231–233°, $[\alpha]^{25}D$ +111°. The identity of the material with the methyl ketoreserpate–sodium methoxide product was demonstrated by mixture melting point determination and by comparison of infrared spectra and paper chromatograms.

Ring Opening of Methyl Ketoreserpate Oxime.—The oxime (1.07 g.) was dissolved in 25 ml. of dry methylene chloride and 0.53 g. of phosphorus pentachloride in the same volume of solvent was added at room temperature. The solution became orange-red and a transient precipitate formed, which however, largely dissolved on standing for 18 hr. The solution was washed with cold 5% sodium carbonate solution, with water and with brine, then dried and evaporated *in vacuo*. The residue was extracted several times with boiling ether. Evaporation of the extracts yielded 0.86 g. of yellow-orange solid, which, by paper chromatographic assay, was 80–90% enol-ether. The product was quite unstable, particularly in polar solvents. Although it could be obtained crystalline from isopropyl alcohol or other alcohols, serious decomposition took place in solution and the crystals were usually obtained with an off-white color. The analytical sample, prepared by recrystallizations from isopropyl alcohol and Darco treatment of ether solutions, melted at about 191–193°, $[\alpha]^{25}D$ −31°. The infrared curve (Nujol) showed a carbonyl band at 1705 cm.,$^{-1}$ a strong absorption at 1645 cm.$^{-1}$ with a shoulder at 1635 cm.$^{-1}$, and nitrile absorption at 2250 cm.$^{-1}$. No absorption in the "3-iso" region was noted below 2850 cm.$^{-1}$ ($CHCl_3$). Further evidence for the β-configuration of the C-3 hydrogen was obtained from the n.m.r. spectrum ($CDCl_3$). The equatorial C_3H signal was observed at 4.31 p.p.m.

Anal. Calcd. for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26; OCH_3, 22.74. Found: C, 67.71, 67.40; H, 6.89, 6.69; N, 10.47; OCH_3, 22.58.

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Study of the Reactions in the Zinc Chloride–Benzaldehyde–Glucose System[1]

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A chromatographic method of analysis was used to study the kinetic and equilibrium properties of the zinc chloride–benzaldehyde–glucose system. 1,2-*O*-Benzylidene-D-glucofuranose was not found to be a product of the system under the conditions employed (liquid phase at 30°). The benzylidenation reactions were found to be consecutive. That is, glucose reacts to give 4,6-*O*-benzylidene-α-D-glucopyranose which then reacts to yield 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose. The equilibrium yields of 4,6-benzylideneglucose and 1,2:4,6-dibenzylideneglucose were both linear functions of the concentration of zinc chloride. This fact is shown to be in accord with the expected behavior of zinc chloride (a Lewis acid) in the presence of benzaldehyde and the water which is produced by the reactions (both Lewis bases). The calculated free energies of the reactions which produce the benzylideneglucoses were used to estimate that the difference in free energy between a five- and a six-membered acetal ring is about 1500 cal./mole.

A method was devised for analyzing for the sugar and sugar-containing species of the zinc chloride–benzaldehyde–glucose system. It involved a chromatographic separation of the various species using a water-saturated isobutyl alcohol solvent and methanol prewashed paper. Subsequently, glucose was determined using the well known technique of Somogyi[2] and the benzylideneglucoses were determined using their color reaction with anthrone.

Studies of the liquid phase of the system at 30 ± 0.2° using the above-mentioned method of analysis indicated that the chemical reactions taking place conformed to the following equilibria:

$$2\,G + ZnCl_2(C_6H_5CHO)_2 \rightleftarrows 2\,M + ZnCl_2(H_2O)_2 \qquad (1)$$

$$2\,M + ZnCl_2(C_6H_5CHO)_2 \rightleftarrows 2\,D + ZnCl_2(H_2O)_2 \qquad (2)$$

where G = glucose; M = 4,6-*O*-benzylidene-α-D-glucopyranose; and D = 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose. The formulas $ZnCl_2\ (C_6H_5CHO)_2$ and $ZnCl_2(H_2O)_2$ were used to represent Lewis acid-base adducts between zinc chloride, benzaldehyde, and water.

