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En Block Approach of Structure Elucidation of Linear Isomeric Aldohexoses as Related to Aldaric (Saccharic) Acids

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ABSTRACT--- ***Structure elucidation of the 16 isomeric linear aldohexoses is approached en block, in a clear, logic, concise, coherent, manner. The main premise, or paradigm, of this paper is structure elucidation of (+)-tartaric acid by Bijvoet. Other premise is a preparative method elaborated by Baer and Fischer, whose instructive potential is disclosed for the first time in this paper. It concerns elucidation of configuration of C-2 by using di-O-isopropylidenic derivatives of hexitols.***

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1. INTRODUCTION

Saccharides (carbohydrates) are polyhydroxy-aldehydes or -ketones with a large distribution in living matter. They were divided, according to their molecular weight and their cleavability to hydrolysis, in monosaccharides, oligosaccharides (di-, tri-, tetra-, etc., decasaccharides) and polysaccharides. Oligo- and polysaccharides are condensed form of monosaccharides. As a function of their molecular weight, monosaccharides have been classified in: trioses (C_3), tetroses (C_4), pentoses (C_5), hexoses (C_6), etc., undecoses (C_{11}) [1,2]. Amongst common natural compounds, aldehido-saccharides are the most susceptible to oxidation. Due to redox characteristics of functional chemical groups of saccharides, especially aldehyde and terminal hydroxyl group, these compounds can be converted to poliols or acidic derivatives, mono- or dicarboxylic acids. In this way, new representatives have been added to saccharides.

It has been mathematically demonstrated that monosaccharides are the most versatile compounds concerning their molecular diversity of oligo- and polymers [3,4,5]. A group of six different monosaccharides can form $>10^{12}$ different hexaosides, the variables being type of the ring, type of configuration, type of branching and diastereomerism [3,5]. With six aminoacids one can construct $<10^5$ hexapeptides [3,5]. Moreover, saccharidic oligo- and polymers are constructed according to a mathematical principle – repetition arrangement, which was regained in genetics [6], chemistry, linguistics [4,7]. (It has been hypothetically speculated that this phenomenon was illustrated for the first time in Homer's Iliad [7,8]).

2. PREMISES

The following premises are necessary for *en block* structure elucidation of the 16 isomeric linear aldohexoses.

2.1. LINEAR ALDOHEXOSES

Linear aldohexoses are aldohexoses that can be converted to n-hexane by strong reduction reaction [9] or to n-heptanoic acid by reaction with hydrogen cyanide and reduction [10,11]. Aldehyde function was indicated by Schiff (1870), although the configurations of hydroxyl groups was equivocal [12] (Fig. 1). According to tetrahedrical model of carbon atom, elaborated by Van't Hoff (1874) [13] and LeBel (1874) [14], and confirmed by E. Fischer [15,16], 16 isomers can be imagined for a compound containing four asymmetric carbon atoms (Fig. 2). The 16 isomers can be equivocally represented by one formula (Fig. 1).

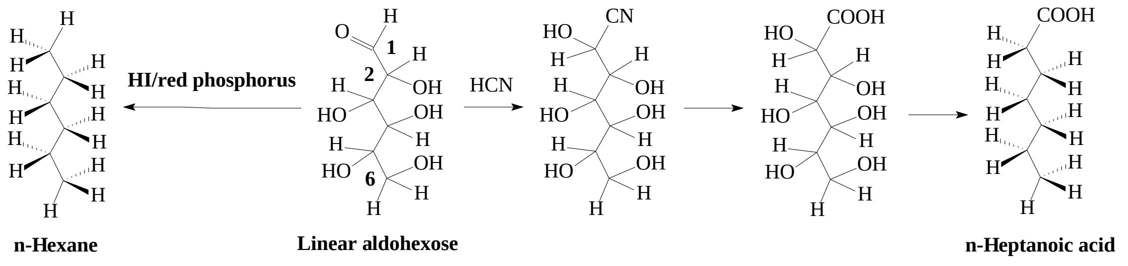

Figure 1. Linear aldohexoses are converted to n-hexane [12] by strong reduction or to n-heptanoic acid, by reaction with hydrogen cyanide and strong reduction [10,11].

