of both values of K, a considerable variation in the energy of activation is found.

Summary

The velocities of the monobromomalonate–thiosulfate reaction and the monobromosuccinate–thiosulfate reaction have been measured at various concentrations and temperatures. The results cannot be accounted for on the basis of the Brönsted theory, but must be explained by means of the La Mer and Kamner theory of orientation. The values of the energies of activation of these two reactions have been calculated. However, the value for the former reaction is so low that little significance can be attached to it.

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The Constitution of Isosucrose

BY JAMES COLQUHOUN IRVINE AND DONALD ROUTLEDGE

It is now recognized that despite many attempts to control and modify the reaction, the condensation of tetraacetylglucose with tetraacetyl-γ-fructose does not lead to the formation of sucrose octaacetate but gives the corresponding derivative of an isosucrose as the only definite product. Faulty manipulation during the condensation or in the course of isolating the products cannot be held responsible for this result as isosucrose is much less stable to hydrolysis than is sucrose and the capacity of the isosucrose octaacetate to crystallize is no more pronounced than is that of sucrose octaacetate. Several explanations may be put forward to account for the failure of the reaction to yield sucrose and among them must be included the possibility that despite the evidence of methylation the accepted constitution of sucrose is incorrect, but the simplest view is that in the synthesis of isosucrose the fructose component reacts as the β-stereoisomeride in place of the α-form. In such an event, sucrose and isosucrose may be regarded as isomeric disaccharides constituted on the same structural model and differing merely in the configuration of the glucosidic-fructosidic linking. If this view be correct, the hydrolysis of a fully methylated isosucrose should give the same products as are obtained from octamethylsucrose, *viz.*: (a) normal tetramethylglucose and (b) tetramethyl-γ-fructose. This we have ascertained to be the case.

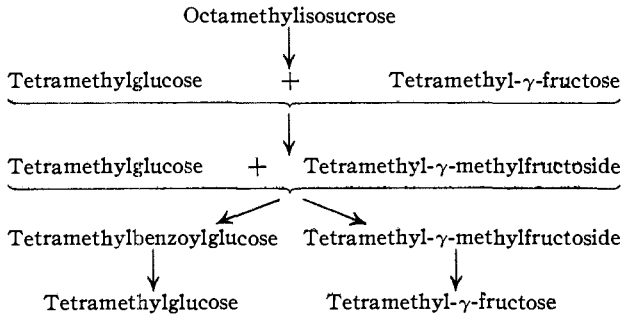
While the reactions involved—methylation, hydrolysis and separation of the scission sugars—are simple in theory, the practical execution is in this instance beset with difficulties. Isosucrose is not readily available in the quantities required, the sugar is much more liable to undergo molecular rupture than is sucrose and the methylation is more tedious. Moreover, when the methylation is conducted by either of the two standard methods, it is arrested sharply at the heptamethyl stage and although as in the case of sucrose itself the hydrolysis of this derivative gives valid evidence of the structure of the parent disaccharide, it was not considered advisable to rely on such a method in the present instance and it became necessary to find a route to octamethylisosucrose.

Our preparations of isosucrose octaacetate have of necessity been carried out on a scale considerably larger than any hitherto attempted. In all, 0.75 kg. of the mixed glucose and fructose tetraacetates was brought into reaction and the fact that no trace of sucrose was found in the product speaks for itself sufficiently. The isosucrose octaacetate was methylated in the first series of experiments by the silver oxide process following the method originally applied by Purdie and Irvine to sucrose.[1] As stated, the methylation could not be extended beyond the heptamethyl stage and the eighth alkyl group could not be introduced. Precisely the same result was obtained when the methyl sulfate method of alkylation was employed either alone or in conjunction with the silver oxide method. This heptamethylisosucrose is not, however, a uniform chemical individual, as hydrolysis revealed that the steric hindrance to methylation was shared to approximately an equal extent by both the glucose and the fructose components. Complete methylation was, however, effected by dissolving the heptamethylate in liquid ammonia and converting it

(1) Purdie and Irvine, *J. Chem. Soc.*, **83**, 1036 (1903).

in this medium into the potassium derivative which was then brought into reaction with methyl iodide. The process worked with the utmost smoothness, giving an excellent yield of the octamethylate and it is significant that attempts to replace liquid ammonia by benzene led to no result.

