ANOMERIC SPECIFICITY OF ENZYMES OF D-GLUCOSE METABOLISM

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Enzymes:

Aldose 1-epimerase (EC 5.1.3.3); Fructosediphosphatase, D-fructose-1,6-bisphosphate 1-phosphohydrolase (EC 3.1.3.11); Fructosediphosphate aldolase, D-fructose-1,6-bisphosphate D-glyceraldehyde-3-phosphate-lyase (EC 4.1.2.13); Fructose-6-phosphate kinase, ATP:D-fructose-6-phosphate 1-phosphotransferase (EC 2.7.1.11); Galactokinase, ATP:D-galactose 1-phosphotransferase (EC 2.7.1.6); Galactose dehydrogenase, D-galactose: NAD^+ 1-oxidoreductase (EC 1.1.1.48); Glucokinase, ATP: D-glucose 6-phosphotransferase (EC 2.7.1.2); Glucose dehydrogenase, β-D-glucose: $NAD(P)^+$ 1-oxidoreductase (EC 1.1.1.47); Glucose oxidase, β-D-glucose: oxygen oxidoreductase (EC 1.1.3.4); Glucose-6-phosphatase, D-glucose-6-phosphate phosphohydrolase (EC 3.1.3.9); Glucose-6-phosphate dehydrogenase, D-glucose-6-phosphate: $NADP^+$ oxidoreductase (EC 1.1.1.49); Glucose-6-phosphate 1-epimerase, not listed; Glucosephosphate isomerase, D-glucose-6-phosphate ketol-isomerase (EC 5.3.1.9); Hexokinase, ATP:D-hexose 6-phosphotransferase (EC 2.7.1.1); Mannosephosphate isomerase, D-mannose-6-phosphate ketol-isomerase (EC 5.3.1.8); Phosphoglucomutase, α-D-glucose-1,6-bisphosphate: α-D-glucose-1-phosphate phosphotransferase (EC 2.7.5.1); β-Phosphoglucomutase, not listed; Xylose isomerase, D-xylose ketol-isomerase (EC 5.3.1.5).

1. Introduction

In aqueous solution aldo- and ketohexoses and their derivatives exist as equilibrium mixtures of various cyclic configurations like α- and β-pyranoses and α and β-furanoses. The cyclic configurations are equilibrated via the open chain configurations, aldehydes and ketones respectively (for references see [1]). This multiplicity of configurations prompts the question whether the enzymes catalyzing reactions of aldo- and ketohexoses are stereospecific with respect to one configuration or are nonspecific.

A knowledge of the anomeric specificity of enzymes is relevant in structural considerations: in the past ten years the three dimensional structure of a number of enzymes, some of which catalyze reactions of sugars, has been presented [2]. However, the interaction between an enzyme and its substrate can only be understood if the three dimensional structure of the substrate is also known. In the case of sugar substrates, which exist as mixtures of several structures, the determination of the configuration of the substrate that is accepted by the enzyme is necessary in the consideration of the structural relationship between enzyme and substrate.

Also in physiological considerations it is important to know the anomeric specificity of enzymes: if an enzyme specifically catalyzes the reaction of only one anomer of an aldo- or ketohexose, comparison of the metabolic flux with the velocity of the spontaneous anomerization reaction of the substrate enables one to judge whether in vivo the anomeric configurations of the substrate are equilibrated or not. On this basis one can decide whether enzyme-catalyzed anomerization would be necessary or not.

In this review letter our present knowledge of the anomeric specificity of enzymes catalyzing the reactions of D-glucose, D-glucose-6-phosphate, D-fructose-6-phosphate and D-fructose-1,6-diphosphate is summarized. This review does not consider reaction mechanisms of enzymes, a subject that has been excellently reviewed by Rose [3–5].

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Table
Equilibrium compositions of D-glucose, D-glucose-6-phosphate, D-fructose-6-phosphate and D-fructose-1, 6-diphosphate

Compound	Equilibrium composition	Method	References
D-Glucose	36% α- and 64% β-pyranose	Polarimetry, NMR	[1,6]
	0.0026% Free aldehyde	Polarography	[7]
D-Glucose-6-phosphate	37-39% α- and 61-63% β-pyranose	Kinetic measurements	[8–10]
	< 0.4% Free aldehyde	IR	[11]
D-Fructose-6-phosphate	20 ± 4% α- and 80 ± 10% β-furanose	NMR	[12,12a]
	~ 24% α- and ~ 76% β-furanose	Kinetic measurements	[13]
	2.5% Free ketone	IR	[11]
D-Fructose-1,6-diphosphate	~ 10% α- and ~ 90% β-furanose	NMR	[14]
	20 ± 4% α- and 80 ± 10% β-furanose	NMR	[12,12a]
	~ 26% α- and ~ 74% β-furanose	Kinetic measurements	[15]
	< 1.7% Free ketone	IR, NMR	[11,14,16]