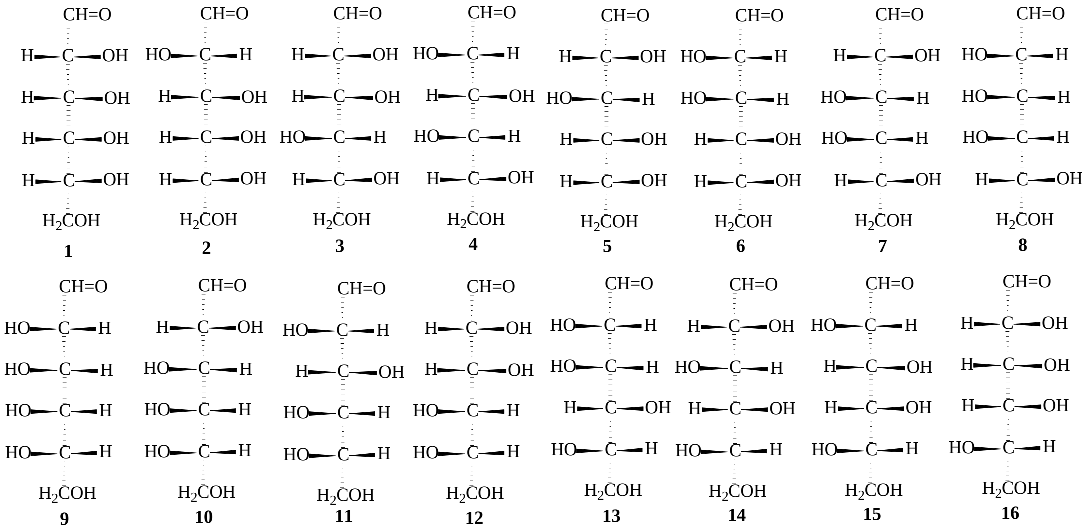

Figure 2. 16 Isomers can be imagined for a linear aldohexose containing four asymmetric carbon atoms.

2.2. CHIRALITY

The phenomenon of chirality was discovered in biology, in connection with morphology of mollusks, especially spiral ones. It was noticed that mollusks, contrary to vertebrates, are devoid of planes of symetry. On the other hand, in every species appeared a number of enantiomorphic organisms in a characteristic ratio [17,18].

In chemistry, chirality was discovered in connection with polarized light [19] as well as with optically active compounds, i. e., natural substances that rotate the plane of polarized light – quartz [20] tartaric acid, sucrose, turpentine, etc [21].

2.3. C_4 SACCHARIDES

C_4 Saccharides have a few remarkable properties: (A) they are the simplest monosaccharides capable of forming cyclic structures (rings) by hemiacetalyzation; (B) they possess chiral aldaric acids. Aldaric acids are natural or synthetic dicarboxylic acids; in the latter case they are produced by nitric acid oxidation of linear aldohexoses [22]. According to tetrahedrical model of carbon atoms, elaborated by Van't Hoff [13] and LeBel [14], and confirmed by E. Fischer [15,16], three isomers are possible for a C_4 linear dibasic acid containing two asymmetric carbon atoms and they were named tartaric acids. A saturated carbon atom is asymmetric (or chiral) when it is linked to four different substituents.