Although 1,2-*O*-benzylidene-D-glucofuranose (I) has been prepared using this system,[3] none was found in this work. I, when added to a zinc chloride solution in benzaldehyde is rapidly converted to D. This information, coupled with the known stability of fused five-membered ring acetals such as I toward hydrolysis,[4] leads to the speculation that I, as prepared by Sowden and Kuenne,[3] might have been the product of a mild hydrolysis of D. If so, the hydrolysis would have to be accompanied by a change from the pyranose to the furanose form.

Reported yields of G, M, and D from the system[3,5,6] are variable. The preparations of Sowden and Kuenne,[3] Zervas,[5] and Wood, Diehl, and Fletcher[6] involved reaction times of 20, 24, and 4 hours, respectively. The data presented in Fig. 1 show that, at these times, the system has not yet come to equilibrium. The yields obtained are therefore dependent upon all factors which affect reaction rates in a two-phase system. Some of these are: glucose particle size, temperature, zinc chloride concentration, and efficiency of agitation. Failure to control carefully any such variable would cause different yields. Also, the previously mentioned preparations involved quenching the reactions by adding water. This could possibly give rise to hydrolyzing conditions which would reduce the yields.

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[1] A portion of a thesis submitted in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor o Philosophy from Lawrence College, Appleton, Wis., June, 1962.

[2] M. Somogyi, *J. Biol. Chem.*, **195**, 1923 (1952).

[3] J. C. Sowden and D. J. Kuenne, *J. Am. Chem. Soc.*, **74**, 686 (1952).

[4] J. A. Mills, *Advan. Carbohydrate Chem.*, **10**, 1 (1955).

[5] L. Zervas, *Ber.*, **64B**, 2289 (1931).

[6] H. B. Wood, H. W. Diehl, and H. G. Fletcher *J. Am. Chem. Soc.*, **79**, 1986 (1957).

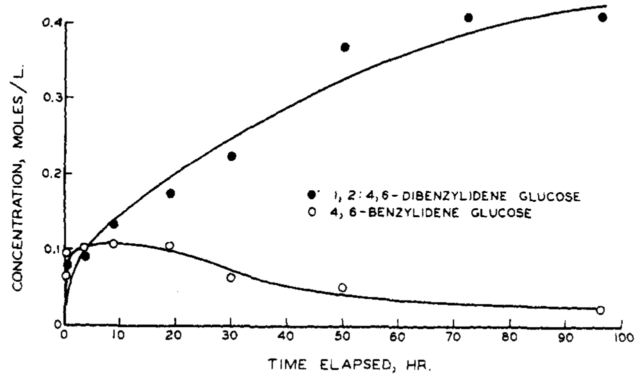

Fig. 1.—Sample kinetic study. 0.408 M $ZnCl_2$ and 0.408 M glucose in benzaldehyde.

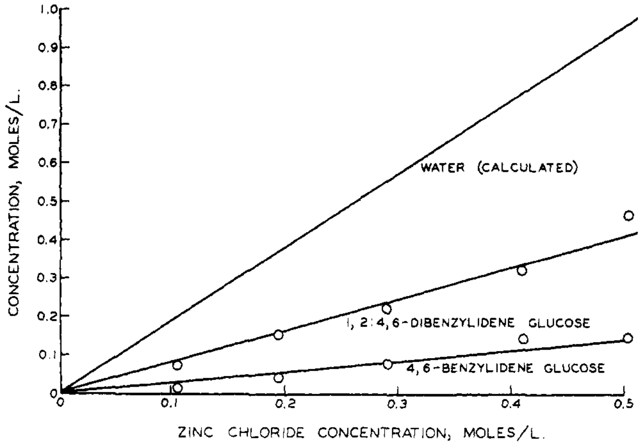

Fig. 2.—Equilibrium yields at 30°.