2. Equilibrium composition of D-glucose, D-glucose-6-phosphate, D-fructose-6-phosphate and D-fructose-1,6-diphosphate

A knowledge of the equilibrium composition of the respective aldo- and ketohexoses is a prerequisite for the determination of the anomeric specificity of enzymes using these compounds as substrates. In the table above the most reliable data on the equilibrium composition of D-glucose, D-glucose-6-phosphate, D-fructose-6-phosphate and D-fructose-1,6-diphosphate are summarized. These data were obtained by polarimetry, polarography, nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy, as well as by kinetic measurements using a stereospecific reaction.

3. Anomeric specificity of enzymes

3.1 *Principles of determination*

The anomeric specificity of an enzyme is usually determined at high enzyme activity, providing an activity constant of the enzyme reaction which is much higher than the rate constant of the spontaneous anomerization reaction of the sugar. One can perform experiments either starting from the equilibrium mixture of a substrate, the composition of which is known, or starting from the pure anomers of a substrate, respectively generating the anomers in stereospecific reactions. Reactions are followed by polarimetry, nuclear magnetic resonance spectroscopy, rapid quench as well as by spectrophotometry, either directly, in the case of dehydrogenases, or by coupling to appropriate indicator reactions. Both the configuration of the substrate accepted by the enzyme and the configuration of the product released by the enzyme can be determined.

3.2. *Enzymes*

Hexokinase:

Hexokinases from yeast [8,17,18] and from Ehrlich ascites tumor cells [8] nonspecifically catalyze the phosphorylation of both α- and β-D-glucopyranose. However, small differences in the Michaelis constants and maximum velocities were observed [8,17,18]. An examination of the composition of the reaction products of the hexokinase reaction, catalyzed by the enzyme from yeast, yielded the result that starting from the equilibrium mixture of D-glucose (36% α- and 64% β-D-glucopyranose), at saturating concentration of ATP-Mg, α- and β-D-glucopyranose-6-

phosphate are produced in a ratio of 40% α to 60% β [18]. A lack of anomeric specificity was also reported for a preparation of particulate rat brain hexokinase [19], rabbit liver glucokinase [20] and pyrophosphate phosphotransferase from rat liver microsomes [8]; the latter enzyme is probably identical with glucose-6-phosphatase [21,22]. On the other hand it could be shown that galactokinase from yeast specifically uses α-D-galactose as substrate, and α-D-galactose-1-phosphate is the exclusive product of this reaction [23,24].

Dehydrogenases:

All dehydrogenases investigated, glucose dehydrogenase from beef liver [25], glucose oxidase from *Penicillium notatum* [26], glucose-6-phosphate dehydrogenase from yeast [8,9,17,27] and from human erythrocytes [28], were shown to catalyze specifically the oxidation of β-D-glucopyranose and β-D-glucopyranose-6-phosphate, respectively. A similar specificity for the β-anomer of D-galactose was reported for galactose dehydrogenase from *Pseudomonas saccharophila* [29].

It should be mentioned also that in chemical oxidation reactions of aldoses by bromine [30] or hypoiodous acid [31] the β-anomers are generally more reactive.

Phosphoglucomutase:

Earlier work on the anomeric specificity of phosphoglucomutase, involved in glycogen breakdown, was summarized by Najjar [32]. It was shown that α-D-glucose-1-phosphate, which is the product of the reaction catalyzed by glycogen phosphorylase [33], is the specific substrate of phosphoglucomutase from muscle [34], and α-D-glucose-1,6-diphosphate is the active coenzyme [35]. Later, Salas et al. [17] reported that α-D-glucopyranose-6-phosphate is the product of the phosphoglucomutase reaction catalyzed by the muscle enzyme. This was confirmed by Lowry and Passonneau [36].

Besides this type of phosphoglucomutase (α-D-glucose-1,6-diphosphate: α-D-glucose-1-phosphate phosphotransferase) in *Neisseria perflava* [37] and in *Euglena gracilis* [38] there exist phosphoglucomutases which specifically use β-D-glucose-1-phosphate as substrate. These enzymes are involved in maltose and trehalose metabolism, respectively, where β-D-glucose-1-phosphate is produced by maltose phosphorylase [39] and trehalose phosphorylase [40].

