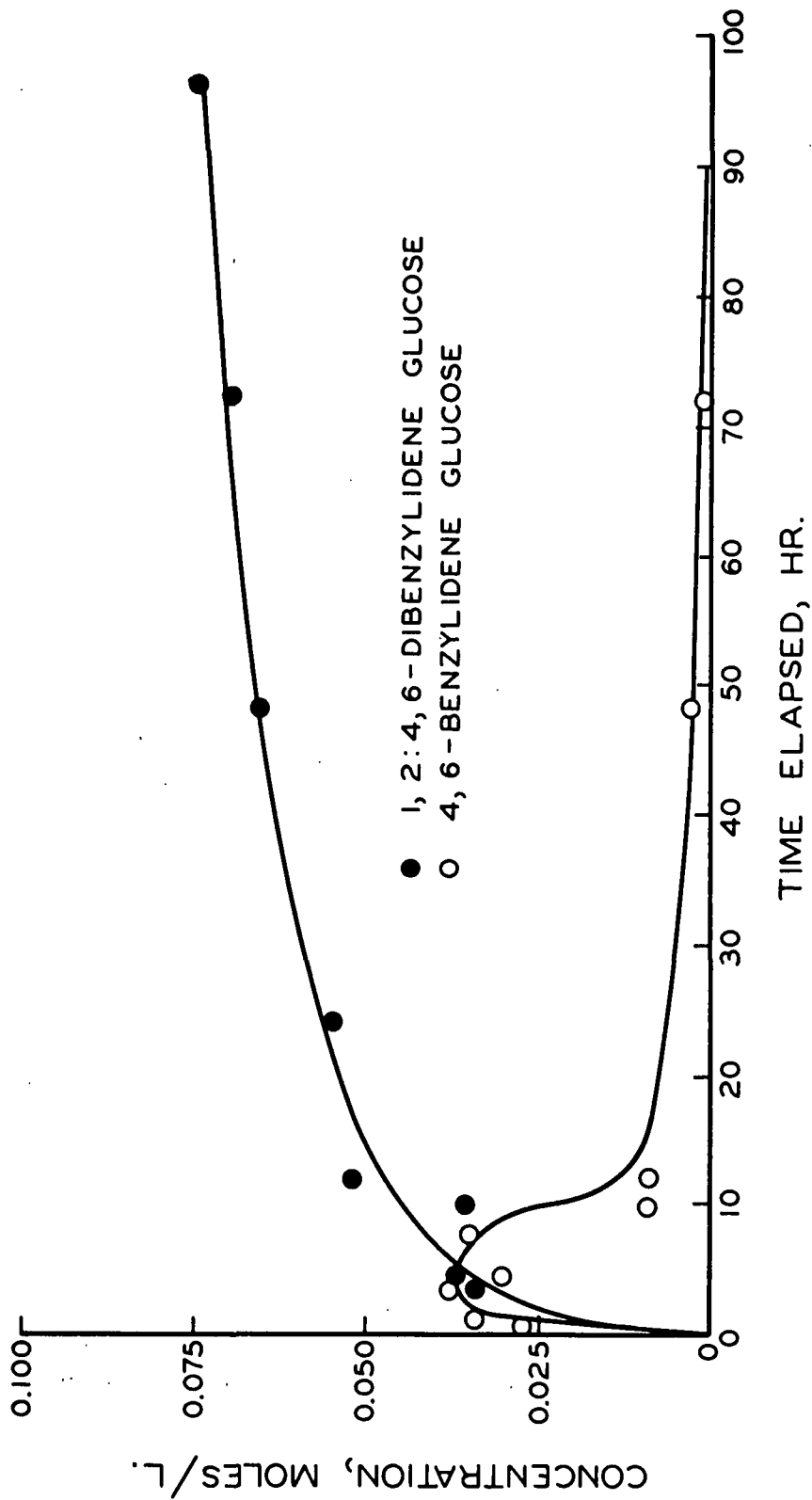


Figure 9. Kinetic Study II: 0.408M $ZnCl_2$ and 0.082M Glucose (30°C.)

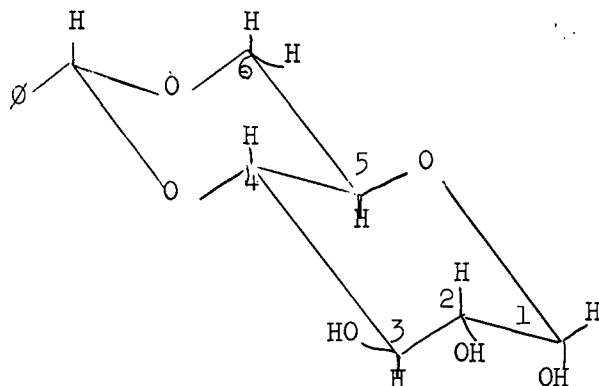


Figure 10. Perspective Formula of 4,6-O-Benzylidene- α -D-glucopyranose

Figure 10 shows that the 4,6-ring does not significantly alter any of the bond angles of the chair-form of glucose and therefore should be easily formed. It also shows that the 1-hydroxyl group is axial whereas the 2-hydroxyl is equatorial. For both of them to participate in the same five-membered ring, they must rotate into approximately the same plane, a less-likely event than the rotation of the glucose primary hydroxyl into a favorable position for formation of the 4,6-ring.

The results of these kinetic studies indicate that the yields of the benzylidene glucoses obtained in the various preparations (8-10) were probably not equilibrium yields. If this is the case, the yields obtained by these procedures would be dependent upon any factor which would influence reaction rates. Such factors might include surface area of the glucose used, temperature, concentrations of the reactants and efficiency of agitation. Failure to closely control these variables may account for the different yields reported.