Tartaric acids was discovered by Scheele (1770) in the sediment deposited in the vats during the grape juice fermentation [23]. This sediment had been called tartar and Scheele boiled tartar with chalk and then acidified the product with sulfuric acid. A sample of tartaric acid was prepared by fermentation by an Alsatian manufacturer, Kestner (1822). Kestner's specimen had the same chemical properties as tartaric acid discovered by Scheele. However, some physical properties (solubility in water, crystalline form, etc.) were different [24]. Nobody, neither Kestner himself, could reproduce his experiment. Fortunately, he had prepared enough material so that many interested specialists could receive a share of it. The compound was called *racemic acid* by Gay-Lussac and *para-tartaric acid* by Berzelius. Subsequently, polarized light [19] and optical activity were discovered [20,21] and polarimeter was invented [25]. So, became evident that the acid discovered by Scheele was (+)-tartaric acid, while the compound prepared by Kestner was devoid of optical activity. Pasteur (1848) [26] prepared the double salt of sodium-ammonium of *para-tartaric acid* and then crystallized it. He noticed two types of crystals, that were enanthiomorphic with one another. Pasteur separated the two types of crystals and found out that their aqueous solutions were dextrorotary and levorotary, respectively. Consequently, the so-called *para-tartaric acid* was in fact a racemic mixture, (±)-tartaric acid. Another isomer, not cleavable by any chemical or biological method, was discovered also by Pasteur and called *meso*-tartaric acid [27].

The discovery of Pasteur increased the dilemma of representation, in other words the relationship between an optically active compound and the structural model assigned to it. This dilemma was solved by X-ray diffraction, i. e., zirconium Kα rays, by sodium rubidium tartrate of the dextrorotary species, and the indicated model (Fig. 3) was assigned to (+)-tartaric acid [28]. This configuration of (+)-tartaric acid had been attributed by E. Fischer by pure intuition [29]. Since (–)-tartaric acid is an enathiomer of (+)-tartaric acid, its configuration became also evident (Fig. 4).

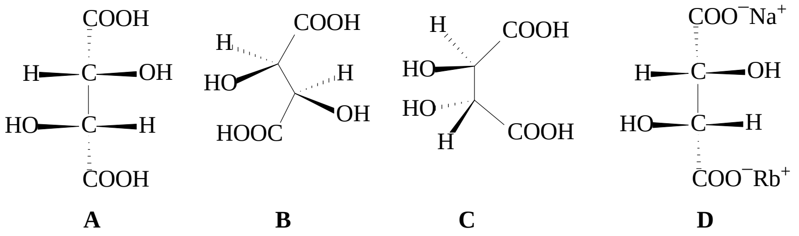

Figure 3. Structural models assigned by Bijvoet et al., [28] (A, B, C) by working with sodium rubidium salt of (+)-tartaric acid (D).

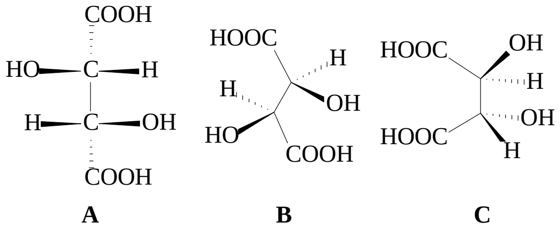

Figure 4. Since (–)-tartaric acid is an enathiomer of (+)-tartaric acid, its configuration became also evident.

(–)-Tartaric acid is interconvertible with (+)-glyceraldehyde, and (+)-tartaric acid is related with (–)-glyceraldehyde, either by chain elongation or chain shortening. Chain elongation is formed of a suite of reaction called Fischer-Kiliani synthesis [10] and chain shortening is based on Malaprade reaction [30-32]. As a result, the configuration of the two aldotrioses was elucidated (Fig. 5).

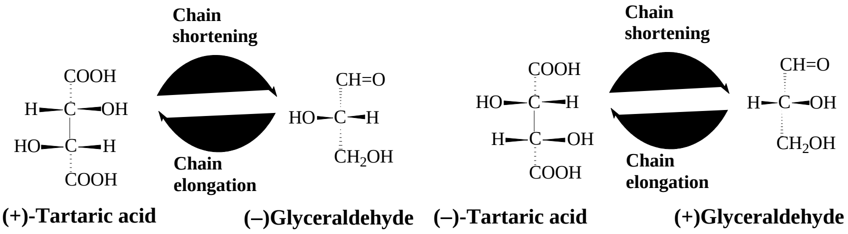

Figure 5. (–)-Tartaric acid is interconvertible with (+)-glyceraldehyde, and (+)-tartaric acid is related with (–)-glyceraldehyde.