Glucosephosphate isomerase and other isomerases:

Following the experiments of Salas et al. [17] and Carlson et al. [41] it could be shown that glucosephosphate isomerase from yeast nonspecifically catalyzes the isomerization of α- and β-D-glucopyranose-6-phosphate to α- and β-D-fructofuranose-6-phosphate [42,43]; however the α-anomers are the preferred substrates [17,42,43]. In addition to the isomerization reaction this enzyme also catalyzes the anomerization reactions of α- to β-D-glucopyranose-6-phosphate [42,43] and α- to β-D-fructofuranose 6-phosphate [43]. Furthermore, it was reported that glucosephosphate isomerase from yeast exhibits anomerase activity towards D-mannose-6-phosphate [44]. Anomerase activity towards D-glucose-6-phosphate could also be demonstrated for glucosephosphate isomerase from rabbit muscle [36], *E.coli, Rhodotorula gracilis*, potato tubers, rat liver, rat kidney and rat muscle [45].

Mannosephosphate isomerase from yeast specifically uses β-D-mannose-6-phosphate as substrate [44]. The anomeric specificity of this enzyme with respect to D-fructose-6-phosphate is not yet known.

D-Xylose isomerase from a *Streptomyces* species, which also catalyzes the isomerization of D-glucose, was shown to be specific for α-D-xylose and α-D-glucose [46,47], and α-D-xylopyranose was reported to be the initial reaction product starting from D-xylulose [46].

Anomerases:

As pointed out above glucosephosphate isomerase catalyzes not only the isomerization of D-glucose-6-phosphate to D-fructose-6-phosphate but as well the anomerization of D-glucose-6-phosphate [17,36, 42,43], D-fructose-6-phosphate [43] and D-mannose-6-phosphate [44].

In addition, in bakers' yeast [10,48] as well as in *E.coli, Rhodotorula gracilis* and potato tubers [45],

enzymes which catalyze the equilibration of the anomeric forms of D-glucose-6-phosphate were discovered. This type of enzyme, called glucose-6-phosphate 1-epimerase, could not be demonstrated to be present in mammalian tissues such as liver, kidney and muscle of the rat [45]. Glucose-6-phosphate 1-epimerase exhibits no or very little activity towards D-glucose [45,48]. The activity constant of purified glucose-6-phosphate 1-epimerase from bakers' yeast towards D-glucose was determined to be 70 000-fold smaller than towards D-glucose-6-phosphate [48].

On the other hand, aldose 1-epimerases (mutarotases) catalyze the anomerization of D-glucose and other aldoses. Aldose 1-epimerases have been shown to occur in *Penicillium notatum* [49,50], *E.coli* [51, 52], higher plants [53] and mammalian tissues [54–61]; some of these enzymes were purified to a high degree.

