



# First principles investigation into the metal catalysed 1,2 carbon shift reaction for the epimerization of sugars



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## ABSTRACT

We investigate the metal catalyzed intramolecular 1,2 carbon shift reaction, usually associated with the epimerization of sugars, using the density functional theory. Metals like molybdenum (Mo), tungsten (W) and vanadium (V), in their oxoanion complex forms (molybdate, tungstate, vanadate) are investigated. The experimentally observed difference in the activity of these metal complexes, in catalyzing 1,2 carbon shift in glucose, at different pH is explained. Formation of larger (polynuclear) metal oxoanions (“metalates”) at higher pH reduces the structural flexibility of the metal complex. Thus, upon binding with glucose, their ability to rearrange the carbon backbone in sugar molecules decreases, resulting in lower activity towards 1,2 carbon shift at higher pH. For example, the activation barrier for 1,2 carbon shift catalyzed by “active” di-nuclear molybdate (exists at pH 2.5–3.5) is 21.1 kcal/mol; whereas it is 26.8 kcal/mol for the tetra-nuclear molybdate (exists at pH 4–5.5). Bonding interaction analysis has been carried out to quantify the flexibility/rigidity of the metal oxoanion complexes. Comparison of catalytic activities of Mo, W and V (as dimetalate) showed that vanadate is more active than the popular molybdate complex and W is the least active of them all. The trend in the catalytic activities of these metals is explained on the basis of the participation of higher orbitals in the complexation of metal oxoanions with glucose. Additionally, the flexibility/rigidity of the metal complex is also shown to be a descriptor of its catalytic activity for the 1,2 carbon shift reaction.

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## 1. Introduction

Epimerization is the reaction of the transformation of saccharides to acquire diverse functions attributable to their stereogenic centers [1,2]. Hence, epimers are diastereomers with the inverted configuration around a chiral center of the substrate [1]. Epimerization is widely used for the production of rare sugars since these rare sugars are monosaccharides and cannot be extracted in large volumes from natural resources. However, they have found wide applications in food, flavour, cosmetic and pharmaceutical industries [3–5]. For example, D-tagatose and D-psicose are used as low calorie sweeteners, replacing classical table sugar in the food industry [6,7]. The main advantage of these rare sugars is that they have low glycemic index, making them suitable for diabetic patients

and as obesity control agents. Rare sugars, such as D-allose and D-ribose, have attracted much attention in pharmaceutical industries in recent years due to their various biological properties such as anti-oxidative and anti-inflammatory nature and immunosuppressant activities [8,9]. D-Mannose, a chiral counter part of D-glucose can be used to treat urinary tract infections too [10].

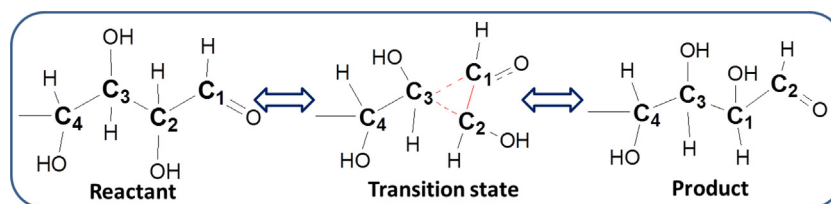
Epimerases are potentially the most useful biocatalysts for the production of rare sugars as they can produce a wide range of stereoisomeric structures, and are highly selective in epimerizing carbohydrates at different carbon positions [5,11]. Though, epimerases are highly selective, unfortunately, they are only active over a small range of temperatures and pH values, dramatically restricting their use [12]. In addition, epimerases are difficult to extract and recycle from the reaction medium [13]. Thus, there is a need for simple and convenient methods for the stereo-controlled construction of C–C bonds in carbohydrate molecules. Therefore, the development of inorganic catalysts for rare sugars production is highly desired, since they can operate under various conditions and overcome some of the challenges associated with enzymatic systems.

Lobry de Bruyn-van Ekenstein transformation is the commonly studied base (NaOH or Ca(OH)<sub>2</sub>) catalysed reaction mechanism for

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**Scheme 1.** Schematic representation of the Bilik mechanism for the epimerization of sugars. It shows the formation of a concerted tricentric structure at the transition state, leading to 1,2 carbon shift.

the epimerization of an aldose to its chiral counterpart, with an enediol as the reaction intermediate [14,15]. Since it needs a basic environment, there are a series of undesired secondary reactions along with the epimerization process, which reduce the product selectivity and distribution ratio [15]. In 1970s, the pioneer work done by Bilik and co-workers [16–20] has shown that aldoses can be epimerized at the C<sub>2</sub>-position without forming complementary ketoses, using molybdate as a catalyst, under acidic conditions. They also proposed a mechanism for the epimerization of sugars, usually referred to as “Bilik reaction”. It involves simultaneous cleavage of the C<sub>2</sub>–C<sub>3</sub> carbon bond and the formation of a new C<sub>1</sub>–C<sub>3</sub> carbon bond (cf Scheme 1). This carbon shift was confirmed by <sup>13</sup>C NMR studies too [21]. However, molybdate can catalyze the epimerization of aldoses only in the pH range of 2.5–3.5, and the rate of epimerization drastically decreases with the increase in the pH [22]. In addition to this, being a homogeneous catalyst, its complete separation and recovery from the product mixture was found to be a difficult task. In 1990s, Tanase et al. [23] reported that Ni-diamine complex can epimerize glucose into its stereoisomer mannose, in methanolic media. But the solubility of glucose in methanol is a limitation. So far, to the best of our knowledge, only Mo and Ni based homogeneous catalysts are reported for the epimerization of sugars.