EQUILIBRIUM STUDIES

It was determined qualitatively that the benzylidenation reactions are reversible. This was demonstrated by the fact that chromatograms of samples taken from a solution prepared to be $0.075M$ in 4,6-benzylidene glucose ($0.4M$ $ZnCl_2$ in benzaldehyde was the solvent) showed spots of glucose (weak), 4,6-benzylidene glucose, and 1,2:4,6-dibenzylidene glucose. Quantitative studies of the equilibrium yields of these compounds afforded the data plotted in Fig. 11. The concentrations of glucose are not plotted here since they fall too close to the base line. The tabulated data for the equilibrium studies are presented in Appendix II. Excess solid glucose was present in all of the solutions. The criterion of equilibrium used was that the analyses of samples of the solutions taken on three successive days had to agree with each other within experimental precision. The first of the three samples was taken from six to ten days after the reaction was started. The individual points on Fig. 11 are averages of from four to six individual determinations. The top line is calculated from the other two lines and represents the concentration of water produced by the reactions. The obvious feature of Fig. 11 is that all three concentrations can be represented as linear functions of the concentration of zinc chloride.

The ensuing discussion will analyze the data of Fig. 11 in light of other observations and information to show that the equilibrium behavior of the system conforms to a system of chemical equations consisting of the benzylidenation reactions and a reaction of

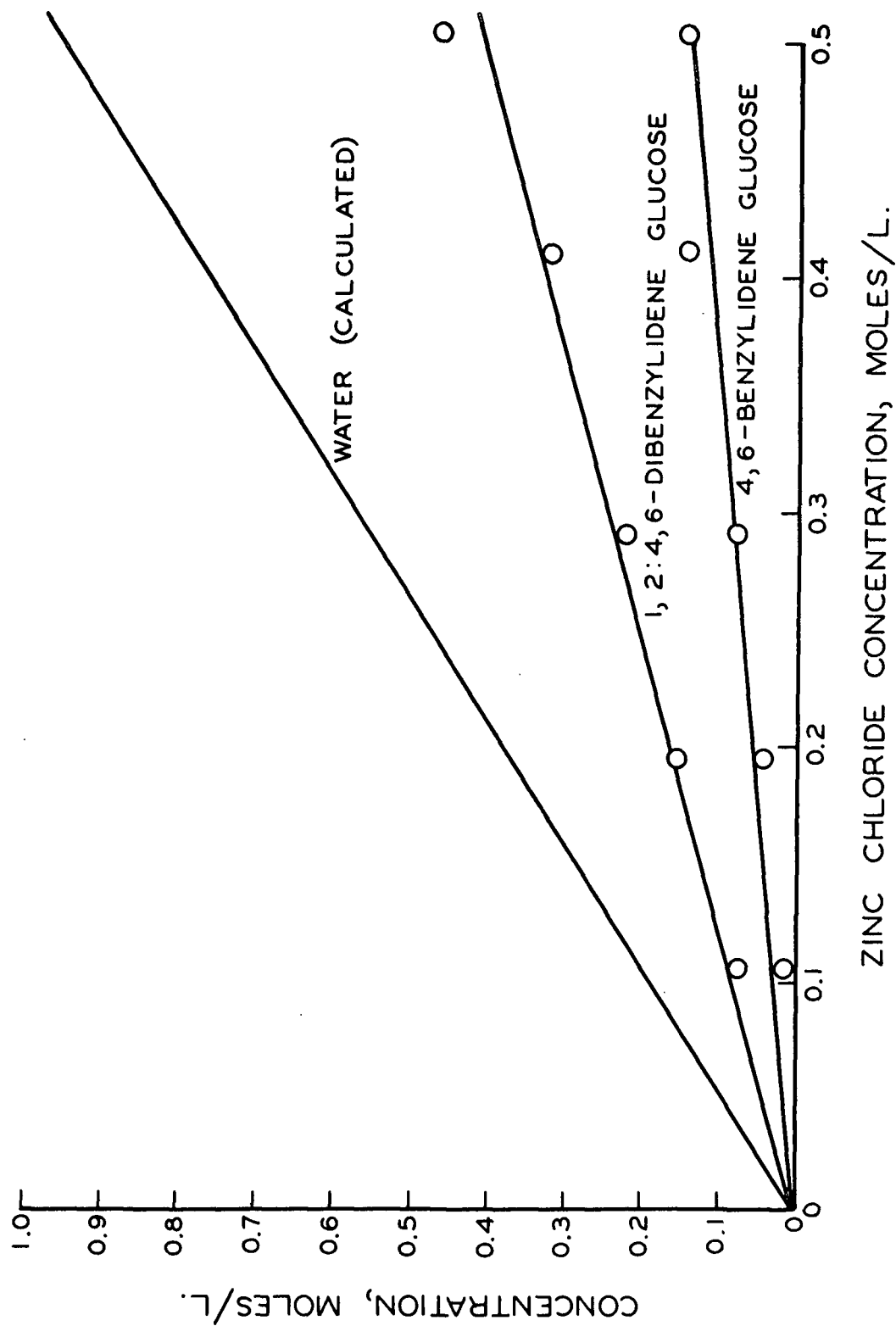
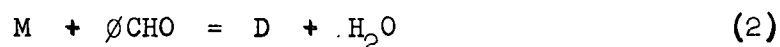
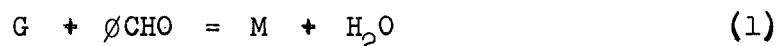


Figure 11. Equilibrium Yields (30°C.)

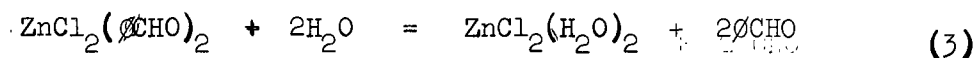
of zinc chloride. The approach which will be taken is to present the equations which appear to represent the reactions in the system and then show how these equations are in accord with the experimental evidence of Fig. 11.