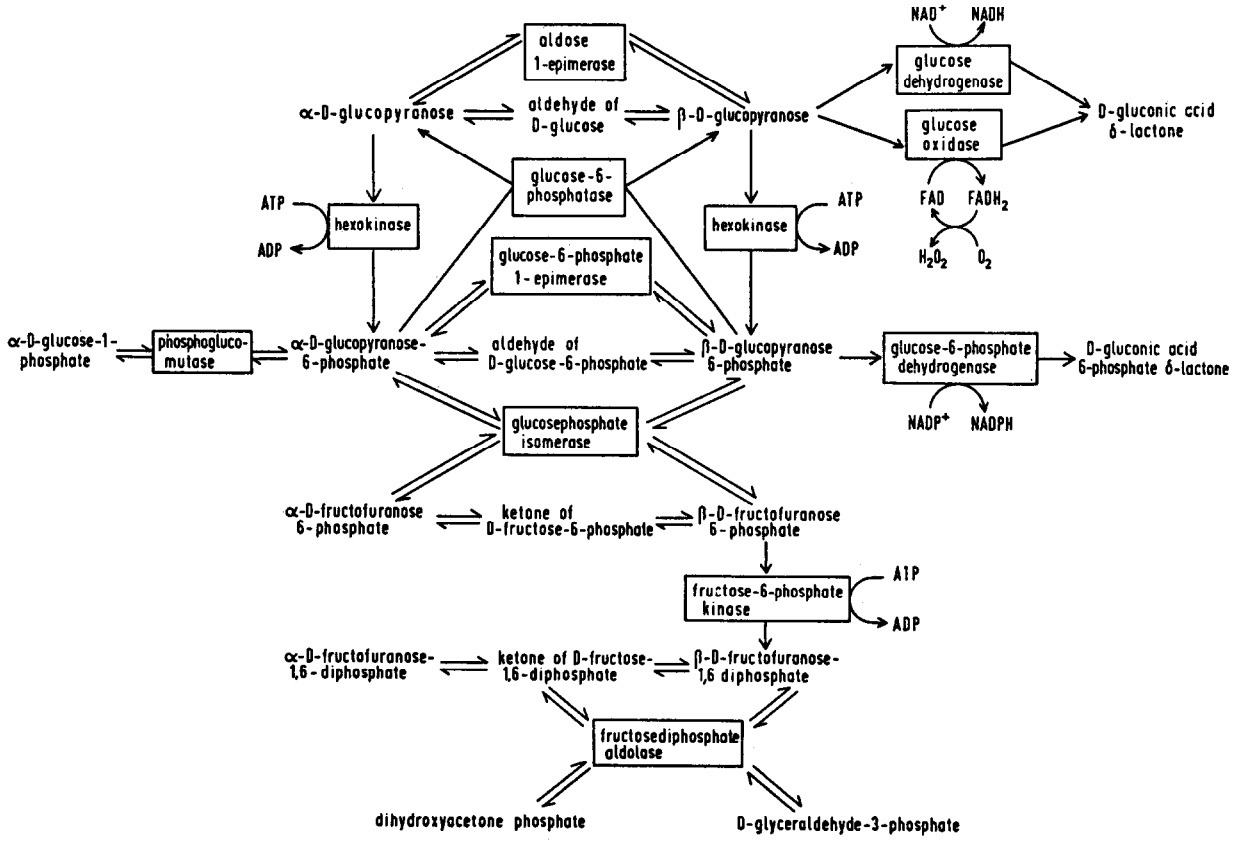
It could be shown that aldose 1-epimerase from beef kidney [8,9] and from *E.coli* [62] does not catalyze the anomerization of D-glucose-6-phosphate.

Fructose-6-phosphate kinase:

Fructose-6-phosphate kinase from rabbit muscle specifically catalyzes the phosphorylation of β-D-fructofuranose-6-phosphate [13], yielding, most probably, β-D-fructofuranose-1,6-diphossphate, as also suggested by independent techniques [13a]. An earlier conclusion that the enzyme from rabbit muscle only uses α-D-fructofuranose-6-phosphate as substrate [63] has been modified by these authors (compare ref. [64] p. 244).

Fructosediphosphate aldolase:

Fructosediphosphate aldolase from rabbit muscle accepts β-D-fructofuranose-1,6-diphosphate but not α-D-fructofuranose-1,6-diphosphate, as substrate [15]. Since fructosediphosphate aldolase cleaves certain ketosephosphates which can exist only in the open chain configuration [65–67], most probably this enzyme also accepts the ketoform of D-fructose-1,6-diphosphate as substrate.



Scheme 1

Phosphatases:

Glucose-6-phosphatase and fructosediphosphatase are both involved in gluconeogenesis. It was shown that glucose-6-phosphatase from rat liver microsomes catalyzes nonspecifically the hydrolysis of α- and β-D-glucopyranose-6-phosphate [8], whereas for fructosediphosphatase from liver a specificity, or at least a preference, for α-D-fructofuranose-1,6-diphosphate was reported [63].

The reaction scheme (scheme 1 on the previous page) of the upper part of D-glucose metabolism considers the anomeric specificity of enzymes using D-glucose, D-glucose-6-phosphate, D-fructose-6-phosphate and D-fructose-1,6-diphosphate, respectively, as substrates. The reactions of mannosephosphate isomerase and fructose diphosphatase were omitted from the reaction scheme, as the anomeric specificity of mannosephosphate isomerase with respect to D-fructose-6-phosphate is not yet known [44], and the anomeric specificity of fructosediphosphatase has, so far, only been published in the form of an abstract [63].

4. Concluding remarks

Some of the enzymes described above are not widely distributed in nature but only occur in certain cells or tissues, e.g. glucose dehydrogenase, glucose oxidase, aldose 1-epimerase and glucose-6-phosphate 1-epimerase. In addition, the enzymes investigated originate from different biological sources. Therefore the reaction scheme should not be considered as being representative for one or all cells.