On hydrolysis, octamethylisosucrose was converted into an equimolecular mixture of tetramethylglucose and tetramethyl-γ-fructose, the separation of which demanded the use of special methods. By condensation with methyl alcohol in the cold only the fructose component of the mixture reacted, being converted into tetramethyl-γ-methylfructoside while the glucose component remained unchanged. In this condition the mixture is still non-separable either by solvents or by distillation but on benzoylation the glucose derivative was converted into tetramethylbenzoylglucose which was isolated through its solubilities as described in the experimental part. The glucose and the fructose derivatives were finally hydrolyzed to give the parent methylated sugars. The various stages of the separation, the validity of which was checked by control experiments, are given herewith.



These final products were identical, respectively, with the tetramethylglucose and the tetramethyl-γ-fructose obtained from sucrose but as the methylated ketose is a sirup it was oxidized, the acid product fully methylated and finally converted into the corresponding amide.[2] Control experiments carried out with authentic tetramethyl-γ-fructose gave identical results and the same final product.

Experimental

Preparation of Isosucrose.—In all, 350 g. of tetraacetyl-γ-fructose were prepared from inulin triacetate by the standard method[3] and the same weight of tetraacetylglucose was obtained from pentaacetylglucose as described by Irvine and Stiller.[4] Two condensations were carried out, in each of which 250 g. of the mixed tetraacetates was dissolved in benzene, dried over sodium, so as to form a 10% solution, and this was shaken continuously for fourteen days with phosphoric anhydride. The dehydrating agent was filtered off and renewed every second day, the residues being washed with benzene. The united washings were worked up in a separate experiment. At the end of a fortnight the solution of the condensation products was exhaustively extracted with water to remove unchanged tetraacetates and the benzene layer, after treatment with sodium sulfate, was taken to dryness, the residue being further dehydrated for one hour at 100° (15 mm.). On cooling, the residual sirup solidified to a glass which, when incorporated with sodium-dried ether, slowly crystallized to give from each experiment 12.5 g. of pure recrystallized isosucrose octaacetate (m. p. 131–132°); in all, 25 g. of the acetate was prepared in this way and an additional 8 g. was also available from other preparations.

Deacetylation and Methylation of Isosucrose.—Two distinct methods were employed.

Method (a).—Seven grams of isosucrose octaacetate dissolved in hot methyl alcohol was decomposed by the addition of 0.5 g. of sodium similarly dissolved. The reaction was violent and the contents of the flask solidified owing to the separation of what appears to be a double compound which was decomposed by neutralizing with acetic acid dissolved in methyl alcohol. The solution thus obtained was mixed with methyl iodide (15 cc.) and silver oxide (10 g.), a little water being added to prevent the separation of isosucrose. Heating was continued on a water-bath for two hours.

The remaining treatment was as described in the case of sucrose by Purdie and Irvine and after six methylations the product was fully soluble in methyl iodide. Accordingly the three final methylations were conducted in the absence of any extraneous solvent. The product was a mobile sirup, weighed 4.1 g., and showed n_D 1.4623.

Anal. Calcd. for $C_{20}H_{38}O_{11}$: OCH_3, 54.6. Calcd. for $C_{19}H_{36}O_{11}$: OCH_3, 49.3. Found: OCH_3, 50.6.

The sirup was acetylated in the usual way and the product then contained 4.9% of acetyl which is equivalent to 3.5% of methoxyl. The above product was deacetylated, the methylated isosucrose recovered and subjected to two further methylations by the silver oxide method; yield, 3.1 g.; found, n_D 1.4618; OCH_3, 49.9. The methylation had accordingly reached its limit, and the product was essentially heptamethylisosucrose.

Method (b).—Twenty-five grams of isosucrose octaacetate was dissolved in 100 cc. of acetone and deacetylated by the cautious addition, with constant stirring, of 15 g. of sodium hydroxide in 30% aqueous solution. The temperature was raised to 30°, and 80 cc. of the same alkali solution added, after which dimethyl sulfate (28 cc.) was introduced drop by drop into the solution with vigorous stirring. In the course of one hour the temperature was raised to 70° and successive additions of sodium hydroxide and dimethyl sulfate in the above proportions were made every ten minutes during this interval. The methylation was completed by heating for one hour at 70° followed by

(2) Haworth, Hirst and Nicholson, *J. Chem. Soc.*, 1513 (1927).
(3) Irvine, Oldham and Skinner, THIS JOURNAL, **51**, 1279 (1929).
(4) Irvine and Stiller, *ibid.*, **54**, 1079 (1932).

one hour at 100°. On cooling, water was added to dissolve the separated sodium methyl sulfate and the liquid was extracted six times with chloroform. The combined extracts, after drying over sodium sulfate, were evaporated under reduced pressure, when 12.5 g. of a fairly mobile sirup remained. This sirup was dissolved in 15 cc. of methyl iodide and heated for six hours with 10 g. of silver oxide, the product being worked up and the treatment being repeated four times. One variation was introduced. After each alkylation, the isolated product was dissolved in chloroform and washed with 1% sodium hydroxide solution in order to remove traces of acid impurity and thereby diminish the risk of hydrolysis. The sirup finally isolated (12.4 g.) consisted essentially of heptamethylisosucrose.