2.4. CHAIN SHORTENING

Chain shortening of monosaccharides [33,34] can be reckoned as being complementary to Fischer-Kiliani synthesis [10]. Both methods of chain shortening are based on oxidation reactions. Wohl method consist in treating the sugar with hydroxylamine, the oxime is dehydrated by peracetylation and then a C_1 unit is cleaved as HCN, by reaction with sodium hydroxide [33]. Ruff degradation is based on oxidative lability of aldehydes within monosaccharides in linear form, which is readily transformed to carboxylic acids. The latter, as calcium salt, is oxidized to the lower sugar and carbon dioxide, with hydrogen peroxide in the presence of a ferrous salt [34].

3. *EN BLOCK* APPROACH OF STRUCTURE ELUCIDATION OF LINEAR ISOMERIC ALDOHEXOSES

Based on the above mentioned premises, the structure of the 16 isomeric aldohexoses can be simultaneosly demonstrated.

I. Three successive chain shortening, either by Wohl [33] or Ruff [34] method, would alternatively produce (+)-glyceraldehyde (compounds 1-8 of Fig. 2) and (–)-glyceraldehye (compounds 9-16 of Fig. 2). Consequently, the first eight compounds belong to D-series, and the configuration of C-5 has been elucidated (Fig. 6). Similarly, compouns 9-16 belong to

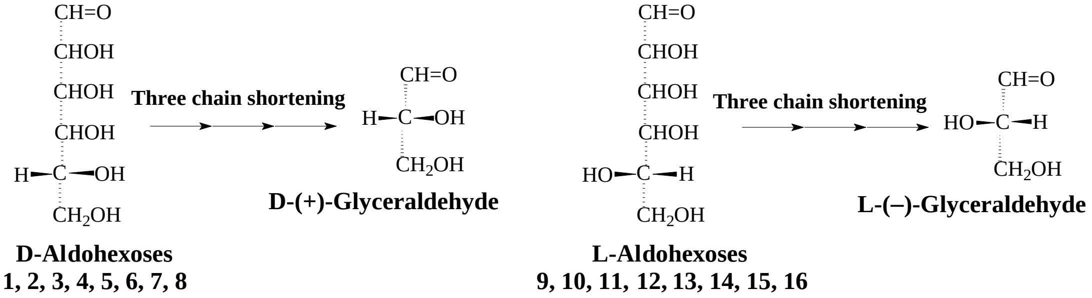

Figure 6. Three consecutive chain shortening would produce D-(+)-glyceraldehyde of eight isomeric linear aldohexoses and the other eight, (–)-glyceraldehyde, respectively.

L-series and the configuration of their C-5 has been elucidated based on the knowledge of the configuration of asymmetric carbon of (–)-glyceraldehye as related to (+)-tartaric acid (see above).

Since the 16 isomers constitute eight pairs of enanthiomers, structure elucidation of the eight isomers of D-series will suffice.

II. Two consecutive chain shortening followed either by reduction or by oxidation would produce either C_4 units devoid of optical activity (compounds 1,2,5,6, Fig. 7) or optically active C_4 units (compounds 3,4,7,8, Fig. 7). In this way, the configuration of C-4 has been elucidated.

