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INTRINSIC CHEMISTRY OF FRUCTOSE

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Abstract - Studies on the mutarotation of D-fructose show that whereas the furanose-pyranose transformation is rapid, the furanose-furanose transformation is very rapid. As fructose mutarotation is found to be multiphasic at ambient temperatures, estimates of the tautomer distribution and the specific rotation of the furanose forms, by application of the unimolecular equation to optical data, are in error. Calculations from fructose tautomer shifts with temperature, and also determinations made from the invertase hydrolysis of methyl β-D-fructofuranoside indicate that the specific rotation of β-D-fructofuranose is +78° and that for α-D-fructofuranose is -120°. The "rules" of rotation and of anomeric specification do not therefore apply to the fructofuranoses.

The saporous unit responsible for the sweet taste of β-D-fructopyranose has been indentified as a tripartite grouping involving the anomeric hydroxyl group, the oxygen atom of the primary alcohol group and the ring methylene carbon atom. These represent, respectively, an appropriate proton donor (AH), and a proton acceptor (B) for an intermolecular hydrogen bonding system and also a hydrophobic bonding site (δ). In the β-D-fructopyranose structure they possess the proper steric disposition to elicit sweet taste. The tasteless furanose forms of fructose do not have the required steric relation between these functional groups.

INTRODUCTION

Although D-fructose is a naturally occurring and an abundant representative of the so-called simple sugars, the intrinsic chemistry of this ketohexose is not well understood. One of the reasons for this fact is that investigators are restricted in their studies by having only one of the four possible ring tautomers available in crystalline form. A second reason is the seemingly ambiguous nature of the data encountered when an attempt is made to characterize the mutarotational behavior of the sugar. As measured by changing optical rotation, the sugar displays first-order (unimolecular) reaction kinetics indicating that only two forms are present in measurable concentration at equilibrium in water. However, other methods such as gas-liquid chromatography (g.l.c.) and nuclear magnetic resonance (n.m.r.) techniques can detect three or more tautomers. In addition, the position of the equilibrium varies greatly with temperature, the polarity of the solvent, and the sugar concentration.

At equilibrium in water at ambient temperatures, it has been deduced that the β-D-pyranose tautomer is the most abundant fructose form. The second most abundant form seems to be β-D-fructofuranose. The latter ring isomer is known to constitute, through glycosidic union with α-D-glucopyranose, the structure of sucrose. However, even so valuable a piece of information as the specific rotation of free β-D-fructofuranose is not known with any degree of certainty and one purpose of this paper will be the derivation of a probable value, with comments on its validity and significance.

Not unrelated to the mutarotational behavior and the structure of the fructose tautomers is the fact that fructose is quite sweet in its taste and that its sweetness varies greatly. Just why this is so leads to an important deduction about at least one of its biologically active structures.

THE ANAMOLOUS MUTAROTATION OF D-FRUCTOSE

By comparing the rapid fructose mutarotation with the complex mutarotation of selected aldoses, and by virtue of sucrose hydrolysis studies, Isbell and Pigman (1) deduced that fructose mutarotation is primarily a pyranose-furanose transformation. Moreover, as measured by changing optical rotation the mutarotation of β-D-fructopyranose at 0° is obviously unimolecular (Fig. 1). Therefore, the two-component equilibrium expression A ⇄ B satisfactorily characterizes the data obtained.

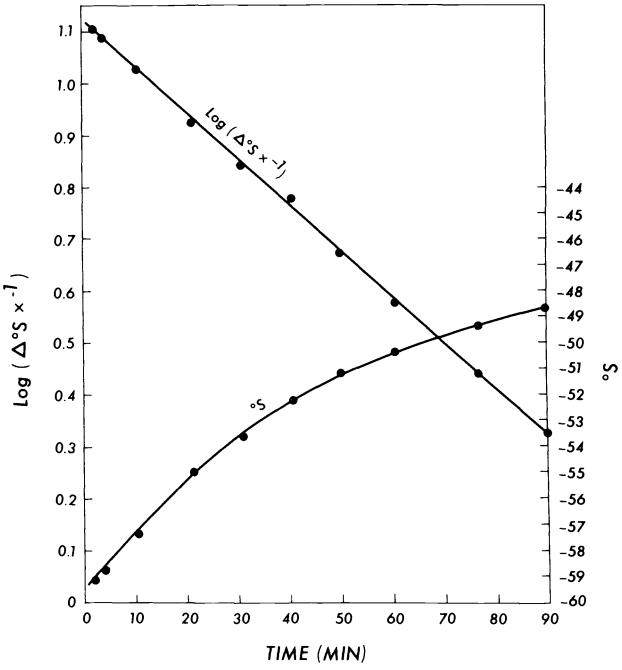


Fig. 1. Unimolecular mutarotation of β-D-fructopyranose at 0°. Data taken from Ref. 1.

Calculations from the first-order equation, using velocity constants established (1,2) that the specific rotation of β-D-fructopyranose is -132.9° at 0°; at 20° it is -132.2°.

