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The kinetics of the molybdate-catalysed epimerization of D-glucose and D-mannose in aqueous solutions

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Abstract

The kinetics of the molybdate-catalyzed epimerization of D-glucose and D-mannose in aqueous solutions have been investigated. Batch experiments were carried out at initial sugar concentrations from 0.3 to 3 kmol m⁻³, molybdenum concentrations from 0.3 to 40 mol m⁻³, temperatures from 330 to 363 K and pHs from 1.9 to 3.1. Titrations of sugar/molybdate solutions with HCl could be described by the formation of dimolybdate complexes. The complexation and ionization equilibria are such that free molybdates can be neglected. The epimerization of D-glucose is faster than that of D-mannose. The rate of epimerization shows a maximum at a pH of 2.5.

The kinetic observations are explained by a reaction sequence with a rate-determining step involving molybdate complexes of D-glucose and D-mannose as reactive intermediates and with the protonation or deprotonation of these intermediates leading to less active complexes.

Introduction

D-Mannitol can be produced by the hydrogenation of D-glucose/D-fructose solutions and subsequent separation of the desired product from the reaction mixture. An alternative route for D-mannitol manufacture consists of the catalytic epimerization of D-glucose to D-mannose, the hydrogenation of D-mannose and the crystallization of D-mannitol [1]. D-Mannose as such can also be applied in the manufacture of more sophisticated chemicals such as D-mannonic acid, D-mannaric acid and 2,6-anhydro-D-mannopyranose.

There have been extensive studies [2–11] on the epimerization of monosaccharides catalysed by molybdic compounds in aqueous media, beginning with those of Bilik and coworkers [2–8]. It has been found that the rate of reaction is highest at a pH from 2.5 to 3.5. Moreover, the conversion of D-glucose to D-mannose is reported to be much faster than the reverse reaction [4, 9].

So far, kinetic data on the epimerization have been mostly analysed in terms of first order kinetics with respect to the monosaccharide [4, 8, 9,

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10]. The first order coefficients were found [8] to be dependent on conversion, however. The only exception is the work of Sankovic *et al.* [12] where kinetic data were interpreted in terms of Michaelis–Menten kinetics. Moreover, neither the influence of pH nor of catalyst concentration on the rate of the epimerization has been accounted for to date.

An extensive investigation of the kinetics of the molybdate-catalysed epimerization of aqueous D-glucose/D-mannose solutions is reported in the present paper. The objective of the kinetic study was to develop a rate equation allowing prediction of conversions for various process conditions and to obtain further insight into the reaction sequence.

Experimental

Titration

Solutions containing D-glucose or D-mannose and Na_2MoO_4 were titrated with 1 N HCl. The pH values were recorded with a potentiometer (Radiometer Titrigraph TTT80) after equilibration. The titration conditions are summarized in Table 1. In total, 402 experimental data with D-glucose and 254 with D-mannose were regressed at ambient temperature.

Batch epimerization

A glass reactor of 350 cm³ was equipped with a stirrer, a reflux condenser, a feed vessel of 100 cm³, a pH-electrode and a thermometer. The reactor and the feed vessel were jacketted and the temperature was controlled within 0.2 K by water circulation.

Each batch experiment was started by adding an ammonium heptamolybdate solution from the supply vessel to the sugar solution in the reactor, both solutions being at reaction temperature. The use of other molybdate sources such as combinations of HCl or H_2SO_4 and MoO_3 or Na_2MoO_4 did not result in different kinetic behaviour. The pH was set by adding an appropriate amount of HCl to the sugar solution. For each experimental run, 15 to 20 samples were withdrawn at specific times, neutralized with a NaHCO_3 solution, stored in the refrigerator at 277 K and analyzed by HPLC.

TABLE 1
Experimental conditions

Parameter	Titration	Batch epimerization	Continuous epimerization
$[\text{G}]_0$ (kmol m ⁻³)	0.1–4.1	0.6–3.0	1.2
$[\text{M}]_0$ (kmol m ⁻³)	0.1–1.3	0.3–1.2	–
Mo_t (mol m ⁻³)	20–70	0.3–40	10
pH	1.5–7.6	1.9–3.2	2.2–3.1
T (K)	298–343	330–363	325–386

The monohydrate of α -D-glucose was used as feedstock for 79 runs, and 25 runs were performed with α -D-mannose as feedstock. A total of 1582 experimental data were regressed. The range of reaction conditions is listed in Table 1. Batch times amounted up to 400 h.