The first requirement of the chemical equations is that they account for all of the species found in the reactions, namely: glucose, (G); 4,6-benzylidene glucose, (M); and 1,2:4,6-dibenzylidene glucose (D). Other requirements are that they be in accord with the findings of the kinetic studies that M and D are produced by separate reactions and that they be reversible. Two such reactions would be:



The symbol $\emptyset\text{CHO}$ is used to signify benzaldehyde. The symbol G denotes only that glucose which is in solution.

Equations (1) and (2) do not take zinc chloride into account. In order to formulate an equation which accounts for the function of zinc chloride it must be recognized that zinc chloride is a Lewis acid and also that the oxygen atoms in carbonyl groups, hydroxyls, water, etc., are potential Lewis bases. It is expected then, that the zinc chloride in the system will tend to be associated with the strongest of the bases present in the system. If it is assumed that water is the strongest base in the system, then Equation (3) can be written for the interaction between ZnCl_2 , H_2O , and $\emptyset\text{CHO}$.



It is supposed that the equilibrium is toward the right.

This equation assumes complexing between zinc chloride and benzaldehyde and also with water. A crystalline complex was isolated from a mixture of zinc chloride and benzaldehyde which had been agitated vigorously. This precipitate contained (on the basis of chloride analysis) one mole of zinc chloride per mole of benzaldehyde. (Calculated: 29.3% Cl; found 30.4% Cl). The infrared spectrum of this material showed no carbonyl absorption, suggesting that complexing takes place through the carbonyl group. When this complex was exposed to the air, it rapidly picked up moisture. The water split up the complex and gave a water solution of zinc chloride and a separate layer of benzaldehyde. This supports the assumption that water is a stronger Lewis base than benzaldehyde and that the equilibrium of Equation (3) is toward the right. At this point in the discussion, the only justification for indicating that two molecules of the bases coordinate with zinc chloride (in solution) is that the usual coordination number of zinc in its complexes is four. More will be said about this point later.

Reactions (1) and (2) have been shown experimentally to occur. Reaction (3) is, at this point in the discussion, no more than a hypothesized interaction. If the assumptions made in formulating Reaction (3) are valid, it should be possible to show that the results of Fig. 11 are in accord with the equilibria of all three reactions. This will now be done.

Assuming that molar concentrations are sufficiently good approximations of the activities, the three equilibrium constants may be expressed as follows:

$$K_1 = \frac{(M)(H_2O)}{(G)(\emptyset CHO)} \quad (4)$$

$$K_2 = \frac{(D)(H_2O)}{(M)(\emptyset CHO)} \quad (5)$$

$$K_3 = \frac{[ZnCl_2(H_2O)_2](\emptyset CHO)^2}{[ZnCl_2(\emptyset CHO)_2](H_2O)^2} \quad (6)$$

The parentheses are used to denote molar concentrations and the species notation is that used previously.

Solving (4) and (5) for (M) and (D),

$$(M) = \frac{K_1(\emptyset CHO)(G)}{(H_2O)} \quad (7)$$

$$(D) = \frac{K_2(\emptyset CHO)(M)}{(H_2O)} \quad (8)$$

The experimental results show (Fig. 11) that (M) and (D) are both linear functions of the zinc chloride concentration. They are, then, linear functions of each other, namely:

$$(D) = (\text{constant})(M) \quad (9)$$

Comparison of (8) with (9) leads to the conclusion that the ratio $(\emptyset CHO)/(H_2O)$ must be constant. This, it will be remembered was deduced from observation and the equilibrium considerations of Reactions

(1) and (2). It will now be shown that the same deduction can be reached using the experimental results and the equilibrium considerations of Reaction (3).

From (6),

$$\frac{(\emptyset\text{CHO})}{(\text{H}_2\text{O})} = \sqrt{\frac{[\text{ZnCl}_2(\emptyset\text{CHO})_2] K_3}{[\text{ZnCl}_2(\text{H}_2\text{O})_2]}} \quad (10)$$

Applying a material balance to the ZnCl_2 -containing species and using the assumption that the equilibrium of Reaction (3) is far to the right.

$$[\text{ZnCl}_2(\text{H}_2\text{O})_2] = Y/2 \quad (11)$$

$$[\text{ZnCl}_2(\emptyset\text{CHO})_2] = Z_0 - Y/2 \quad (12)$$

In Equations (11) and (12), Z_0 is the original concentration of zinc chloride and Y is the concentration of water produced by Reactions (1) and (2).

When Equations (11) and (12) are inserted in (10), the result is

$$\frac{(\emptyset\text{CHO})}{(\text{H}_2\text{O})} = \sqrt{\frac{K_3 (Z_0 - Y/2)}{Y/2}} \quad (13)$$

It can be seen that the right-hand side of (13) will be a constant when Z_0 is equal to a constant times Y , say cY .

then

$$\frac{(\emptyset\text{CHO})}{(\text{H}_2\text{O})} = \sqrt{2K_3 (c - 1/2)} \quad (14)$$

In fact, it was observed (Fig. 11) that \underline{Z}_0 does equal a constant times \underline{Y} . Thus, the same conclusion $[(\text{CHO})/(\text{H}_2\text{O})=\text{constant}]$ has been drawn as previously and Reaction (3) is shown to be in accord with the experimental data.

It is interesting to inquire whether modifications of Reaction (3) would give rise to similar results. It may be shown readily that as long as the coefficients of the water and the benzaldehyde in Reaction (3) are equal, the same conclusion will result. If they are not, it will not. This lends some status to the assumption that the coefficients are both two since the amount of water produced in the reactions is only slightly less than two moles per mole of zinc chloride. At any rate, it makes a coefficient of one impossible and coefficients of three or more are unlikely.