The shapes of the curves of Fig. 1 indicated that M and D were formed from consecutive reactions.[7] The two reactions may be written:

$$G + C_6H_5CHO \rightleftharpoons M + H_2O \tag{3}$$

$$M + C_6H_5CHO \rightleftharpoons D + H_2O \tag{4}$$

Reactions 3 and 4 do not include zinc chloride, however, and the equilibrium yields of M and D are linearly dependent upon the concentration of zinc chloride as shown by the data presented in Fig. 2. In order to account for this fact, reaction 5 is postulated.

$$ZnCl_2(C_6H_5CHO)_2 + 2\ H_2O \rightleftharpoons ZnCl_2(H_2O)_2 + 2\ C_6H_5CHO \tag{5}$$

Presumed by reaction 5 is complexing between zinc chloride and benzaldehyde and also that water is a sufficiently strong Lewis base to displace benzaldehyde effectively from the complex. The ability of zinc chloride to form a complex with benzaldehyde is shown by the fact that a crystalline complex was isolated which had a 1:1 mole ratio of zinc chloride to benzaldehyde as determined by chloride analysis. The infrared spectrum of this material showed no carbonyl absorption, so complexing presumably takes place through the carbonyl group. The complex is hygroscopic. Water or water vapor reacts with the material to give a water solution of zinc chloride and a separate layer of benzaldehyde. This, it is felt, justifies the assumption regarding the relative basic strengths of benzaldehyde and water.

The stoichiometry of reaction (5) is based upon the assumption that the zinc atom exhibits a co-ordination number of four in solution.[8] Orgel[9] points out that this is not necessarily the case in crystalline complexes. It is felt that the 1:1 complex could still have the co-ordination number of four with each molecular unit consisting of dimers bonded through bridge chlorine atoms. Since the 1:1 complex of benzaldehyde with zinc chloride was isolated, it is expected that the more common two-ligands-per-zinc chloride complex containing benzaldehyde also exists.

Reaction 5 is shown to be in accord with the linear nature of Fig. 2 in the following way: Comparison of the expressions for the equilibrium constants of reactions 3 and 4 and the linearity of the concentrations of M and D *vs.* Z_0 (zinc chloride concentration) leads to the conclusion that the mole ratio of benzaldehyde to water must be a constant. A similar comparison of the expression for the equilibrium constant of reaction (5) and the linearity of the yield of water (calculated from the concentrations of M and D) *vs.* Z_0 leads to the same conclusion if reaction 5 is assumed to proceed far to the right. It is therefore concluded that reactions 3, 4, and 5 comprise an equilibrium system which is in accord with the experimental results. These equations predicted yields of G, M, and D which agreed with the measured values when water was added to the system and also when M was used as the reactant instead of G.

Reactions 3 and 4 are combined with reaction 5 to obtain reactions 1 and 2, from which free energies of reaction were calculated as follows: If it is assumed that the water produced by the reactions is almost entirely associated with zinc chloride, the expressions for the free energy changes (ΔF) become

$$\Delta F_1 = -RT \ln \frac{[M]^2}{[G]^2} \frac{Y/2}{(Z_0 - Y/2)} \tag{6}$$

$$\Delta F_2 = -RT \ln \frac{[D]^2}{[M]^2} \frac{Y/2}{(Z_0 - Y/2)} \tag{7}$$

In equations 6 and 7, R is the gas constant; T is the absolute temperature; $[G]$, $[M]$, and $[D]$ refer to the molar concentrations of the compounds previously indicated; Y is the molar concentration of water produced by the reactions ($[M] + 2[D]$); and Z_0 is the molar concentration of zinc chloride.

The experimentally determined relationships involving the various quantities are

$$[M] = 0.28\ Z_0 \tag{8}$$

$$[D] = 0.82\ Z_0 \tag{9}$$

$$[G] = 0.0085\ Z_0 \tag{10}$$

By substituting equations 8, 9, and 10 into equations 6 and 7, the free energies were found to be $\Delta F_1 = -6200$ cal. and $\Delta F_2 = -3200$ cal.

