6. New Mechanistic Proposal for Some Heptamolybdate-Ion-Catalyzed Isomerizations

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Heptamolybdate-ion(HM)-catalyzed C(2) epimerization of D-glucose and racemization of D-glyceraldehyde proceed with comparable rates and activation parameters; HM catalyzes the isomerization of glucal and galactal triacetates as well. For all of the above transformations, a common, new mechanism is proposed that invokes stabilization of 3-oxa-allylic cation species by the central Mo(VI) atom.

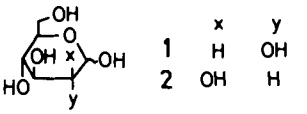
1. Introduction. – The catalytic effect of molybdate ions on the epimerization at C(2) of various monosaccharides was observed by *Bilik et al.* [1] [2] and subsequently studied in more detail [3–6].

Heptamolybdate ion (HM) is thermodynamically the most preferred species among the numerous polyanions of molybdic acid present in an aqueous solution [7] [8]. It is particularly favoured at lower pH values, where an enhanced rate of the molybdate-ion-catalyzed epimerization was observed. This suggests that the heptamolybdate ion could be the actual catalytic species, irrespective of the initial anion used.

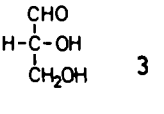
Bilik et al. [4] have demonstrated that tritium does not exchange with solvent H-atoms during the molybdate-ion-catalyzed epimerization of D-[1-^{3}H]glucose to D-[2-^{3}H]mannose, thus eliminating the traditional mechanism *via* a free ene-1,2-diol as the intermediate. *Barker*'s group performed a nice ^{13}C-NMR study and have surprisingly found [6] that C(2) epimerization of aldoses coinvolves C(1)$\rightleftharpoons$C(2) transposition, and the vicinal-proton-exchange mechanism [4] [5] operates only to a limited extent. Both authors explained the catalytic effect of the molybdate ion by a steric strain imposed on an aldopyranose ring upon complexation [6] [9].

2. Results and Discussion. – On the basis of our preliminary data (see the *Table*), we believe that *oxo*-complexation and steric strain cannot be the only driving force for C(1)$\rightleftharpoons$C(2) transposition and H-shift between C(1) and C(2) of complexed monosaccharides. Moreover, the earlier mechanistic considerations [3–6] [9] have not, in our opinion, addressed adequately the catalytic role of the central Mo-atom of heptamolybdate. While waiting for the data on the electronic structure of heptamolybdate[1]), we have undertaken

[1]) The crystal structure parameters for HM ion have repeatedly been determined by X-ray single-crystal analysis [10–12]. To our best knowledge, however, no spectroscopic or quantum-chemical data on orbital energies or hybridization states in HM are published.



1 x = H, y = OH
2 x = OH, y = H



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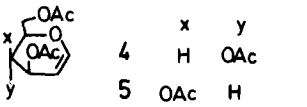
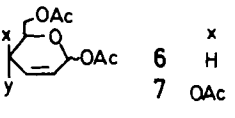


4 x = H, y = OAc
5 x = OAc, y = H



6 x = H, y = OAc
7 x = OAc, y = H

kinetic and preparative (equilibrium) experiments to shed more light on the mechanism of this important transformation[2]).

Rate measurements for the epimerization of D-glucose (**1**) into D-mannose (**2**) and for the racemization of **3**, both catalyzed by heptamolybdate ion under otherwise analogous conditions (*Table, Runs 1–8*), revealed comparable kinetic and thermodynamic parameters for these processes. A somewhat lower activation energy for epimerization of **1** either indicates the influence of steric strain as has been proposed by *Bilik et al.* and *Barker* and coworkers, or it is the consequence of a higher ratio of a nonhydrated to a hydrated

Table. *Rates and Thermodynamic Parameters of Heptamolybdate-Catalyzed* D-*Glucose* (**1**) *Epimerization and* D-*Glyceraldehyde* (**3**) *Racemization*

Run	Compound	Temp. [° ± 0.1°]	Conc. of **1** or **3**	Conc. of HM	pH	$k_{obs} \times 10^3$ [min^{-1}][b])	$\Delta G^{\neq}_{298.16}$ [kJ/mol]	$\Delta H^{\neq}$ [kJ/mol]
1	**1**	70.2	0.1M	3.6×10^{-2}M	5.5	12.9 ± 0.6		
2	**1**	75.1	0.1M	3.6×10^{-2}M	5.5	23.3 ± 0.5	107.0 ± 4.1	97.6 ± 3.1
3	**1**	80.4	0.1M	3.6×10^{-2}M	5.5	37.1 ± 0.3		
4	**1**	85.5	0.1M	3.6×10^{-2}M	5.5	59.1 ± 3.2		
5	**3**	75.2	0.1M[a])	3.6×10^{-2}M	5.5	0.29 ± 0.02		
6	**3**	80.0	0.1M	3.6×10^{-2}M	5.5	0.64 ± 0.04		
7	**3**	84.3	0.1M	3.6×10^{-2}M	5.5	0.82 ± 0.03	118.6	107.3 ± 13.7
8	**3**	90.2	0.1M	3.6×10^{-2}M	5.5	1.49 ± 0.06		
9	**1**	85.0	62.5%	5.0×10^{-4}M[c])	2.5	13.2 ± 0.6		
10	**1**	100.5	62.5%	5.0×10^{-4}M	2.5	20.4 ± 1.8	102.9 ± 13.3	49.7 ± 10.4
11	**1**	120.5	62.5%	5.0×10^{-4}M	2.5	63.2 ± 1.4		
12	**1**	103.0	62.5%	3.6×10^{-2}M[d])	5.5	19.5 ± 0.25		
13	**1**	113.5	62.5%	3.6×10^{-2}M	5.5	30.05 ± 2.0		

[a]) At this concentration, only the monomeric hydrated form of **3** is present [15].