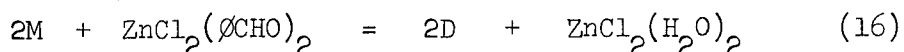
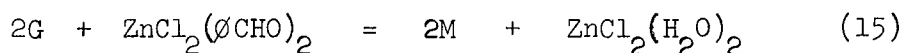
The assumptions made in formulating Reaction (3) were subjected to a further test. It was reasoned that if the assumptions regarding the coefficient of the water in the reaction being two and the state of the equilibrium being far to the right were correct, adding water to a reaction mixture should have the effect of reducing the "apparent" concentration of zinc chloride. That is, under the assumptions, if the original solution were made up to be \underline{Z}_0 molar in zinc chloride and \underline{X} molar in water, the yields of M and D obtained should be those expected from an originally anhydrous solution which was $(\underline{Z}_0 - \underline{X}/2)$ molar in zinc chloride. This was tested by running a reaction which was 0.503M in zinc chloride and 0.568M in water (excess glucose). The results are shown in Table III. The predicted values are from Fig. 11 corresponding

to an "apparent" zinc chloride concentration of 0.219M. It can be seen that the agreement is good, further verifying the assumptions of Reaction (3).

TABLE III
EQUILIBRIUM YIELDS OF BENZYLIDENE GLUCOSES
(WATER ADDED TO SYSTEM)

Compound	Predicted Yield, moles/l.	Experimental Yield, moles/l.
4,6-Benzylidene glucose	0.062	0.063
1,2:4,6-Dibenzylidene glucose	0.185	0.195

It has been established, then, that Equations (1), (2), and (3) can account for the equilibrium behavior of the system. For the purpose of calculating equilibrium constants, it is convenient to combine Equations (1) and (2) with Equation (3) to give Equations (15) and (16).



The corresponding equilibrium constants are:

$$K_{15} = \frac{(M)^2}{(G)^2} \frac{[\text{ZnCl}_2(\text{H}_2\text{O})_2]}{[\text{ZnCl}_2(\text{ØCHO})_2]} \quad (17)$$

$$K_{16} = \frac{(D)^2}{(M)^2} \frac{[\text{ZnCl}_2(\text{H}_2\text{O})_2]}{[\text{ZnCl}_2(\text{ØCHO})_2]} \quad (18)$$

These constants were estimated (see Appendix III) from the data of Fig. 11 and found to be: $K_{15} = 26,000$ and $K_{16} = 206$. The corresponding

free energy changes are: $\Delta F_{-15} = -6200$ cal. and $\Delta F_{-16} = -3200$ cal.

These values are for the reactions as written.

For the purpose of further testing Equations (15) and (16) and the assumptions which they represent, a reaction was run in which 4,6-benzylidene glucose was the reactant. The equilibrium yields were to be used to calculate, from this independent data, the equilibrium constants and free energies of reaction. The reaction consisted of a 0.224M solution of 4,6-benzylidene glucose in 0.503M zinc chloride (benzaldehyde solvent). The equilibrium yields were: (G) = 0.000, (M) = 0.012, and (D) = 0.210. Since glucose was not present in sufficient quantity to be detected, K_{-15} and F_{-15} could not be calculated from these data. The failure to find glucose, however, is in agreement with the fact that K_{-15} is large. Using the previously estimated value of $K_{-15} = 26,000$ with the experimentally determined concentrations of M and D, the concentration of glucose was predicted to be 0.00012M. This concentration would not have been detected chromatographically. The data were used to calculate K_{-16} and F_{-16} : The results were: $K_{-16} = 70$ and $F_{-16} = -2600$ cal. Although these values are lower than the corresponding ones calculated from Fig. 11, they appear to agree within experimental error since the results of the calculations are very sensitive to the experimental concentrations used.

An interesting point about the free energies of reaction is that they differ by about 1600 cal./mole, which is in accordance with the expectation (see "Introduction") that the difference would be less than

the energy of a hydrogen bond (about 5000 cal./mole). The energy of Reaction (15) (formation of a six-membered ring) is larger than that of Reaction (16) (formation of a five-membered ring involving some strain), which was also to be expected.

REACTION MECHANISM

The primary emphasis of this work was placed on studying the equilibria of the system, but some of the evidence may possibly have a bearing on the mechanism involved. This possibility will now be discussed.

Bell and Darwent (17) have shown that the acid-catalyzed hydration of acetaldehyde proceeds through a hydrogen-bonded complex between the carbonyl group and the catalyzing acid. The carbonyl group is thereby polarized, making it more susceptible to nucleophilic attack. Since zinc chloride is a Lewis acid and has been shown in this work to complex with benzaldehyde--probably through the carbonyl group, it would not seem unreasonable that the means by which it catalyzes the reactions is also carbonyl polarization. Something of this nature might also be inferred from the kinetic studies (Fig. 8 and 9) of this work. These studies show that the maximum rate of production of 1,2:4,6-dibenzylidene glucose occurs before the maximum concentration of 4,6-benzylidene glucose has been reached. This would be the expected behavior if a zinc chloride-benzaldehyde complex were involved. The concentration of such a species would be high initially and decrease as the reactions proceeded, thereby producing water which, being

a stronger Lewis base than benzaldehyde, would combine with the zinc chloride, rendering it useless for further polarizing carbonyl groups.

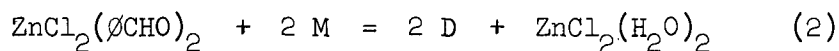
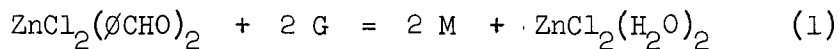
It is felt that more information would be needed before further speculation about reaction mechanisms would be warranted. Such information would necessarily contain more precise kinetic studies, something for which the method of analysis used in this work is not well suited.