Anal. Calcd. for $C_{19}H_{36}O_{11}$: OCH_3, 49.3. Found: OCH_3, 50.5; $n^{18}D$ 1.4575.

The above values remained unaltered after four additional methylations by the silver oxide method. Before resorting to the use of liquid ammonia as a solvent, an attempt was made to introduce the eighth methoxyl group by refluxing a benzene solution of heptamethylisosucrose with excess of sodium, filtering from unchanged metal and heating the resulting solution with methyl iodide. The product was, however, unchanged in composition and showed the same refractive index.

Methylation of Heptamethylisosucrose in Liquid Ammonia.—As this method is still novel the process is described in detail. Liquid ammonia contained in a large Dewar flask was dried by the addition of metallic sodium until a very faint blue coloration persisted in the solution. By means of a small air pump supplying dry air at low pressure the liquid was forced over into a second Dewar vessel containing 11.3 g. of heptamethylisosucrose. The reaction vessel was then disconnected from the ammonia reservoir and closed with a fitting carrying a mercury-sealed stirrer, a side-limb for the addition of metallic potassium, a quicklime tube to serve as a release for any pressure and a tap funnel for the addition of methyl iodide. One gram of clean dry potassium was added through the side-limb in small pieces, the tube being stoppered between the additions. When all the alkali metal had reacted, as shown by the disappearance of the intense blue color, 4 g. of methyl iodide was added gradually from the tap funnel, the liquid being stirred gently during the reaction. The addition of the methyl iodide occasioned a vigorous ebullition which quickly subsided.

After standing for thirty minutes the contents of the reaction vessel were poured with great caution (the operator wearing a gas mask) into an open beaker, and the liquid was allowed to evaporate in a fume cupboard, it being no longer necessary to adhere to strictly anhydrous conditions at this stage. After all the solvent had evaporated the residue was extracted thoroughly with chloroform and the combined extracts, after treatment with sodium sulfate, were taken to dryness under reduced pressure. The product (10.8 g.) was a clear mobile sirup which was distilled under diminished pressure. The main fraction, b. p. 180–185° (0.3 mm.), weighed 7.8 g.

Anal. Calcd. for $C_{20}H_{38}O_{11}$: C, 52.8; H, 8.37; OCH_3, 54.6. Found: C, 52.6; H, 8.37; OCH_3, 53.9; $n^{18}D$ 1.4588.

Hydrolysis of Octamethylisosucrose.—7.4 grams of octamethylisosucrose was dissolved in 150 cc. of 0.01 *N* hydrochloric acid and the solution was boiled under a reflux condenser, the course of the hydrolysis being followed polarimetrically. After fifteen minutes the specific rotation, which was initially +61.5°, had diminished to +54.8°, and this value remained constant after boiling for an additional period of thirty minutes. The cooled solution was extracted four times with chloroform and the combined extracts, after drying over sodium sulfate, were taken to dryness under diminished pressure, 7.3 g. of a mobile yellow sirup being thus obtained. This consisted of tetramethylglucose and tetramethyl-γ-fructose in equal amounts, which were separated by the reactions described below.

Condensation of the Mixed Sugars with Methyl Alcohol.—In order to convert the tetramethylfructose component into the corresponding fructoside without affecting the tetramethylglucose constituent, the total product obtained as above was dissolved in 73 cc. of cold methyl alcohol containing 1% anhydrous hydrogen chloride. After standing at room temperature in a stoppered vessel for twenty-four hours, the system was rendered neutral to congo red by the addition of barium carbonate and the filtrate was thereafter extracted four times with chloroform, the combined extracts being evaporated under diminished pressure after drying over sodium sulfate. A pale yellow sirup (7.2 g.) consisting of tetramethyl-γ-methylfructoside and tetramethylglucose was thus obtained.

Benzoylation of the Tetramethylglucose Component.—The sirup was dissolved in 2 cc. of pyridine to which 2 cc. of benzoyl chloride had previously been added and after an interval of twenty-four hours the excess of benzoyl chloride was destroyed by the cautious addition of water. The mixture was then thoroughly incorporated with benzene, the benzene solution extracted ten times with water to remove the fructose component which was, in turn, isolated from the aqueous extracts by thorough extraction with chloroform. Each chloroform extract before drying was treated with anhydrous potassium carbonate to remove acidity, and the combined extracts were finally taken to dryness under reduced pressure. In this way 3.5 g. of tetramethyl-γ-methylfructoside was obtained.