The difference between these two values (1500 cal./mole) is felt to be due mainly to the difference in strain between the five- and the six-membered acetal rings. The acetal ring of 4,6-benzylideneglucose can assume a relatively unstrained chair form whereas the five-

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[7] S. Glasstone, "Textbook of Physical Chemistry," 2nd ed., Van Nostrand, New York, N. Y., 1946, p. 1077.

[8] J. Bailar, ed., "Chemistry of the Coordination Compounds," Reinhold, New York, N. Y., 1956, p. 372.

[9] L. E. Orgel, *J. Chem. Soc.*, 4186 (1958).

membered ring at the 1 and 2 positions must be nearly planar. Some strain must be introduced to allow the number 1 hydroxyl, which is ordinarily axial, and the number 2 hydroxyl, which is ordinarily equatorial, to be in the same plane. The fact that the difference in free energies is less than the energy associated with hydrogen bonding (about 5000 cal./mole) is in agreement with the contention of Foster, Haines, and Lehmann[10] that the energy of the hydrogen bond is sufficient to alter the usual tendency for six-membered rings to form. They feel that it is the difference between the hydrogen bonding capabilities of the primary and secondary hydroxyl groups of glycerol which causes the predominance of five-membered cyclic acetals prepared from glycerol.[11]

Bell and Darwent[12] showed that the acid-catalyzed hydration of acetaldehyde proceeds through a hydrogen-bonded intermediate between the catalyzing acid and the carbonyl group. The carbonyl group was thus polarized, making it more susceptible to nucleophilic attack at the carbon atom. Since zinc chloride is believed to form a complex with benzaldehyde through the carbonyl group, it is possible to speculate that zinc chloride catalyzes the benzylidenation reaction by polarizing the carbonyl group of benzaldehyde. Since water, a stronger Lewis base than benzaldehyde, is produced by the reactions, it presumably combines with the zinc chloride, rendering it ineffective in further catalyzing the reactions.

The kinetic data are in agreement with such a scheme. If the rate of production of D were proportional to the product of the concentrations of M and a zinc chloride–benzaldehyde complex, the maximum rate would be expected to occur before the maximum concentration of M. The data presented in Fig. 1 show that this is what happens.

Experimental

NOTE ADDED IN PROOF. Professor Bengt Lindberg of the Swedish Forest Products Research Laboratory informs us that the isomeric dibenzylidene derivatives of glucose have nearly identical paper chromatographic R_f values. Our values of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose may therefore be the total of the isomeric dibenzylidene glucoses present. Such a result would in no way negate the stepwise production of 4,6-*O*-benzylidene-α-D-glucopyranose to the di-derivatives nor the general features of the equilibria herein established.

Reagents.—Reagent-grade D-glucose was ground to pass a 170-mesh screen. Zinc chloride was reagent grade. Water was removed by fusing the zinc chloride in a furnace (350°) immediately prior to using. Benzaldehyde (chlorine-free, b.p. 177–179°) was distilled twice from toluene (nitrogen atmosphere) to remove water and oxidation products. 4,6-*O*-Benzylidene-α-D-glucopyranose (m.p. 185–187° and $[\alpha]^{20}\mathrm{D}$ −4.9, final methanol, *c* 2.6) was prepared by the method of Wood, Diehl, and Fletcher.[6] 1,2:4,6-di-*O*-Benzylidene-α-D-glucopyranose (m.p. 160–162° and $[\alpha]^{20}\mathrm{D}$ +113, pyridine, *c* 1.47) was prepared by the method of the same authors. A sample of 1,2-*O*-benzylidene-D-glucofuranose (m.p. 175–176°) for chromatographic comparisons was kindly provided by Dr. J. C. Sowden.