SUMMARY AND CONCLUSIONS

A method was devised for analyzing for the sugar and sugar-containing species of the zinc chloride-benzaldehyde-glucose system. It involved a paper chromatographic separation of the various species using a water-saturated isobutanol solvent. Subsequently, glucose was determined using the well-known technique of Somogyi and the benzylidene glucoses were determined using their color reaction with anthrone.

Kinetic studies were made of the reactions in the liquid phase at 30°C. The shapes of the yield vs. time curves led to the conclusion that the reactions producing 4,6-O-benzylidene- α -D-glucopyranose and 1,2:4,6-di-O-benzylidene- α -D-glucopyranose were consecutive.

The equilibrium yields (in the liquid phase at 30°C.) of the two benzylidene glucoses mentioned were studied as functions of the concentration of zinc chloride. It was shown that the data obtained conformed to the following equilibria:



The symbols used are: G = glucose, M = 4,6-O-benzylidene glucose, D = 1,2:4,6-di-O-benzylidene glucose, and ØCHO = benzaldehyde. The formulae $\text{ZnCl}_2(\text{ØCHO})_2$ and $\text{ZnCl}_2(\text{H}_2\text{O})_2$ represent Lewis acid-base adducts. The free energies of reaction at 30°C. were estimated to be:

$\Delta F_1 = -6200$ cal. and $\Delta F_2 = -3200$ cal. It is felt that the difference between these values is largely due to the difference in strain of the six-membered acetal ring of 4,6-O-benzylidene glucose and the five-membered acetal ring of 1,2:4,6-di-O-benzylidene glucose.

Evidence was found which points to the possibility that the mechanism by which zinc chloride catalyzes the benzylidene reactions is through polarization of the carbonyl groups of benzaldehyde. Such a polarization would render the carbonyl group susceptible to nucleophilic attack by glucose hydroxyls. The water which is produced by the reactions, being a stronger Lewis base than benzaldehyde, would then combine with the zinc chloride and render it incapable of further polarization of carbonyl groups. Supporting this view is the fact that a zinc chloride-benzaldehyde complex (complexing taking place through the carbonyl group) was isolated from mixtures of zinc chloride and benzaldehyde. Also, deviations of the results of the kinetic studies from those predicted by consecutive monomolecular reactions can be explained by postulating that a zinc chloride-benzaldehyde complex is a reactant in the rate-controlling step of the production of 1,2:4,6-dibenzylidene glucose.

EXPERIMENTAL PROCEDURES

PREPARATION OF BENZYLIDENE GLUCOSES

Reference samples of pure 4,6-O-benzylidene- α -D-glucopyranose and 1,2:4,6-di-O-benzylidene- α -D-glucopyranose were prepared by the method of Wood, Diehl, and Fletcher (9) as described in the introduction. Table IV gives the comparison of physical constants.

TABLE IV

PHYSICAL CONSTANTS OF BENZYLIDENE GLUCOSES

Compound	$[\alpha]_D^{20}$		m.p., °C.	
	This work	Ref. (9)	This work	Ref. (9)
4,6-Benzylidene glucose	-4.8 ^a	-4.9 ^a	185-187	186-187
1,2:4,6-Di-benzylidene glucose	+113 ^b	+107 ^b	160-162	161-162

^a (Final, methanol, c 2.6)

^b (Pyridine, c 1.47)

Some difficulty was encountered in purifying these compounds to obtain the indicated physical properties. It is not known whether this was due to the presence of stereoisomers, to dimorphism, or to some other cause.

A sample of 1,2-O-benzylidene-D-glucofuranose (m.p. = 175-176°C.) was provided by Dr. J. C. Sowden.

PREPARATION OF ANHYDROUS SOLUTIONS
OF ZINC CHLORIDE IN BENZALDEHYDE

Reagent-grade zinc chloride was fused in a furnace (350°C.) and the melt was poured into a one-liter, ground-glass stoppered bottle which contained about 1/4 pound of glass beads. The bottle and beads had been predried in an oven (90-100°C.) for three or four hours, with the molten zinc chloride being poured in while the bottle was still hot. The bottle was then stoppered with a rubber stopper vented through a calcium chloride drying tube. After stoppering, the bottle was shaken vigorously to break up the solidified zinc chloride. This was continued until the action of the glass beads had ground the zinc chloride to a powder. By this time, the bottle and its contents had cooled to about room temperature, whereupon it was flushed with dry nitrogen and attached to the benzaldehyde distillation apparatus as shown in Fig. 12.

Benzaldehyde was distilled into the zinc chloride-containing bottle in a nitrogen atmosphere. The benzaldehyde which was supplied to the still had been distilled previously from a mixture of benzaldehyde and toluene to remove water. When the receiving bottle was about full it was removed, stoppered and shaken to facilitate the dissolving of the zinc chloride. The resulting stock solution was stored in the dark and opened only in a dry box where the relative humidity was less than 5%. After each opening, the bottle was flushed with dry nitrogen before it was again stoppered.