It has been suspected (3-5) for some time, however, that fructose mutarotation is quite complex and that for certain calculations, the first-order equation is not applicable. For example, Nelson and Beegle (4) found that whereas the specific rotation of β-D-fructopyranose (-130.8°) is independent of temperature over the range 0.15°-37°, the equilibrium rotation value was not independent of temperature. Thus, the fact that equilibrium fructose exhibits thermal mutarotation (1) can be taken as strong evidence to indicate that fructose mutarotation is complex. Consequently, first-order estimates of the proportion of isomers present at equilibrium and especially the specific rotation of those isomers would be in error.

Nevertheless, by application of the first-order kinetic equation, it has been calculated (6) that an aqueous solution of fructose at equilibrium at 25° contains 31.56% of β-D-fructofuranose and 68.44% of β-D-fructopyranose and that the specific rotation of the β-D-furanose isomer is -4.58°. This percentage distribution of the pyranose and furanose forms and the specific rotation assigned to β-D-fructofuranose seems to be generally accepted for both pedagogical (7) and technological (8) purposes. However, yeast fermentation specificity studies (9) suggest that the furanose equilibrium concentration is only ~ 22%, and the fact that previous estimates of the specific rotation of β-D-fructofuranose show no agreement whatsoever cannot be ignored.

THE COMPLEX (MULTIPHASIC) NATURE OF FRUCTOSE MUTAROTATION

With the advent of g.l.c. and n.m.r. techniques, it has become apparent that aqueous solutions of fructose contain more than two fructose tautomers in measurable concentration (10-13). In theory (2) those isomers possible and their structure are shown in Fig. 2.

As detected by n.m.r. techniques (11-13), aqueous solutions of D-fructose at equilibrium contain β-D-fructopyranose, β-D-fructofuranose, α-D-fructofuranose and a trace only of α-D-

fructopyranose. Angyal and Bethell (13) found that the % β-D-furanose varied from 21% at 27° to 33% at 85° and that the ratio of α-furanose to β-furanose also varied from 0.19 to 0.33. In solvents of lower polarity, measurable amounts of the α-pyranose, and even the keto form can be detected. For example, in solution in pyridine the equilibrium position is 46% β-D-pyranose, 7% α-D-pyranose, 30% β-D-furanose, 12% α-D-furanose and 5% keto structure (14).

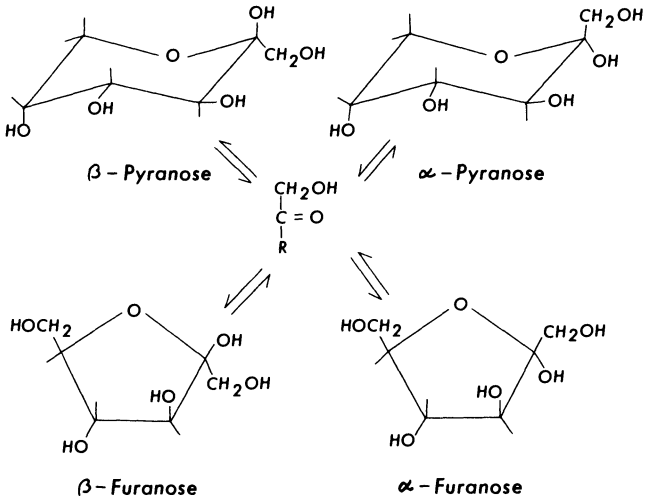


Fig. 2. Structure of the fructose tautomers possible in solution.

Using g.l.c. techniques we have also been aware, as have others (10) that three tautomers of D-fructose can be detected in aqueous solution. Before studying the fructose mutarotation with this technique, however, experience was gained by monitoring the mutarotations of solutions of glucose, mannose, and galactose in water (15,16) using the procedure of Bentley and Botlock (17). The reason for these studies was to determine whether or not the trimethylsilylation procedure might alter the mutarotation position. Because of the excellent agreement found between kinetic and thermodynamic information calculated either from optical rotatory or g.l.c. data, it was concluded that the silylation procedure did not alter the proportions of the sugar tautomers during mutarotation, and it might then also be applicable to the study of a ketohexose.

The course of the β-D-fructopyranose mutarotation as followed by transposition of individual fructose tautomers as indicated by g.l.c. with time, is shown in Fig. 3. Although the distribution of the isomers at equilibrium (76.4%, 19.5%, and 4.1%) suggested that the compound in second-most abundance is β-D-fructofuranose, we turned to the trick of rapidly hydrolyzing sucrose with invertase as an aid in confirming its identity. The data obtained are shown in Fig. 4.

It seemed to us at the time that the tautomer capable of being extrapolated to 100 mole percent at zero time would conclusively establish the identity of the g.l.c. β-D-fructofuranose signal. However, this rationale would only be true if the rate of furanose-furanose interconversion is not instantaneous. If the latter is the case, then there was a good chance of transposing the identity of the two furanose forms. As can be seen in Fig. 4, an unambiguous decision cannot be made as to whether the tautomer labeled β-furanose or the tautomer labeled α-furanose is initially liberated from sucrose, or if indeed the furanose assignments are not transposed. For these reasons these data have not heretofore been published.

