Investigating the Metabolism of Glucose: An Alternative to 13C-Hyperpolarized Pyruvate

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Introduction

The living cell uses glucose as a source of energy, at the same time it is a metabolic intermediate. The glucose molecule can exist in an open-chain (acyclic) and ring (cyclic) form (in equilibrium), the latter being the result of a covalent bond between the aldehyde C atom and the C-5 hydroxyl group to form a six-membered cyclic hemiacetal. In water both forms are in equilibrium and at pH 7 the cyclic form is predominant. In this ring, each carbon is linked to a hydroxyl side group with the exception of the fifth atom, which links to a sixth carbon atom outside the ring, forming a CH_2OH group. The phosphate thereof, the D-glucose-6-phosphate can be dehydrogenated to yield the corresponding enol-6-phosphate. If thereupon this unsaturated form is re-hydrogenated using parahydrogen[1], the resulting glucose-6-phosphate is obtained with hyperpolarized nuclei, if the reaction is carried out at appropriate low magnetic fields. Two stereoisomers of the aldohexose sugars are known as glucose, but only the D-glucose is biologically active. The mirror-image of this molecule, L-glucose, cannot be metabolized by the biochemical process known as glycolysis. Therefore, it is imperative that chiral catalyst are used that produce the appropriate stereo-isomer exclusively. The homogeneous Rh(I) hydrogenation catalyst with sugar-derived chiral ligands as outlined in Figure 2 can accomplish this challenging task.

Methods and Results

If either ^{13}C-MRI[2] or ^{13}C-MRS are to be applied to investigate or image certain aspects of glucose metabolism, some form of signal enhancement is a prerequisite such as ^{13}C-hyperpolarization derived from PHIP[1]. Accordingly, *in situ* parahydrogenation of the glucose-derived enol-6-phosphate outlined in Figure 1 can assist boosting the sensitivities of these methods, theoretically up to a 10^5–fold.

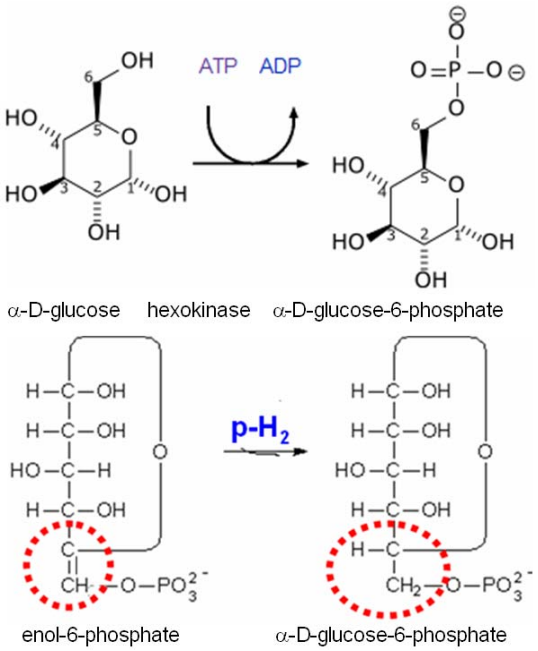
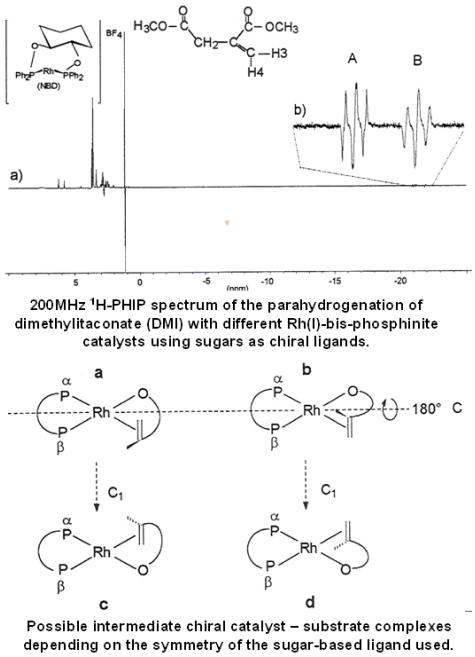


Fig. 1: Glucose and unsaturated enol-6-phosphate



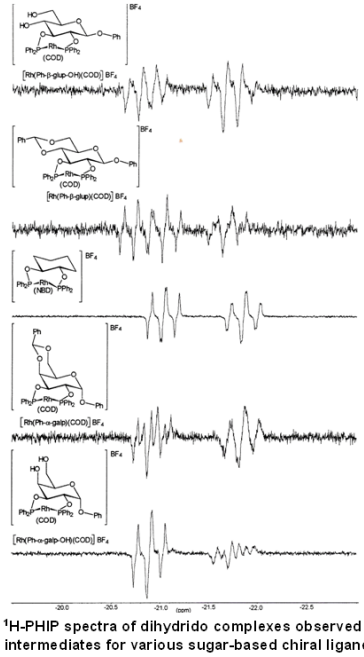


Fig. 2: ^{1}H-PHIP spectra and dihydrido catalyst-substrate intermediates observed.

Various model systems have been tested successfully to test this concept. Using dimethylitaconate (DMI) as an unsaturated starting material, the ^{1}H-PHIP spectra as outlined in Figure 2 not only contain the expected resonances of the hyperpolarized hydrogenation product, namely the dimethylester of methylsuccinate, but in the region of negative chemical shifts additional resonances document the intermediate occurrence of chiral catalyst-substrate dihydrido complexes, which reveal their stereochemistry upon careful analysis of their spectral parameters. Using different ligands derived from the chiral pool of naturally occurring sugars the dihydrido complex not only differ in the positions of their corresponding resonances around -20 ppm, but the spectra reveal that the number of possible stereo-complexes depends on the symmetry of the ligands. As outlined in Figure 2, either 2 or 4 different stereoisomers can occur, depending on the symmetry of the ligand applied. Since an appropriate geometry and stereochemistry of the hyperpolarized hydrogenation product is of the essence for investigating the metabolic fate of glucose, these intermediates can guide the search for the most appropriate and effective homogeneous hydrogenation catalyst to be used. – Another advantage of these sugar-based catalysts is their solubility in water and their positive charge, which allows their removal using ion-exchange resins and prevents deactivation through dimerization.

References

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