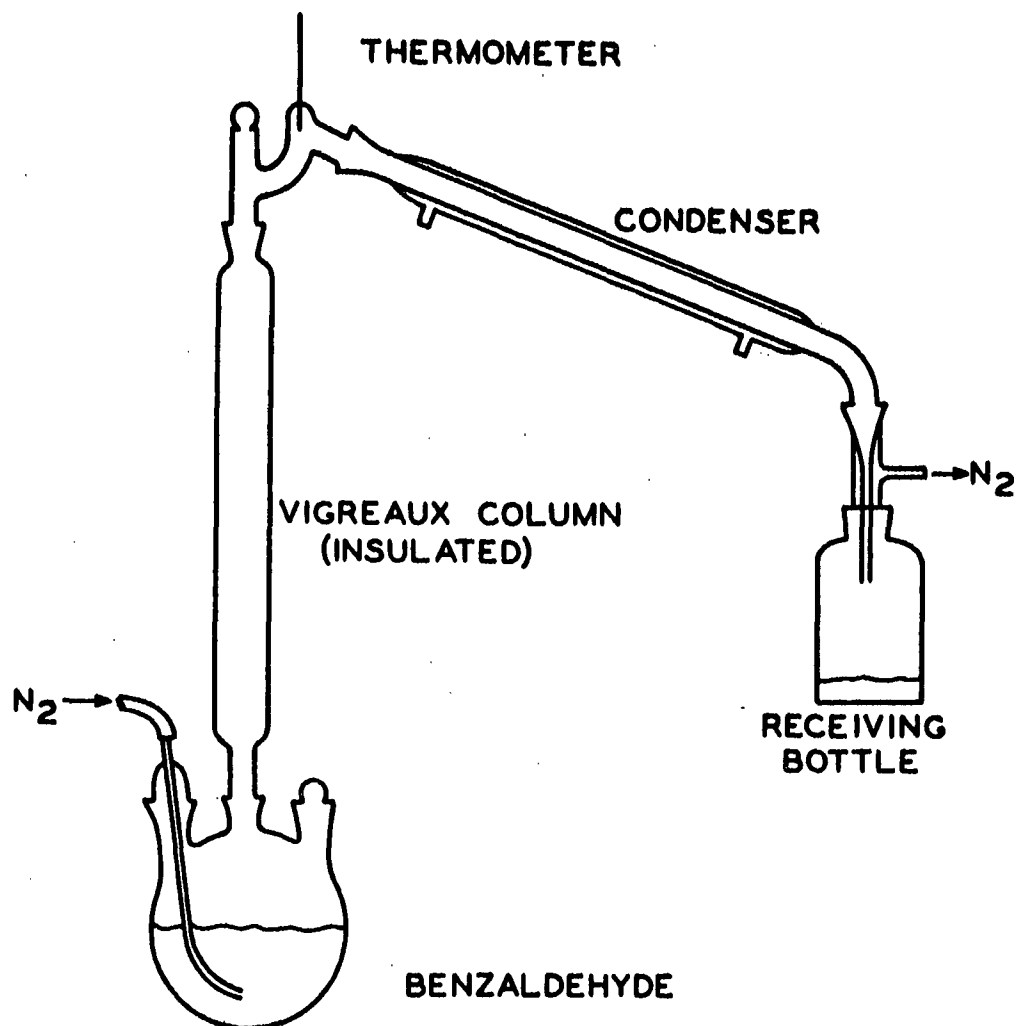


Figure 12. Benzaldehyde Distillation Apparatus

The water content of the solution thus prepared was estimated by toluene distillation and found to be less than 0.03%. The chloride content of the solution (and also those solutions made by dilution of the stock solution with benzaldehyde) was determined by titration in the presence of excess water with 0.1N aqueous silver nitrate. The sodium salt of dichlorofluorescein was used as an adsorption indicator (18).

PROCEDURES FOR CARRYING OUT REACTIONS

The procedures used in both the kinetic and equilibrium studies were essentially the same, the only difference being the times that samples were taken. The solid glucose (or 4,6-benzylidene glucose) was weighed and transferred to the reaction tube. The tube and its solid contents were dried in a vacuum oven ($60^{\circ}\text{C}.$) for about four hours, after which the tube was fitted with its stirrer and nitrogen inlet. The assembly was then clamped in position in the constant temperature bath ($30 \pm 0.2^{\circ}\text{C}.$) as shown in Fig. 13 and allowed to stand for 15 minutes to come to temperature. During this period, the reaction tube was purged with dry nitrogen. The desired volume of zinc chloride solution (in benzaldehyde) was pipetted into the tube, the stopper replaced, and the stirrer turned on.

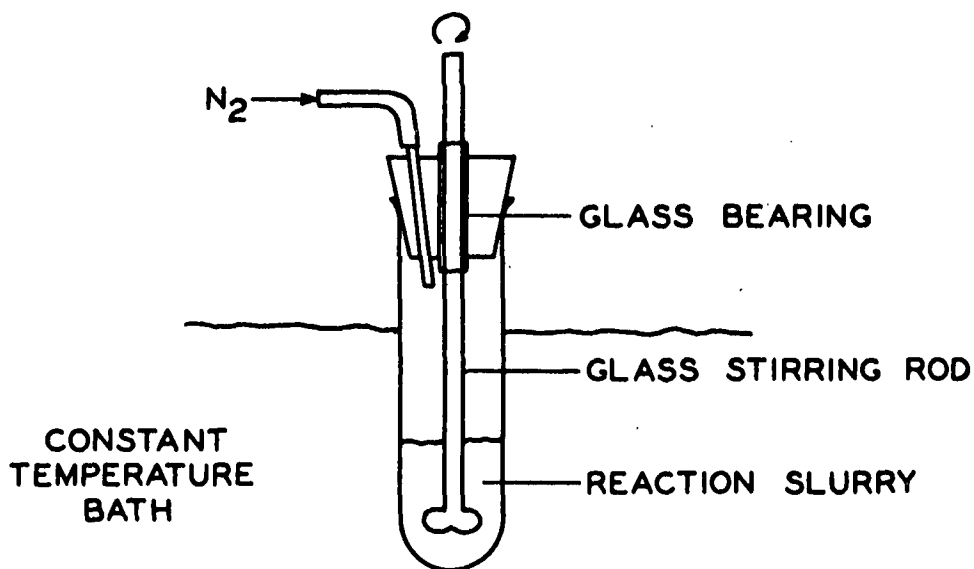


Figure 13. Reaction Apparatus Setup

SAMPLING AND SAMPLE TREATMENT

Samples of about 0.5 ml. were withdrawn from the reaction tubes using long eyedroppers so that entrance of air and water vapor would be minimized. The samples were quickly filtered through Celite to remove the undissolved glucose. The clear supernatant in each case was then spotted on chromatograms for the separation of dissolved glucose, 4,6-benzylidene glucose, and 1,2:4,6-dibenzylidene glucose. (See Fig. 3 for the physical layout of the chromatograms.) Spotting was done with micropipets.