The benzene solution, after drying over sodium sulfate and evaporating under diminished pressure, yielded 4.7 g. of a viscous sirup consisting of tetramethylbenzoylglucose.

Isolation and Identification of Tetramethyl-γ-fructose.—The tetramethyl-γ-methylfructoside isolated as above described was hydrolyzed by dissolving in 60 cc. of 0.1 *N* hydrochloric acid and heating in boiling water until the specific rotation which was initially +60° diminished to the constant value +33°, a change which required treatment for ninety minutes. The cooled solution was neutralized with pure barium carbonate free from hydroxide and after filtering was extracted four times with chloroform. The extracts were dried and evaporated under diminished pressure, when 3.3 g. of tetramethyl-γ-fructose remained as a colorless mobile sirup. The physical constants of the product agreed in every respect with those of a standard specimen prepared from sucrose and the identity was further confirmed by the method of oxidation followed by amide formation.

Three grams of the tetramethyl-γ-fructose was dissolved in 21 cc. of nitric acid (1.42) in a round-bottomed flask.

The temperature was taken rapidly to 70° when a vigorous reaction ensued and torrents of nitrous fumes were evolved. In the course of one hour the temperature was raised to 92° and maintained at this point for one hundred minutes. The solution was then diluted with twice its volume of water and the flask attached to a continuous distillation apparatus in which 1.5 liters of water was distilled forward in the course of eight hours. The stream of water was then replaced by methyl alcohol and the distillation continued until the whole of the water and the bulk of the nitric acid had been removed. The product on isolation was a sirup which was boiled under reflux for four hours with excess of methyl alcohol so as to complete the esterification and after removal of the solvent 3.4 g. of the corresponding methyl ester remained.

Residual nitric acid was neutralized by the addition of 1 g. of silver oxide, after which the ester was methylated for six hours by heating with 10 g. of silver oxide and 10 cc. of methyl iodide. The methylated ester (3.1 g.) was a pale yellow sirup which yielded 2.8 g. of pure product on distillation (b. p. 135–137° (0.7 mm.), $n^{17}D$ 1.4478).

For conversion into the corresponding amide the sirup was dissolved in 20 cc. of dry methyl alcohol and dry ammonia was passed through the solution for fifteen minutes. The flask was then firmly stoppered and after forty-eight hours the solvent was removed in a current of dry air. In a few hours the product solidified to a crystalline mass from which, by repeated extraction with petroleum ether, 0.97 g. of the pure amide was obtained melting at 100–101° and giving $[\alpha]D$ in water −75.8° for $c = 1.2$.

In a control series of experiments, 3 g. of tetramethyl-γ-fructose derived from octamethylsucrose gave 2.3 g. of pure methylated ester, 1.1 g. of crude amide and 0.87 g. of the pure compound melting at 100–101°. A mixed melting point of the two specimens of amide gave the same value.

Isolation of Tetramethylglucose.—Control experiments having shown that the benzoyl group is removed almost instantaneously from tetramethylbenzoylglucose by solution in glacial acetic acid containing hydrogen bromide, the following procedure was adopted. The 4.7 g. of tetramethylbenzoylglucose obtained in the course of the present work was dissolved in 38 cc. of glacial acetic acid and mixed with 9 cc. of a saturated solution of hydrogen bromide in glacial acetic acid. After fifteen minutes the reaction product was added to a large excess of water and the opaque solution extracted repeatedly with chloroform. The extracts after drying over sodium sulfate were evaporated under diminished pressure, when 3.4 g. of residue remained. This crystallized immediately and, after four recrystallizations from petroleum ether, 2.5 g. of pure tetramethylglucose was isolated and definitely identified.

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Summary

1. The condensation of tetraacetylglucose and tetraacetyl-γ-fructose has been carried out on a large scale but no trace of sucrose octaacetate has been detected.

2. Isosucrose displays pronounced steric hindrance to methylation. Using the ordinary methods the final product is essentially heptamethylisosucrose which on hydrolysis gives a mixture of methylated hexoses.

3. The methylation can be completed in liquid ammonia and on hydrolyzing the octamethylisosucrose thus obtained tetramethylglucose and tetramethyl-γ-fructose are produced in equal amounts.

4. The results are consistent with the idea that sucrose and isosucrose are similarly constituted and are simple stereoisomerides.

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