Since it is now known, by virtue of ^{13}C- n.m.r. spectroscopy (11-13) that the third most abundant compound found in mutarotated aqueous solutions is α-D-fructofuranose, the assignments shown in Figs. 3 and 4 are believed to be correct. To the generalization (1), therefore, that a pyranose-pyranose mutarotational transformation is relatively slow and a pyranose-furanose transformation is rapid, it can be added, that a furanose-furanose transformation is very rapid. This is one of the reasons for the observation that fructose exhibits unimolecular mutarotation kinetics when the reaction is followed by optical rotatory change, but not when monitored by other techniques.

With this knowledge at hand efforts were directed to the determination of the specific rotation of the two D-fructofuranose anomers.

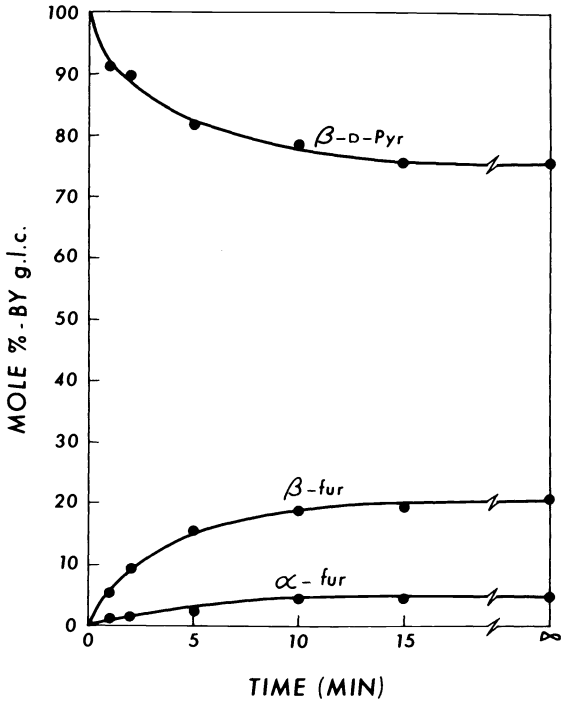


Fig. 3. Mutarotation at 20° of β-D-fructopyranose as monitored by determination of individual D-fructose tautomers.

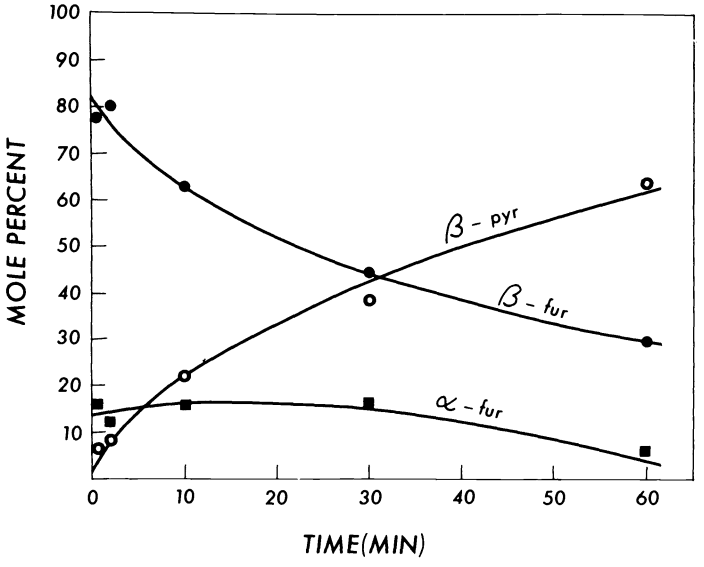


Fig. 4. Mutarotation at 4° of β-D-fructofuranose liberated from sucrose by invertase hydrolysis.

SPECIFIC ROTATION OF β-D- and α-D-FRUCTOFURANOSE

Attempts by investigators to derive the probable specific rotation of β-D-fructofuranose and the method used are summarized in Table 1.

TABLE 1. Observations on values applicable to the probable specific rotation of β-D-fructofuranose

Investigator (s)	$[\alpha]_D$	Method
Hudson (18)	-77°	Calculated by analogy with the rotations of the arabinoses.
Hudson (19)	+17°	Calculated from the structure of sucrose.
Haworth and Law (3)	(highly +)	Hydrolysis of octamethyl sucrose.
Hudson and Yanovsky (20)	-21°	Sugar solubility studies.
Bailey and Hopkins (5)	+15 to +17°	Invertase hydrolysis of sucrose.
Levi and Purves (21)	(+45°?)	Invertase hydrolysis of methyl β-D-fructofuranoside.
Andersen and Degn (6)	-4.58°	Invertase hydrolysis of sucrose.
Shallenberger et al. (23)	+64°	Statistical calculation from fructose thermal-shift data.
Cleland (24)	+78°	Algebraic calculation from the data in Ref. 23.