The paper used was Whatman No. 1 chromatographic paper which had been prewashed with methanol. The washing was accomplished by allowing reagent-grade methanol to run down the sheets for 12 to 24 hours, as in ordinary descending chromatography. Each sheet was removed from the washing tank and dried immediately prior to its use.

The spotted chromatograms were developed with water-saturated isobutanol for about 15 hr., after which the sheets were dried and the guide strip was separated from the blank strip and the sample strip. The guide strip was then sprayed with a suitable spray reagent to locate the spots. The p-anisidine spray reagent consisted of 1.0 g. p-anisidine hydrochloride, 10 ml. water, 20 ml. 95% ethanol, 170 ml. butanol, and 10 g. chloroacetic acid--added in that order. The permanganate-periodate spray consisted of four volumes of 2% sodium metaperiodate and one volume of 4% potassium permanganate in 2% sodium carbonate. It was used principally for the detection of 1,2-benzylidene glucose.

The sprayed guide strip was used to locate the spot-containing regions of the sample strip. Once the sample-containing regions were located and cut out, their corresponding areas from the blank strip were also cut out. Care was taken to cut both areas to the same size and shape. In the remainder of this description all corresponding sample and blank tabs were given the same treatment. The ends of the tabs were clamped between glass plates and eluted into elution pipets. A schematic diagram of the elution apparatus is shown in Fig. 14.

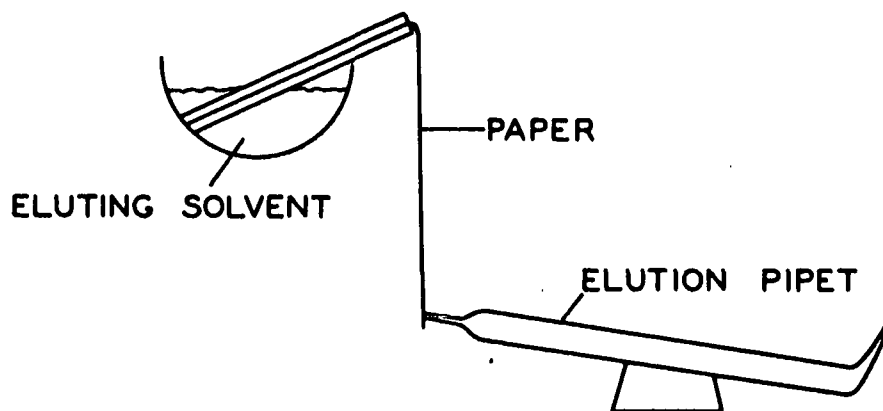


Figure 14. Elution Apparatus

The solvent used for eluting the tabs containing glucose was water and the elution pipets were $3/8$ ml. Methanol was used to elute the benzylidene glucoses and the elution pipets were 1 ml.

No further treatment was given to the eluted glucose samples prior to their determination.

The eluted benzylidene glucose samples were poured into 10-ml. volumetric flasks through the bent end of the elution pipets. Each

pipet was then washed twice with methanol with the washings also being added to the flask. The flask was diluted to the mark and shaken to assure homogeneity before the contents of the flask were poured through a clean glass wool filter to remove any lint. A sample of the filtered solution of suitable size for analysis was then pipetted into an 18 by 150 mm. test tube and subsequently dried under a stream of hot air prior to analysis. The operations of filtering and sampling (pipetting) were done as rapidly as possible to minimize errors due to evaporation of the methanol.

ANALYSIS OF PREPARED SAMPLES

The details of the Somogyi or Forest Products method for determining glucose is well described in reference (13) and will not be dealt with here.

The anthrone determination was carried out as follows: Each sample was redissolved by pipetting 1.0 ml. of methanol into the tube. The tube was tipped and rotated until the sample was completely dissolved. Into this solution was pipetted 10.0 ml. of a solution of anthrone in sulfuric acid. The proportions used in preparing the anthrone solution were: 0.354 g. anthrone (recrystallized from benzene-petroleum ether) in 100 ml. of diluted sulfuric acid (760 ml. reagent H_2SO_4 + 240 ml. distilled water). The anthrone was dissolved in the acid (at room temperature) just prior to use.

After addition of the anthrone solution, each tube was shaken to mix the solutions thoroughly and then placed in a water bath

(90°C.) for 15 min. to develop the characteristic green color. Each tube was removed from the water bath and cooled by plunging it into cold water.

The absorbances at 620 $m\mu$ of the solutions thus prepared were read on a Beckmann Model D.U. spectrophotometer using 1-cm. cells and a slit width of 0.035 mm. All readings were taken within two hours of the development of the color and were compared to a distilled water blank. The difference in absorbance between any given sample and its corresponding blank elution sample was taken as the absorbance due to the sample. It was this difference which was used in conjunction with the calibration curve (Fig. 7) to determine the amount of sample present.

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APPENDIX I

RESULTS OF KINETIC STUDIES

Tables V and VI give the concentrations of the benzylidene glucoses as functions of time. Zero time was marked when the glucose and the zinc chloride solution were mixed together. The initial concentrations for Study I were 0.408M zinc chloride and 0.408M glucose; for Study II, they were 0.408M zinc chloride and 0.082M glucose. The temperature in both cases was 30°C.