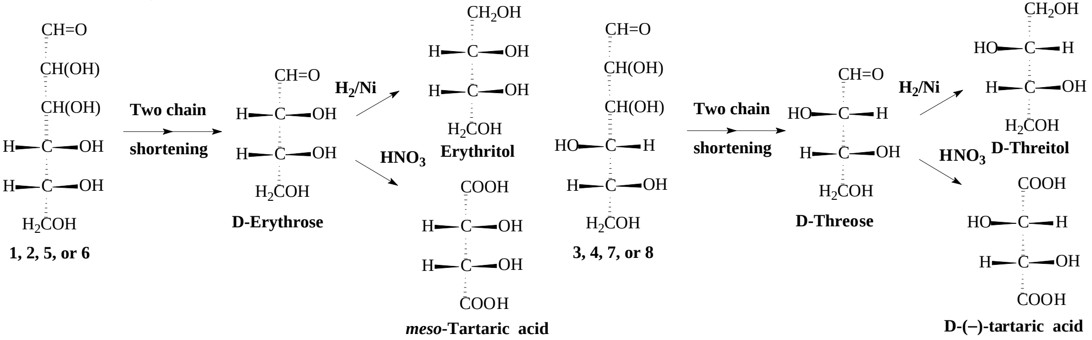

Figure 7. Two chain shortening, followed either by reduction or oxidation would produce symmetric or chiral C_4 units.

III. One chain shortening (Fig. 8), followed by either reduction or oxidation would produce symmetrical (compounds 1, 2, 3, 4) or chiral C_5 units (compounds 5, 6, 7, 8). Hence, the configuration of C-3 has been elucidated, in correlation with the configuration of the priorly indicated chiral carbon atoms of linear form.

Hydrogenation of aldehyde function in compounds 1-8 (or oxidation with HNO_3) (Fig. 2) would produce two *meso*-compounds: *meso*-allitol (or *meso*-allaric acid) from compound 1 and *meso*-galactitol (or *meso*-galactaric acid) from compound 7. The configuration of all chiral carbon atoms of compounds 1 and 7 is in this moment elucidated, provided a correlation of all chiral centers is taken into account. Hexitols (or aldaric acids) of compounds 2, 3, 4, 5, 8, are all chiral, and specific methods are necessary for the elucidation of configuration of C-2. In fact, the correlation of all chiral carbons of linear form of aldohexoses constituted the reasoning of E. Fischer [15,16]. He noticed that by reversing the ends of D-mannose, the same compound was obtained, since the configuration of C-5 and C-4 is enanthiomorphic to C-2 and C-3.

IV. Synthesis of two important groups of natural compounds, triglycerides and phospholipids, indicated (+)- and (–)-glyceraldehyde as ideal precursors, as well as their preparation from D- and L-mannitol, respectively [35,36]. We suggest that this reaction has not only a preparative but also an exceptional teaching value. We have used it for decades to this aim, i. e., to distinguish between diastereomeric aldohexoses that are epimeric to C-2, or as indicated by E. Fischer [15,16], aldohexoses producing the same osazone. If two such monosaccharides are submitted to the suite of reactions indicated [35,36], the result is quite different (Fig. 9): compounds 1, 3, 5, 7, of Fig. 2 give a mixture of (+)- and (–)-glyceraldehyde while compounds 2, 4, 6, 8, of Fig. 2 give two mole of (+)-glyceraldehyde per mole of sugar. The cleavage of dihydroxy-diisopropylidenic hexitol can be made by oxidation with lead tetraacetate [35,36] or with periodic acid [37]. 1,2:5,6-Di-O-isopropylidene-D-glucitol (sorbitol) has been synthesized and characterized [38,39].