Reaction Mixtures.—All reactions were carried out in a nitrogen atmosphere at 30 ± 0.2°. and were stirred continuously. Extreme care had to be exercised to eliminate or reduce contact of benzaldehyde and zinc chloride with water vapor or oxygen after they had been purified. The procedures for carrying out the kinetic and equilibrium studies were nearly identical. That is, the solid reactant (usually glucose) was measured into the reaction vessel and dried. Then a solution of zinc chloride in benzaldehyde was pipetted in, the vessel purged with nitrogen and the stirrer turned on. Samples were withdrawn with long eyedroppers and then filtered through Celite.

The experimental criterion of equilibrium was that the analyses of samples taken on three consecutive days had to be in agreement with each other. The first of these samples was taken from 7 to 10 days after the reaction was started. The values reported in Fig. 2 are averages of from four to six determinations.

Chromatographic Separation.—The components of the filtered samples of the reaction mixtures were separated on methanol prewashed sheets of Whatman no. 1 chromatographic paper using water-saturated isobutyl alcohol as the developing solvent. The R_f values of the compounds of interest under the conditions used were: glucose, 0.06; 4,6-benzylideneglucose, 0.71; 1,2-benzylideneglucofuranose, 0.80; and 1,2:4,6-dibenzylideneglucose, 0.94. Each sheet was divided into three vertical regions, the sample-containing region, a guide strip, and a blank region. The samples were spotted with micropipets. After developing, the spot locations were determined by spraying the guide strip with *p*-anisidine spray reagent which had been acidified with chloroacetic acid. 1,2-Benzylideneglucofuranose, which did not react with this spray, was detectable with periodate–permanganate spray. Using the guide strip, the sample-containing areas were cut from the sample strip and areas of corresponding size, shape, and position were cut from the blank region. These pairs of tabs were eluted (glucose with water and the benzylideneglucoses with methanol) using the method of Saeman, Moore, Mitchell, and Millet.[13]

Color Reactions.—Glucose was determined using the method of Somogyi.[2,13] Each methanol solution of the benzylideneglucoses (and its corresponding elution blank) was diluted to 10.0 ml. A suitable fraction of this was pipetted into a test tube and dried under a stream of warm air. The dried sample was redissolved in 1.0 ml. of methanol. 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. of anthrone (recrystallized from benzene–petroleum ether) in 100 ml. of diluted sulfuric acid (760 ml. of reagent sulfuric acid + 240 ml. of 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°) 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 mμ of the solutions thus prepared were read on a Beckman DU spectrophotometer using 1-cm. cells and a slit width of 0.035 mm. All readings were taken within 2 hr. 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 was taken as the absorbance due to the benzylideneglucose.

Calibration of the anthrone reaction was made with samples of 4,6-benzylideneglucose, 1,2:4,6-dibenzylideneglucose, and glucose. These compounds all gave the same calibration line (absorbance *vs.* mμ analyzed).

The author is indebted to Mr. A. J. Morak who supplied the necessary solutions and calibration for the Somogyi determination.

It was found that the over-all process of analysis including chromatography was capable of determining the pure benzylideneglucoses within about 0.04 mμ.

Zinc Chloride–Benzaldehyde Complex.—The crystalline complex was prepared by mixing together approximately equal weights of anhydrous zinc chloride and benzaldehyde. After the crystals formed, the liquid phase was filtered off and the crystals were washed extensively with petroleum ether and dried in a stream of dry nitrogen. All operations were carried out in a dry, oxygen-free system. The final product was odorless and hygroscopic. The chlorine content of the solid was determined by weighing samples into water and titrating with silver nitrate. The sodium salt of dichlorofluorescein was used as an adsorption indicator. The theoretical chlorine content of a 1:1 complex is 29.3%. The experimental value was 30.4%.

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[11] S. M. Trister and H. Hibbert, *Can. J. Chem.*, **14B**, 415 (1936).

[12] R. P. Bell and B. de B. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950).

[13] J. F. Saeman, W. E. Moore, R. L. Mitchell, and M. A. Millet, *Tappi*, **37**, 336 (1954).