The initial report of -77° for the specific rotation of β-D-fructofuranose by Hudson (18) is based upon the application of his rules of rotation in an attempt to derive the probable specific rotation of the "α-form" of D-fructose. Since it was derived by analogy with the known specific rotations of the two arabino(pyran)oses, which are, of course, aldoses, this value can at best only be a crude approximation of the specific rotation of that compound now known as α-D-fructopyranose. The second value offered by Hudson later in the same year (19) was calculated from the known structure and specific rotation (+66°) of sucrose and also from the known specific rotation of α-D-glucose (+109°) as follows:

$$(109°)\ (0.525) + (x)\ (0.525) = +66°;\ x = +17°$$

The justification for the calculation is now known to be inapplicable.

In their studies of octamethyl sucrose, Haworth and Law (3) observed that upon acid hydrolysis, the specific rotation rose initially from +66.7° to +75-78°. Such a high value could not be due solely to tetramethyl α-D-glucose and the authors conclude that the results are due to a fructose constituent in a highly dextrarotatory form.

Several years after the initial estimates, Hudson and Yanovsky (20) reported the value -21° for the "α-form" of fructose based upon the difference observed between the rotatory power of fructose in aqueous solution versus solutions in alcohol. This value seems to now apply to an unknown furanose anomeric ratio.

Utilizing the thesis that the transformation of the fructose liberated from sucrose by rapid invertase hydrolysis to equilibrium fructose is unimolecular, Bailey and Hopkins (5) calculated the specific rotation of (2,5)-fructose to be +15° to +17° at 17°. Yet, for reasons not given, these authors considered the values obtained to apply to a mixture of unknown position for the two possible furanose forms. Using essentially the same method and the tenet that the fructose mutarotation consists of one and only one reaction (i.e., it is unimolecular) Andersen and Degn (6) derived the often cited and utilized value of -4.58° for the specific rotation of β-D-fructofuranose.

The value (+45°) shown in Table 1 is deduced by the present writer from the Levi and Purves (21) calculations as applied to data originally published by Purves and Hudson (22). The latter investigators had monitored the change in optical rotation that occurred when a mixture of methyl D-fructosides is treated with yeast invertase. They also determined the generation of free fructose during the course of the reaction. The change in the specific rotation of the fructose liberated during the course of the hydrolysis as calculated by Levi and Purves (21) is shown in Fig. 5.
Knowing that invertase acts only upon methyl β-D-fructofuranoside the authors state that Curve III of Fig. 5 clearly corresponds to that of an initial form (of free fructose) much more dextrarotatory than -51°, the specific rotation of the parent methyl glycoside. Because of the complex shape of the curve, however, and also because of the very large accumulated error in the calculation of the initial rotations, Levi and Purves did not

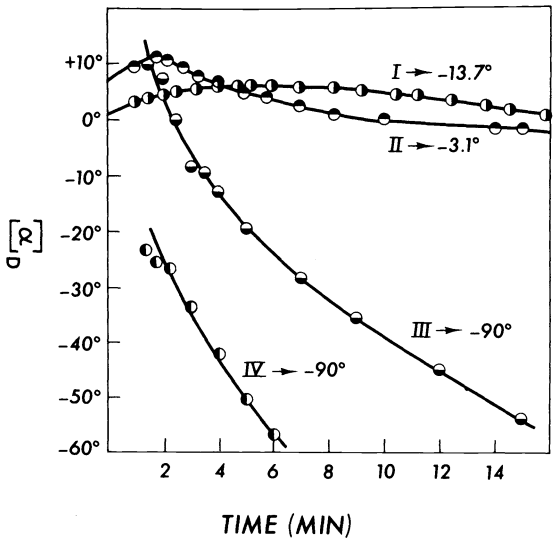


Fig. 5. Change in the specific rotation of D-fructose (III) liberated from methyl β-D-fructofuranoside by the action of invertase. Data of Levi and Purves (21). Reproduced by permission of Academic Press, Inc.

attempt an extrapolation of their data to zero time. Since after an elapsed time of two minutes which is an eternity at the initial stages of fructose mutarotation, the calculated specific rotation for β-D-fructofuranose is +10°, the present writer did attempt the extrapolation and found the value of ~ +45°.

Recently, we determined the probable specific rotation of β-D-fructofuranose (23) by a procedure designed to circumvent the problems now known to be inherent in conventional time-monitored fructose mutarotation studies. The procedure employed was to estimate by g.l.c., the shift in the tautomer composition of equilibrium fructose at different temperatures and to correlate the shift with the specific rotation of the solutions at the different temperatures. The results obtained are shown in Fig. 6.

A second reason for the "anomalous mutarotation" of fructose is evident in Fig. 6. At <10°, the mutarotation may very well seem to be unimolecular, since the α-furanose isomer is not present at equilibrium.