[b]) The ratio of epimers (**1** and **2**) was determined by HPLC. The separation was performed on a *Bio Rad*'s *Aminex HPX-87C* monosaccharides analysis column (300 × 7.8 mm) equipped with a thermostated jacket, with H_2O at 85.0° as the eluant. The compounds were detected with a refractive index detector connected to an integrator. The rate of racemization of **3** was determined with a *Perkin-Elmer M141* polarimeter equipped with thermostated cells. The presence of dihydroxy-acetone was controlled by ^{13}C-NMR, and was found to be *ca.* 10% after 24 h at 80°, in accordance with an earlier finding of *Königstein* for D,L-glyceraldehyde [16].

[c]) In these runs, the concentration of the catalyst and of **1**, and the pH were those usually applied in the industrial scale isomerization process [13].

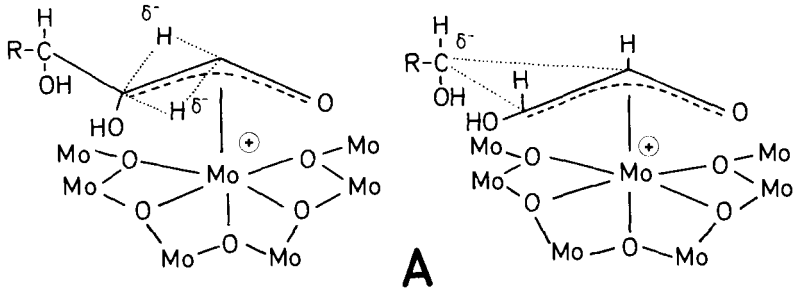
[d]) The catalyst was anhydro-heptamolybdate.

[2]) This process is used for the industrial-scale production of D-mannose and subsequently for D-mannitol [13] [14].

carbonylic (acyclic) form in a D-glucose solution than in a D-glyceraldehyde solution, at higher temperatures[3]).

We have also found that heptamolybdate catalyzes the isomerization of tri-*O*-acetyl-D-glucal (**4**) and tri-*O*-acetyl-D-galactal (**5**) into pseudo-glycals **6** and **7**, respectively at 110° in Ac_2O. The equilibrium **4**⇌**6** and **5**⇌**7** was established after approximately 10–15 min, with the reactant to product ratio of approximately 35:65. We noticed that this reaction was accompanied by an interesting and reversible thermochromic effect; at *ca.* 110°, the reaction solution became slightly yellow, but changed to green on cooling. Following this observation, we prepared a deep-blue crystalline material from ammonium heptamolybdate by a brief heating in Ac_2O at reflux temperature, which we named 'anhydro-heptamolybdate' in the absence of the exact structural data[4]). This new compound catalyzed the isomerization of **1** with approximately the same rate as the heptamolybdate (*Table, Runs 12* and *13*), without the loss of its characteristic blue colour.

On the basis of the results outlined, we believe that the driving force for the C(2) epimerization is not simply the oxo-complexation of a monosaccharide molecule by molybdate ions [5] [6], but also involves a d-π interaction between the central Mo(VI) atom of the heptamolybdate ion and the carbonylic (acyclic) form of the monosaccharide. This interaction could enable a H-shift between C(1) and C(2), or nucleophilic attack of C(3) on C(1) *via* transitory tricentric bond [6], *via* an oxaallylic cation-like transition state **A**.



A

It is known that in some Mo(VI) d^{18}-complexes [18] [19], H^- and AcO^- ions attack intermolecularly at one terminus of the allylic cation ligand. The central Mo(VI) atom in heptamolybdate apparently catalyzes analogous intramolecular nucleophilic processes in **1**–**7**, leading to the equilibria discussed above. A study of this processes with other monosaccharides is in progress[5]).

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[3]) D-Glyceraldehyde is completely hydrated at 80° in 0.1M solution [15]; analogous data for D-glucose are not published.

[4]) The Mo content in this compound (*ca.* 85%) was found to be much higher than for recently described molybden oxides [17]. Spectroscopic data does not allow structure assignment, while microcrystalline samples obtained as yet were inconvenient for X-ray single-crystal structure determination.

[5]) After this manuscript was submitted for publication, a paper appeared [20], in which epimerization of aldoses by [nickel(II)(tmen)$_2$(H_2O)$_2$$Cl_2$] complex (tmen = *N,N,N'*-trimethylethylenediamine) is described. This result also excludes the oxo-complex formation of monosaccharides as the substantial driving force for C(2)-epimerization, while a metal-aldose electronic interaction could be expected in this process, as well. The authors announced clarification of the detailed mechanism of this reaction [20].

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