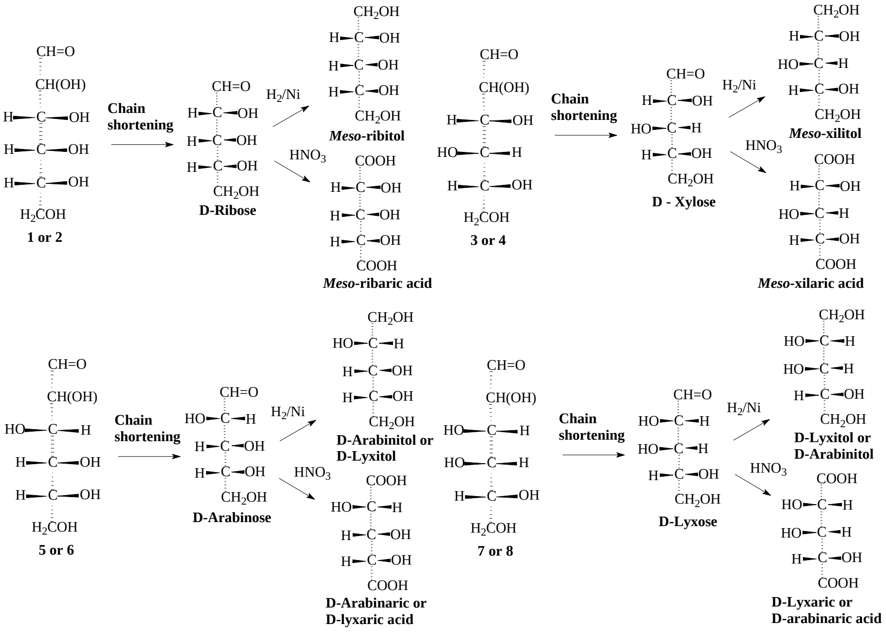

Figure 8. One chain shortening, followed by reduction or oxidation, would produce symmetric or chiral products.

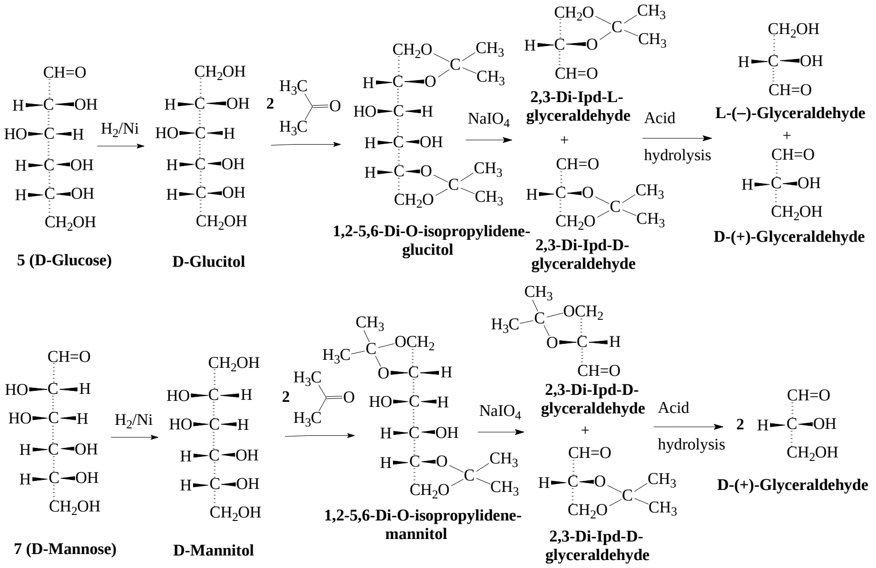

Figure 9. Reduction of aldohexoses that are epimeric at C-2, followed by isopropylidenation and Malaprade oxidation, would produce a a mixture of enanthiomers or a unitary product.

However, less papers dealt with its periodate oxidation, probably since the product is a racemic mixture.

The ensemble of reactions I-IV constitute an individual and characteristic pattern for the aldohexoses 1-8, e. g., compound producing D-(+)-glyceraldehyde by reaction I, *meso*-erythritol (or *meso*-tartaric acid) by reaction II, D-arabinitol (or D-arabinaric acid) by reaction III, and a racemic mixture of (+)- and (–)-glyceraldehyde by reaction IV, is D-(+)-glucose (5). This reasoning can be applied to all compounds 1-16 and will give specific results in every case. In this way it was concluded that 1 is D-allose; 2, D-altrose; 3, D-gulose; 4, D-idose; 5, D-glucose; 6, D-mannose; 7, D-galactose; 8, D-talose, and compounds 9-16 are their enanthiomers, respectively.

4. CONCLUSIONS

We have presented a clear, new, *en block* approach of structure elucidation of linear aldohexoses, based essentially on the knowledge of configuration of (+)-tartaric acid as accomplished by Bijvoet. Chain shortening by Wohl or Ruff method, followed either by reduction or oxidation will disclose the configuration of chiral carbons C-5, C-4, C-3. The suite of reactions indicated by Baer and Fischer will add the knowledge of C-2.

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