Proposal: The Antibody-catalyzed regioselective protection of (β-1-6) D-Galactose-D-Mannose Disaccharide as a Showcase of the use of Antibodies as Catalysts in Oligosaccharide Chemistry

David Kogan

I. Introduction

With the ever-increasing importance of carbohydrates in general, and oligosaccharides, in particular, in biopharmaceuptical and biotechnological solutions, a constant demand for new synthetic tools that deal with oligosaccharides is created, particularly tools with various selective properties. Due to their inherent exquisite catalytical properties, enzymes have been explored, and have been successfully utilized in many cases(1). However, enzyme catalysis faces the constant problem of a lack of diversity in naturally occuring specimens. This paper will propose a solution to the topic using the natural diversity of antibodies and the power of the vaccination selection mechanism, while concentrating on a simple reaction to showcase both the possibilities and the challenges that such an approach faces.

II.The Abzyme Approach

The catalytic antibody approach, or the 'abzyme' approach, while still being a mostly undeveloped field in terms of commercial applications, shows great promise in the scope of uses, due to the nature of somatic recombination, the process that gives rise to the great variety of antibodies, and has the ability to biogically synthesize antibodies in a manner that we can control through the vaccination process. While many various applications of these have been explored, and the general procedure in their creation and harvesting has been already widely described in literature(2), this paper will include a short schematic explanation of the function of the antibody, and the logic and technique leading to it's application as a catalyst, as to put the proposal into the correct context.

The general logic of the Abzyme approach is that if antibodies have a biological function to capture and attach themselves to certain molecular structures, that attachment is favoured thermodynamically, and thus, if vaccination occurs with a molecule that has similar steric and electronic properties to the transition state of the rate-determining state of a reaction, the result will be an enzyme that will be able to lower the energy of the transition state of said reaction, and thus will be an effective catalyst.

III.The Galactose Mannose disaccharide acetalation reaction

The acetalation reaction is a staple protection reaction in both carbohydrate chemistry, and in organic chemistry in general. It's the reaction between a cis 1,2-diol group, and a carbonyl to form a acetal ring. The parallel 1,2-trans-diol reaction doesn't occur due to steric reasons. the reaction is very useful in carbohydrate chemistry in the selective protection of many monosaccharides, in order to selectively prepare them for other chemical reactions. However, while dealing with oligosaccharides, this isn't always possible, since the reaction can unselctively occur in several locations. For example, in our case both the Galactose and the Mannose units present cis-dihydroxy regions in which such a reaction can occur (fig. 1)

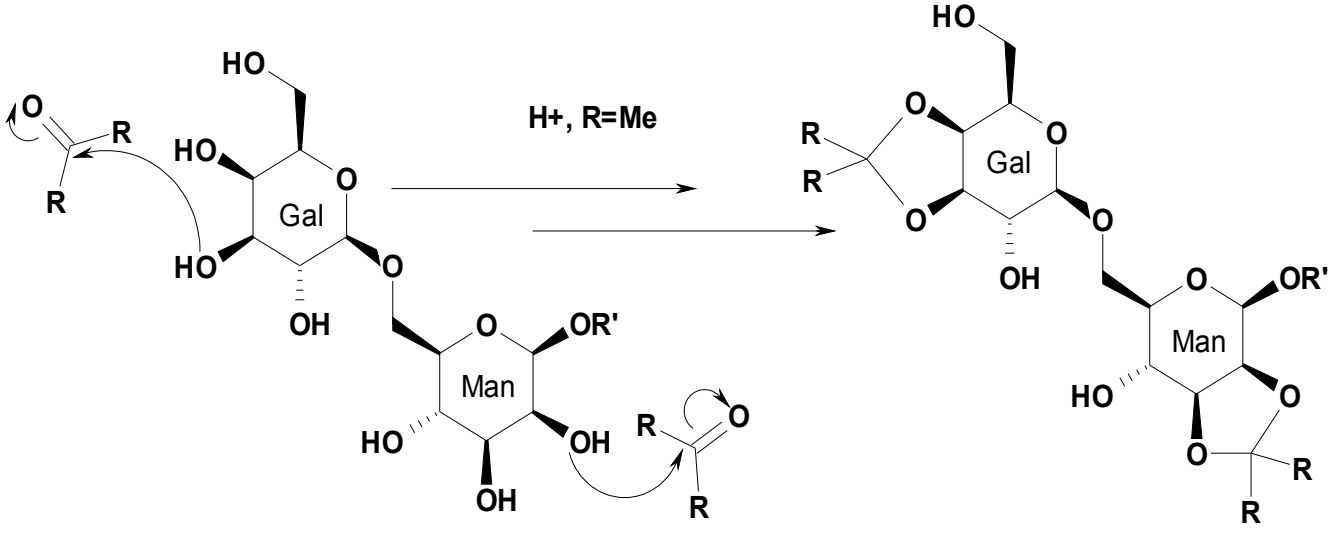

fig. 1: the reaction proceeds at both the of the units of the disaccharide.