In 2001, Corma et al. [24] developed a heterogeneous Lewis acid Sn-beta zeolite catalyst for the Bayer–Villiger oxidation of ketones and Meerwein–Ponndorf–Verley (MPV) reduction of ketones and aldehydes. Davis and co-workers [25,26] showed that Sn-beta zeolite in aqueous media isomerises the glucose into fructose, via Lewis acid catalyzed intramolecular 1,2 hydride shift. Upon switching to methanol as a solvent, they observed that, instead of isomerization, glucose undergoes epimerization, following the Bilik mechanism [27]. But the low solubility of glucose in methanol significantly limited the epimerization process. Using *ab initio* molecular dynamics calculations, Mushrif et al. [28] explained that the activation barrier for the 1,2 hydride shift (catalysed by Sn-beta alone) is very high in methanol, and that inhibits the possible isomerization reaction. Román-Leshkov and co-workers [29,30] have shown that Sn-beta zeolite, in combination with borate salts, epimerizes sugars at 80 °C in neutral aqueous media, and they confirmed, using <sup>13</sup>C labelling, the presence of 1,2 carbon shift in the reaction. Recently, we also simulated the entire reaction pathway for the epimerization of glucose to mannose, catalysed by Sn-beta zeolite and borate salts [31] and demonstrated that borate salt inhibits the isomerization reaction and catalyzes 1,2 carbon shift for the epimerization reaction. 1,2 carbon shift was found to be the rate determining step in the reaction [30]. Rai et al. [32] have also shown that 1,2 carbon shift is the rate determining step in the epimerization of sugars catalysed by Sn-beta zeolite. Despite of its good product selectivity and distribution ratio, the synthesis of Sn-beta zeolite is a tedious process. Hence, to overcome some of the limitations of Sn-beta zeolite catalyst, it is necessary to investigate simple and efficient catalysts for the epimerization reaction.

Inspired by Bilik's work, Ju et al. [33] reported a molybdate based polyoxometalate (heteropolyatomic-ion) as a catalyst for

the epimerization of sugars in acidic conditions, and it was found to be an efficient and highly selective heterogeneous catalyst for epimerization. They suggested that molybdate plays a similar role, as explained by Bilik in the case of homogeneous catalysis, and follows the same “Bilik reaction” pathway to form the epimer product. It was confirmed by <sup>13</sup>C labelling studies [33]. It shows that molybdenum, either in homogeneous or heterogeneous phase, only catalyses the epimerization in a selected pH range of 2.5–3.5 and, above this pH, the rate of epimerization is reduced. However, to the best of our knowledge, there is no literature to explain the decrease in the catalytic activity of molybdates at higher pH.

The literature on molybdenum speciation in aqueous solutions shows that the relative proportion of molybdate and polymolybdate ions depends on the pH and on the concentration of Mo [34–36]. At neutral or basic pH, with low Mo concentration (<0.04 M), only mononuclear Mo (VI) species are predominant; whereas, several dimeric and polymeric molybdate Mo(VI) species are present in more concentrated Mo solutions in acidic conditions [37,38]. This was confirmed by EXAFS (Extended X-ray Absorption Fine Structure) and XANES (X-ray Absorption Near-Edge Structure) studies [39]. Tytko et al. [40] also showed the presence of dimeric/polymeric molybdate ions in Mo solutions in acidic conditions. It has also been understood from the experiments that the compounds which crystallise from the solution under various conditions consist of linked dimolybdate ions [41,42]. From EXAFS spectra, Borg et al. [39] showed that there is no existence of MoMo bonding in molybdate solution and confirmed the presence of a bridging oxygen between the two molybdate ions (Mo–O–Mo).

To summarize, a collective analysis of the dependence of Mo speciation and of its epimerization activity on the pH of the solution suggests that there are only certain Mo species which are active in catalyzing the epimerization reaction, in particularly the 1,2 carbon shift, since that is likely the rate limiting step. However, there is no direct evidence of one of the molybdates species being more/less active than others for the 1,2 carbon shift reaction. Hence, the focus of the present research work is as follows:

1. To compare the catalytic activities of different molybdates species for the 1,2 carbon shift step, in the epimerization reaction and to explain the key characteristics of the molybdates species that govern this catalytic activity.
2. Compare the catalytic activity of Mo for the 1, 2 carbon shift step with other transition metals like W and V, which exist in a similar metalate/oxoanion form as that of Mo. An additional motive behind testing these metals for their activity towards 1, 2 carbon shift reaction is that these metals are reported to form a complex with glucose and to reduce the free glucose molecule in the living system. In addition, ‘V’ and ‘W’ can also be used for the synthesis of metal based polyoxometalates, a heterogeneous catalyst for epimerization.

It has to be noted that, based on our recently published work [31], we believe that, 1,2 carbon shift is the rate determining step in the epimerization reaction, since other steps like catalyst binding to

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