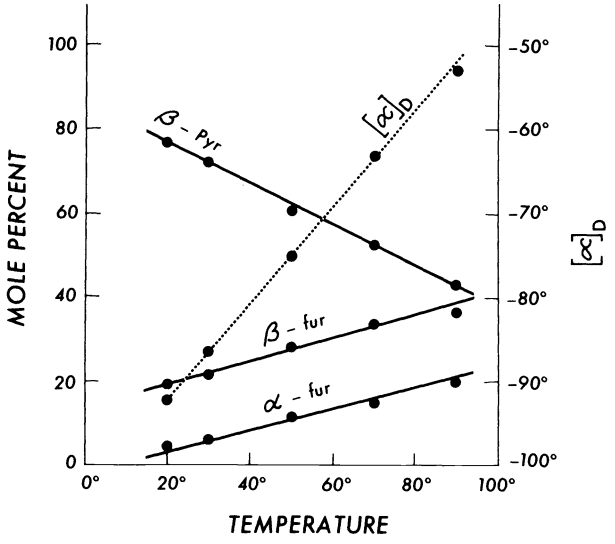


Fig. 6. The mole percent of D-fructose tautomers at equilibrium in aqueous solution at different temperatures, and also the D-fructose specific rotation at those temperatures. From Ref. 23. Reproduced by permission of Elsevier Scientific Publishing Co., Amsterdam.

The linear regression equations for the plots shown in Fig. 6 are:

$$\% \beta\text{-pyranose} = -0.48t + 86.72$$
$$\% \beta\text{-furanose} = 0.26t + 14.32$$
$$\% \alpha\text{-furanose} = 0.23t - 0.55$$
$$[\alpha]_D^t = 0.56t - 102.6$$

It is possible to calculate the probable specific rotation of α-D- and β-D-fructofuranose from these data in several different ways. We (23) chose to solve statistically the simultaneous equation

$$(M_{\beta\text{-p}})\ ([\alpha]_{D,\beta\text{-p}}) + (M_{\beta\text{-f}})\ ([\alpha]_{D,\beta\text{-f}}) + (M_{\alpha\text{-f}})\ ([\alpha]_{D,\alpha\text{-f}}) = [\alpha]_D$$

where M is mole percent, by computer solution of ten possible sets of data containing three unknown values (the specific rotation of each of the three tautomers). The statistical procedure used was "Gaussian elimination".

The results obtained for the specific rotations are as follows:

β-D-fructopyranose, -131° ± 11°
β-D-fructofuranose, + 64° ± 64°
α-D-fructofuranose, -106° ± 92°

As the value obtained for β-D-fructopyranose is so near to the accepted value for the specific rotation of this compound (either -130.8° or -132.2°) it was reasoned that the values obtained for the two furanoses were accurate to within at least 10%. The high deviation found is due to the fact that the equations for the generation of the furanoses with increasing temperature are nearly colinear (parallel). Therefore, the simultaneous equation to be solved was nearly inconsistent. This fact, coupled with the experimental variation obtained, led to several "absurd" solutions for certain sets of the data. These were nevertheless used in calculating both the mean values and the deviations.

A second method for calculating the probable specific rotation for the fructofuranoses from the data shown in Fig. 6 was suggested by Professor W. W. Cleland (24). It utilizes the fitted regression equations for the plots shown in Fig. 6 and results in an algebraic solution as follows.

When the equation for specific rotation as a function of temperature is set equal to the sum of the products of the specific rotations of the tautomers and the mole fractions (as a function of temperature) for the corresponding tautomers, two equations are obtained from the temperature dependent, and the temperature independent terms in which the unknowns are the three specific rotations. Then, if a value for the specific rotation of β-D-fructopyranose is adopted, there are two equations in two unknowns and a unique solution for the specific rotations of the two furanoses can be obtained. The value for β-D-fructofuranose is more sensitive to the temperature independent terms, and that for the α-D-fructofuranose is more sensitive to the temperature dependent terms. Graphical representation of values calculated for the specific rotations of the furanoses by this method is shown in Fig. 7.

Fig. 7 illustrates that the calculated specific rotations of the furanoses depend upon the value that is adopted for the specific rotation of β-D-fructopyranose. For example, with the value for the specific rotation of the β-pyranose tautomer set at -131°, those obtained for the β- and α-furanoses are +70° and -106°, respectively. When the value for the pyranose tautomer is set at -132°, the corresponding values for the furanoses are +78° and -124°, respectively. Nevertheless, the values obtained with the β-fructopyranose tautomer set at -131° are in fair agreement with those calculated from the data by statistical solution of the simultaneous equation containing three unknown values. The high positive values obtained for the specific rotation of β-D-fructofuranose, and by the same token, the high negative values obtained for α-D-fructofuranose are surprising. Whereas the numerical values are of the magnitude to be expected by analogy to the known (22) specific rotations of the methyl D-fructofuranosides, the signs of the rotations are just the opposite of those to be expected either from Hudson's rules of rotation or from the rotations of the methyl fructosides. Consequently, we attempted confirmation by direct determination of the probable specific rotation of β-D-fructofuranose using the enzyme hydrolysis procedure of Purves and Hudson (22) since pure methyl β-D-fructofuranoside can now be prepared in quantity for use as the substrate.