IV.General Reaction Mechanism

The regular acetalation reaction mechanism, while simple, is crucial to understand the problems that antibody catalysis faces in this case. The mechanism can be either Brønsted acid catalyzed or Lewis Acid catalyzed (fig. 2). The mechanisms are in essense very similar, in the fact that in both, the ketone is polarized, and is more accomodating for a nucleophilic attack. However, a the Brønsted acid path includes a protonation of the carbonyl oxygen, when protonation of the attacking hydroxy group is much more suitable for protonation.

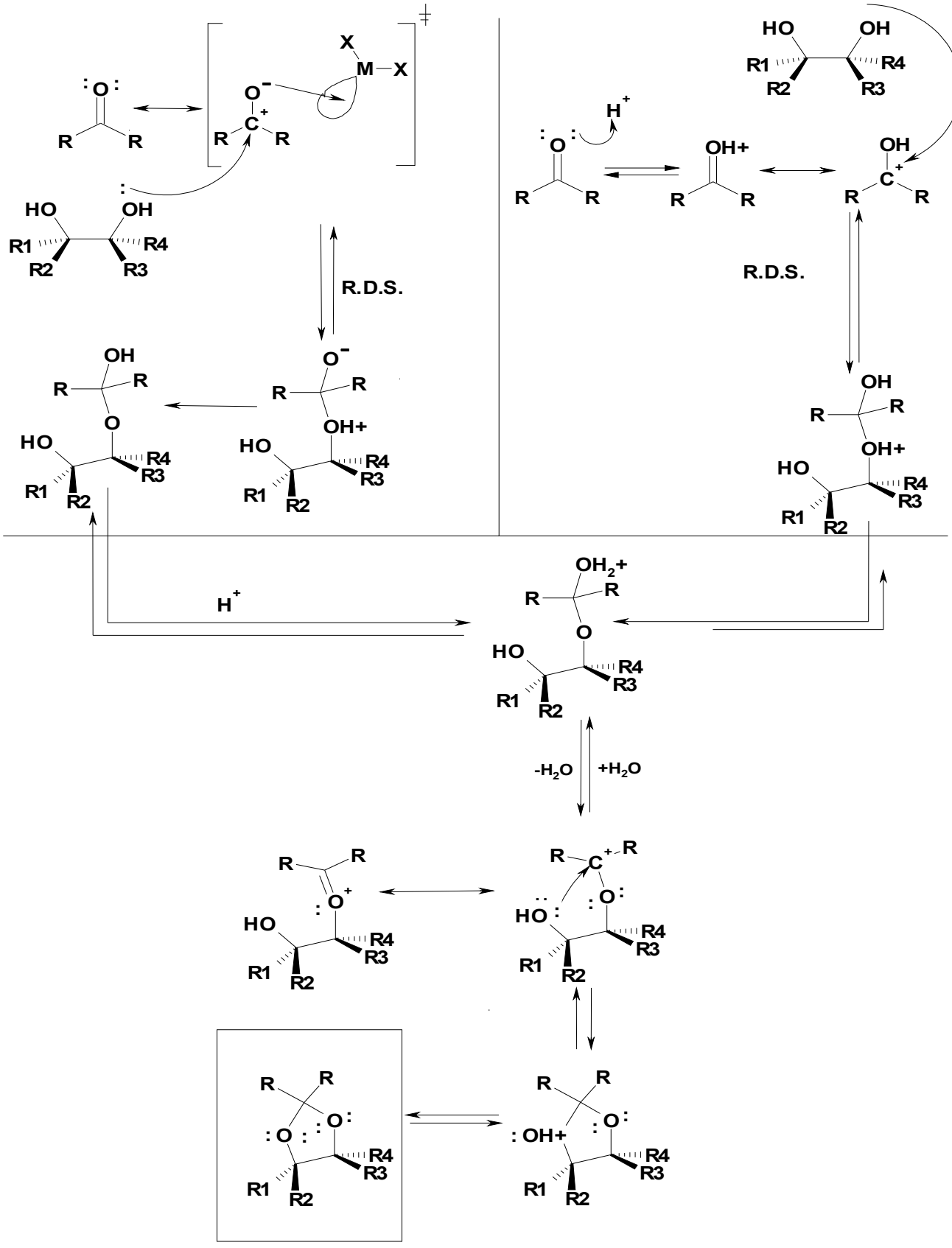

fig.2 The Brønsted and Lewis acid catalyzed mechanisms

References:
(1) Ichikawa Y, Look GC, Wong CH, Anal Biochem. 1992 May 1;202(2):215-38.
(2) *Catalytic Antibodies,* E. Keinan, Wiley, ISBN: 3-527-30688-9