TABLE V

DATA FROM KINETIC STUDY I

Time, hr.	4,6-Benzylidene glucose, moles/l.	1,2:4,6-Dibenzylidene glucose, moles/l.
0.25	0.064	0.047
0.5	0.095	0.057
1.0	-	0.081
4.0	0.101	0.090
9.0	0.107	0.133
19.0	0.105	0.175
30.0	0.064	0.223
50.0	0.051	0.368
72.0	0.007	0.408
96.0	0.024	0.411

TABLE VI

DATA FROM KINETIC STUDY II

Time, hr.	4,6-Benzylidene glucose, moles/l.	1,2:4,6-Dibenzylidene glucose, moles/l.
0.5	0.028	0.013
1.0	0.028	0.030
1.0	0.034	0.031
1.5	0.029	0.033
2.0	0.036	0.030
2.5	0.035	0.035
3.5	0.038	0.034
4.5	0.031	0.037
7.5	0.035	0.035
10.0	0.009	0.036
12.0	0.008	0.052
24.0	-	0.055
48.0	0.003	0.066
72.0	0.001	0.070
96.0	0.0	0.075

APPENDIX II

RESULTS OF EQUILIBRIUM STUDIES

Tables VII and VIII give the equilibrium yields of the components at different levels of zinc chloride concentration. Table VII gives the raw data and Table VIII gives the averages which are plotted in Fig. 11, along with the 95% confidence limits. In both tables, the concentrations are in moles/liter.

TABLE VII

DATA FROM EQUILIBRIUM STUDIES

ZnCl ₂	Glucose	4,6-Benzylidene glucose, moles/l.	1,2:4,6-Dibenzylidene glucose, moles/l.
0.106		0.012	0.055
0.106		0.014	-
0.106	0.0007	0.012	0.050
0.106		0.013	0.061
0.106		0.019	0.094
0.106		0.022	0.094
0.194		0.036	0.139
0.194		0.043	0.153
0.194	0.0020	0.045	0.164
0.194		0.040	0.157
0.194		0.041	0.172
0.291		0.076	0.181
0.291		0.081	0.210
0.291	0.0026	0.079	0.219
0.291		0.080	0.247
0.291		0.074	0.255
0.410		0.137	0.254
0.410		0.159	0.317
0.410	0.0011	0.117	0.333
0.410		0.146	0.350
0.410		0.152	0.350
0.503		0.143	0.436
0.503		0.144	0.421
0.503	0.0070	0.138	0.470
0.503		0.143	0.470
0.503		0.150	0.505
0.503		0.158	0.495

TABLE VIII

AVERAGE EQUILIBRIUM CONCENTRATIONS

ZnCl ₂	4,6-Benzylidene glucose, moles/l.	1,2:4,6-Dibenzylidene glucose, moles/l.
0.106	0.015 ± 0.008	0.071 ± 0.043
0.194	0.041 ± 0.009	0.157 ± 0.022
0.291	0.078 ± 0.004	0.222 ± 0.039
0.410	0.142 ± 0.032	0.321 ± 0.077
0.503	0.146 ± 0.018	0.466 ± 0.065

APPENDIX III

CALCULATION OF EQUILIBRIUM CONSTANTS

The equilibrium constants of Reactions (15) and (16) were calculated as follows: The expressions for the equilibrium constants are

$$K_{15} = \frac{(M)^2}{(G)^2} \frac{[ZnCl_2(H_2O)_2]}{[ZnCl_2(\emptyset CHO)_2]} \quad (17)$$

$$K_{16} = \frac{(D)^2}{(M)^2} \frac{[ZnCl_2(H_2O)_2]}{[ZnCl_2(\emptyset CHO)_2]} \quad (18)$$

Using the assumption that the water produced by the reactions (Y) is almost entirely associated with the zinc chloride, (17) and (18) become

$$K_{15} = \frac{(M)^2}{(G)^2} \frac{Y/2}{Z_o - Y/2} \quad (19)$$

$$K_{16} = \frac{(D)^2}{(M)^2} \frac{Y/2}{Z_o - Y/2} \quad (20)$$

As a means of obtaining values of the equilibrium constants which are unaffected by random variations of the individual experimentally determined concentrations, the quantities on the right-hand sides of (19) and (20) were calculated from the straight lines of Fig. 11. The equations of the lines involving the various quantities are:

$$Y = 1.92 Z_o \quad (21)$$

$$M = 0.28 Z_o \quad (22)$$

$$D = 0.82 Z_0 \quad (23)$$

$$G = 0.0085 Z_0 \quad (24)$$

Equation (24) is based on the assumption that the glucose concentration is a linear function of Z_0 . The justification for this assumption is that comparison of Equations (7) and (9), page 26, predicts that it should be. Because of the low concentrations of glucose encountered and the limited sensitivity of the analytical method, this point could not be experimentally proven or disproven. The constant 0.0085 in Equation (24) is the average of the five (G/Z_0) values calculated from the data of Table VII, Appendix II.

The remainder of the calculation consists of substituting Equations (21) through (24) into (19) and (20), cancelling terms and carrying out the multiplications. Doing this,

$$K_{15} = \left(\frac{0.28}{0.0085} \right)^2 \cdot \left(\frac{0.96}{0.04} \right) = 26,000$$

$$K_{16} = \left(\frac{0.02}{0.28} \right)^2 \cdot \left(\frac{0.96}{0.04} \right) = 206$$

The corresponding free energies of reaction were calculated from the relationship $\Delta F = -RT \ln K$. They turned out to be

$$\Delta F_{15} = -6200 \text{ cal.}$$

$$\Delta F_{16} = -3200 \text{ cal.}$$

The equilibrium constants and free energies of reaction thus determined are felt to be valuable principally as order-of-magnitude estimates since the values obtained are sensitive to the slopes used.