INVERTASE HYDROLYSIS OF METHYL β-D-FRUCTOFURANOSIDE

Chromatographically pure methyl β-D-fructofuranoside was prepared according to the method of Horvath and Metzenberg (25) in 5-6 g quantities. Solutions of the fructoside were then hydrolyzed with yeast invertase at pH 4.60 and the course of the changing optical rotation

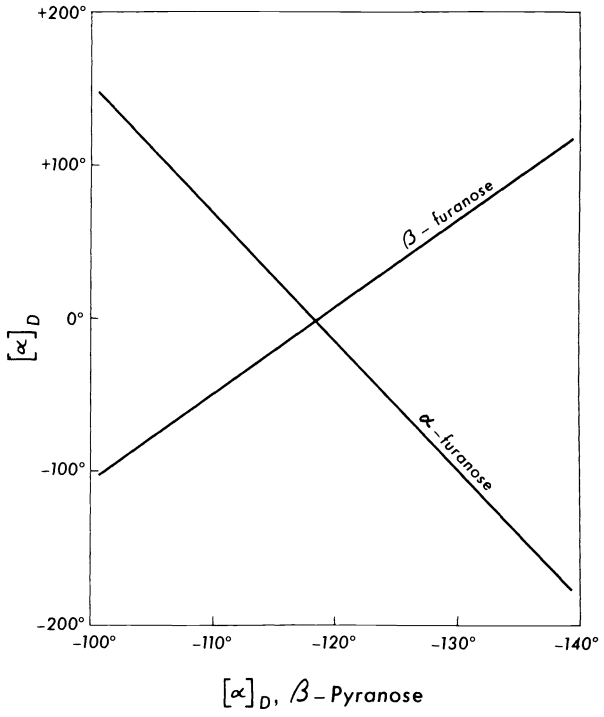


Fig. 7. Dependence of calculated fructofuranose specific rotation on the accepted specific rotation of β-D-fructopyranose.

was followed with an automatic (Rudolph) polarimeter. The generation of free fructose during the course of the reaction was monitored by Nelson's method (26). The actual change in the observed rotation of the hydrolysis-mutarotation reaction is shown in Fig. 8. This curve agrees well with the curve predicted by Schulbach and Rauschalles (27) and obtained by Purves and Hudson (22).

The calculated specific rotation of the mutarotating fructose generated by the action of the invertase is shown in Fig. 9, and a semilogarithmic plot of the equilibrium kinetics for the mutarotating fructose is shown in Fig. 10. The data clearly show two phases for the mutarotation of β-D-fructofuranose. An initial very rapid phase (I) not heretofore recorded is assigned to furanose-furanose transformation. The slower phase (II) is assigned to furanose-pyranose transformation. At equilibrium, the fructose solution has $[\ ]_D^{23}$ -91.3°. Extrapolation of the data for phase I to zero time leads to an intercept of 2.23°. Therefore, a direct estimate of the specific rotation of the fructofuranose liberated from methyl β-D-fructofuranoside by the action of invertase is

(Antilog 2.23°) + (-91.3°) = +78.5°

This value is in excellent agreement with that previously calculated from the thermal mutarotation data and which, in turn, was based upon the value of -132° for the specific rotation of β-D-fructopyranose. Although the hydrolysis procedure employed for this determination is subject to the same uncertainties described by Levi and Purves (21) the agreement between the value for β-D-fructofuranose obtained with that from thermal mutarotation data does not seem to be fortuitous. Thus, possible reasons for the high positive value for the specific rotation of β-D-fructofuranose such as epimerization or transglyosylation by the enzyme can be discounted.

FRUCTOSE SWEETNESS

Sweetness is also an intrinsic chemical property of fructose. Moreover, it is the sweetest of the naturally occurring sugars. Its sweetness is also the most variable of that encountered among the naturally occurring sugars, and this variation is directly related to mutarotational behavior. Thus, freshly prepared solutions of crystalline fructose are almost twice as sweet as sucrose, but when mutarotation is complete, fructose solutions are only slightly sweeter than those of sucrose. Moreover, when the temperature of equilibrium fructose is increased, the sweetness markedly decreases (28,29).

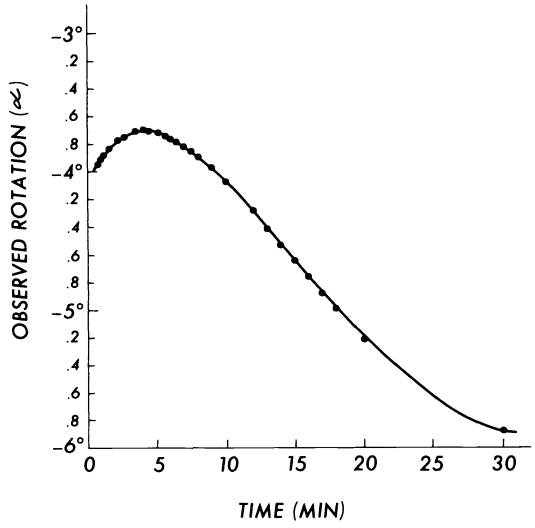


Fig. 8. Change in the optical rotation with time due to the action of invertase on methyl β-D-fructofuranoside and the subsequent mutarotation of the liberated fructose.