A priori one cannot conclude that analogous enzymes from different biological sources exhibit the same anomeric specificity, and this is especially true if analogous enzymes possess different properties as is the case with the two types of fructosediphosphate aldolase [66,68]. However, in the case of hexokinase, glucose-6-phosphate dehydrogenase and glucosephosphate isomerase the anomeric specificity of analogous enzymes from various biological sources was found to be identical.

Generalizing from the results on the anomeric specificity of the enzymes reviewed in this paper, one can divide the enzymes into two classes, stereospecific enzymes and nonspecific enzymes:

1. If the reaction occurs at the anomeric carbon atom of the substrate (or at a groups attached to the anomeric carbon atom) the enzymes are specific for one anomeric form of the substrate, as observed for galactokinase, dehydrogenases, phosphoglucomutase, mannosephosphate isomerase, xylose isomerase, fructose-6-phosphate kinase and fructosediphosphatase.

2. If the reaction occurs distant from the anomeric carbon atom of the substrate the enzymes show no anomeric specificity, as is the case with hexokinase, glucokinase, pyrophosphate phosphotransferase and glucose-6-phosphatase.

Glucosephosphate isomerase and fructosediphosphate aldolase belong to neither of the two classes. However, these enzymes differ from the other enzymes in catalyzing additional reactions: besides the aldose–ketose isomerization glucosephosphate isomerase catalyzes the anomerization of D-glucose-6-phosphate [42,43], D-fructose-6-phosphate [43] and D-mannose-6-phosphate [44], and fructosediphosphate aldolase most probably catalyzes the ring opening of β-D-fructofuranose-1,6-diphosphate [15] prior to the aldol cleavage.

Anomeric specificity of enzymes arose by natural selection in cases where reactions occur at the anomeric carbon atom of the substrate. Enzyme catalysis requires stereospecificity towards the group of the substrate that is involved in the reaction. However, stereospecificity towards one anomeric form of the substrate causes a disequilibration of the anomers. Therefore, enzymes capable of accelerating the equilibration of the anomeric forms of sugar substrates had to evolve. They are the price for selectivity of catalysis.

For D-glucose, D-glucose-6-phosphate and D-fructose-6-phosphate anomerization reactions, catalyzed by aldose 1-epimerase, glucose-6-phosphate 1-epimerase and glucosephosphate isomerase, respectively, occur. A possible function of aldose 1-epimerase in sugar transport, as originally postulated by Keston [54], remains debatable [69]. At the level of D-glucose-6-phosphate, where phosphoglucomutase and glucose-6-phosphate dehydrogenase stereospecifically catalyze the reaction of either the α- or the β-anomer of D-glucose-6-phosphate, enzyme-catalyzed anomerization is important. In all cells and tissues investigated, the anomerization of D-glucose-6-phosphate was shown to be catalyzed by glucosephosphate isomer-

ase. In addition, in some cells the anomerization of D-glucose-6-phosphate is catalyzed by a second enzyme, namely glucose-6-phosphate 1-epimerase. At pH 7.6 and 25°C quantitative results on the spontaneous and enzyme-catalyzed anomerization of α- to β-D-glucopyranose-6-phosphate were obtained: the rate constant of the spontaneous reaction is 3.8 min^{-1} [42,48], whereas for bakers' yeast the activity constant of glucosephosphate isomerase was determined as 220 min^{-1} per gram yeast [62] and the activity constant of glucose-6-phosphate 1-epimerase as 412 min^{-1} per gram yeast [48]. These data lead to the suggestion of a possible biological function of glucose-6-phosphate 1-epimerase, in the starving, glycogen catabolizing yeast cell, when glucosephosphate isomerase is inhibited by metabolites of the pentose-phosphate pathway [48].

Neither glucosephosphate isomerase from yeast nor glucose-6-phosphate 1-epimerase from yeast were capable of catalyzing the anomerization of D-fructose-1,6-diphosphate [15]. In fact, fructose-6-phosphate kinase specifically catalyzes the phosphorylation of β-D-fructofuranose-6-phosphate, yielding β-D-fructofuranose-1,6-diphosphate, which is the furanose configuration of D-fructose-1,6-diphosphate that can be accepted as substrate by fructosediphosphate aldolase. Therefore, an enzyme-catalyzed anomerization of D-fructose-1,6-diphosphate does not seem to be necessary in the glycolytic pathway.

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