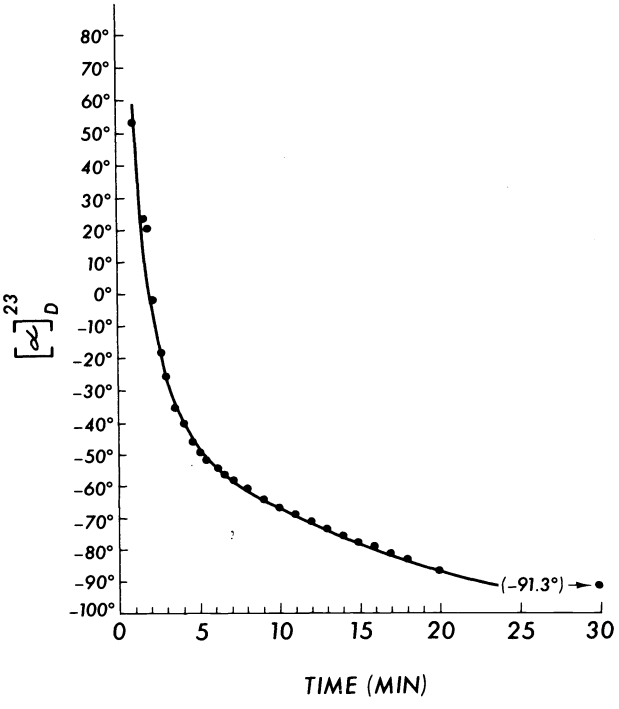


Fig. 9. Change in the specific rotation, with time, of fructose generated from methyl β-D-fructofuranoside by the action of invertase.

Based upon the correlation between fructose sweetness as related to its mutarotational behavior, it was deduced that the fructofuranoses were nearly void of sweet taste. The structure of the fructofuranoses, therefore, served as a model in the development of a general theory of sweetness (30). In that theory it was pointed out that the saporous unit common to all compounds that taste sweet was an AH,B system as usually used to define and describe the hydrogen bond. In addition, it was decided that the initial chemistry of sweet taste must, therefore, be a concerted intermolecular hydrogen bonding phenomenon between AH,B of the sweet compound and a sterically commensurate AH,B unit at the receptor site.

The specific role played by the fructofuranoses was the disposition (conformation) of the vicinal hydroxyl groups on the furan ring. Since the synperiplanar or antiperiplanar

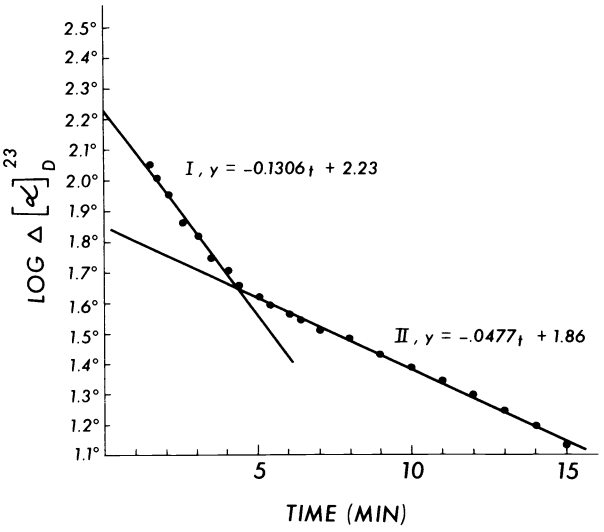


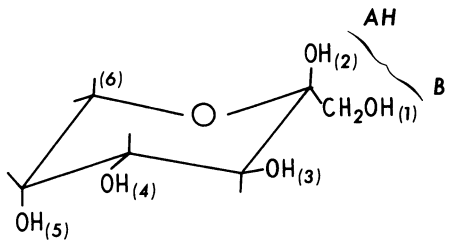
Fig. 10. Biphasic equilibrium kinetic plot of the mutarotation of fructose released from methyl β-D-fructofuranoside by the action of invertase.

disposition of fructofuranose hydroxyl groups seemed incapable of eliciting sweet taste, this observation assisted in the decision that the AH proton must be ~ 3 Å from an electronegative orbital (B) in the hydrogen bonding system in order for maximum sweetness to occur. Only the synclinal glycol conformation, therefore, seemed capable of eliciting sweet taste in the sugar series. Subsequently, it was found that 5-thio-β-D-fructofuranose is tasteless (31), and the previously mentioned methyl β-D-fructofuranoside is also tasteless and slightly bitter.

THE SWEETNESS FUNCTION IN β-D-FRUCTOPYRANOSE

Although any pair of vicinal hydroxyl groups was initially viewed as constituting a sugar sweet unit, provided the AH,B distance was 3Å (staggered glycol conformation) studies elsewhere, notably those by Birch and others (32-34), indicated that just one pair of vicinal hydroxyl groups is the primary AH,B unit for sweet taste in the sugar series. For D-glucose, they identified HO-4 in the C1 conformation as being the primary AH and O-3 was identified as B.

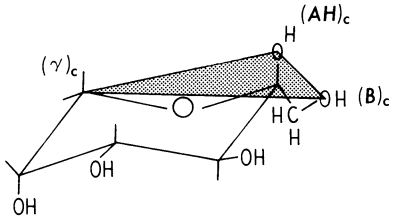
For β-D-fructopyranose, Lindley and Birch (34) identified the anomeric hydroxyl group (HO-2) as AH and O-1 as B. The same assignment was made also by this writer (30) somewhat on an intuitive basis, but the assignment in Ref. 34 was made after careful consideration of the sweetness of pertinent model compounds.



A third component (35) was subsequently identified rendering the saporous sweet unit of the sugars tripartite (36). The third component is essentially a hydrophobic site (γ) and was assigned to the methylene ring carbon (C-6) of the fructopyranose structure. Its role was viewed as being capable of participation in the hydrophobic bond and that such bonding is somehow related to sweetness intensity. AH,B on the other hand was viewed as being a prerequisite for the primary sensory quality of sweetness. A secondary role assigned to the third site, but not restricted to it, is that of lipophilicity. The tripartite saporous unit for β-D-fructopyranose is shown below where the subscript c indicates AH,B and γ respectively, for the structure of the compound.

Interestingly, if the only unambiguous choice for a "γ-function" in the glucopyranose structure is assigned to C-6, then the steric distances and angles for the planar saporous

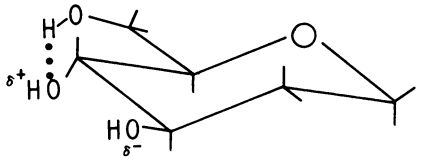
unit for D-glucopyranose are identical to those for β-D-fructopyranose (36). Such relations are described as "multiple group stereogeometry" (37), and introduce, in turn, intriguing chiral problems (38).



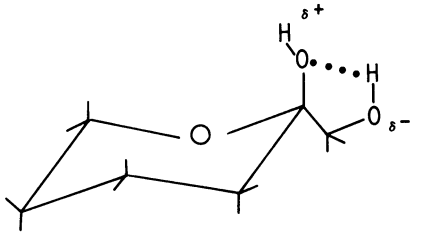
THE LEMIEUX EFFECT

With the identification of the γ site in β-D-fructopyranose, and the identification of the primary saporous unit for fructose as HO-2 and O-1, a serious problem arose. Firstly the B unit of the fructose AH,B system is not fixed in space because the primary alcohol group is capable of free rotation. What force then fixes it at a distance of ~ 3 Å from the proton of HO-2? Secondly, and perhaps more seriously, if the primary AH,B unit for sweet taste in the D-fructose structure is HO-2 and O-1 then why do the fructofuranoses not taste sweet? The original rationalization that their lack of sweet taste is due to the nearly syn- or antiperiplanar disposition of vicinal hydroxyl groups on a furan ring is not now adequate.

However, when we applied the developing principles of hexopyranoid CH_2OH-C-bond rotomer conformations (39) to the sweetness problem (36), an answer seemed to develop. When D-glucose, for example, is placed in a hydrophobic environment, the HO-6 is then disposed to hydrogen bond, intramolecularly to O-4. This increases the proton donating capacity of HO-4 as shown below.



Since HO-4 is also suspected of being the glucopyranose AH function for sweet taste, it seemed to us that this was in a sense confirmation of that specification. Interestingly, this is a case of intramolecular hydrogen bonding promoting sweet taste and the initial chemistry of sweet taste has long been suspected of occurring in a relatively non-polar environment. If HO-1 of β-D-fructopyranose can be expected to behave in the same manner, as HO-6 of glucose, then it would bond either HO-2 or HO-3 and in either case, its position would be fixed in space. An AH,B system with a fixed distance of 3 Å would then result. The bonding to the anomeric hydroxyl group (AH) is shown below.



Without doubt, the fructofuranoses then also possess an AH,B unit since the steric arrangement of HO-1 and HO-2 is not altered in transposing from a six-membered to a five-membered ring. However, the stereogeometry of the AH,B,γ tripartite structure is altered. In addition, the furanose ring can be viewed as a barrier between the usual planar relation between AH,B and γ. It is, perhaps, because of the inadequate fructofuranose tripartite structure that the fructofuranoses are void of sweet taste.

In view of the recent findings on the probable role of one fructofuranose anomer in gluconeogenesis, and of the probable role of the other fructofuranose anomer in glycolysis (40), it is becoming increasingly apparent that the different fructose tautomers have different biochemical roles. It has already been established that yeast ferments preferentially a fructofuranose tautomer and it now seems that only the β-D-pyranose tautomer possesses sweet taste. In addition, evidence has been obtained to explain the varying sweetness of the fructose tautomers.

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