Continuous flow epimerization

The continuous flow experiments were carried out in a glass, jacketted reactor containing 160 cm³ of liquid, equipped with a stirrer, reflux condenser and an additional electrical heater. Thermostatted water was circulated through the jacket. The temperature inside the reactor was maintained constant within 0.2 K. The solutions of (NH₄)₆Mo₇O₂₄ and sugar were continuously fed to the reactor by piston pumps. The volumetric feed flow rate ranged from 0.022 to 0.070 cm³ s⁻¹. The pH of the solution was measured at the outlet and appropriately adjusted by acidifying the molybdate feed solution with HCl.

Steady-state conditions were reached after 10 h only. After this period, 6 to 10 samples were taken over a period of 3 to 5 h. In total 16 runs were performed. Table 1 shows the range of reaction conditions.

Analysis

Samples were diluted 10- to 20-fold with water to obtain a concentration of 60 to 120 mol m⁻³. Calibration samples were made up from standard D-glucose and D-mannose solutions with compositions covering the experimental conversion range: D-glucose/D-mannose ratios from 100/0 or 0/100 to 65/35.

The samples of 10 μ l were analyzed by HPLC. The column, with a length of 25 cm and a diameter of 4.6 mm, was packed with BC-X8-H⁺ resin and kept at 338 K. The eluent consisted of 0.005 M H₂SO₄ at a flow rate of 0.2 cm³ min⁻¹. The detection was based on refraction and occurred at 313 K. The detector signal was integrated digitally. No side products were detected.

Conversion and reaction rate

The conversion was calculated from:

$$X = \frac{[G]_0 - [G]}{[G]_0 + [M]_0} = \frac{[M] - [M]_0}{[G]_0 + [M]_0} \quad (1)$$

neglecting density changes. The analytical procedure led to an absolute error below 1% for the conversion.

As the selectivity for epimerization amounted to 100%, the epimerization rate was obtained directly from the mass balance for D-glucose or D-mannose. The corresponding continuity equation in the batch reactor is given by:

$$\frac{dX}{dt} = \frac{r}{([G]_0 + [M]_0)} \quad (2)$$

At low enough conversions the effect of conversion on the rate can be neglected, *i.e.* the reactor is operated differentially, and the continuity equation

leads to:

$$r_0 = \frac{X}{t} ([G]_0 + [M]_0) \quad (3)$$

with r_0 the initial rate of epimerisation. In the continuous flow stirred tank reactor, the continuity equation for D-glucose leads to:

$$X = \frac{V_r/F}{([G]_0 + [M]_0)} r \quad (4)$$

Parameter estimation

The regression of the experimental data was based on the maximum-likelihood criterion. Parameter estimates were obtained by minimization of the sum of squares of the residuals between the observed and the calculated values of the pH in the case of titrations and of the conversion in the case of batch epimerization. This minimization was achieved with a single-response Marquardt algorithm [13]. The mathematical models leading to calculated values consisted of algebraic equations originating from equilibrium relations in the case of titrations or from the continuity equation (2) in the case of batch epimerization.

The parameter estimates were tested for statistical significance by means of their approximate individual t values. The limits on the parameter estimates shown in Tables 2 and 3 correspond to the individual 95% confidence intervals. The linear correlation between two parameter estimates is expressed by the binary correlation coefficient, defined as the ratio of the covariance to the square root of the product of the corresponding variances. The statistical significance of the global regression was expressed by means of the ratio of the mean regression sum of squares to the mean residual sum of squares, which is distributed according to F [14]. A high value of the F ratio corresponds to a high significance of the global regression. The adequacy of the mathematical models used for the regression was tested by an analysis of the residuals. Discrimination among rival models was based on this statistical testing, whenever it was not possible by direct observation or by physico-chemical laws.

TABLE 2

Estimates for the major equilibrium constants shown in Fig. 2 by regressing the titration data with eqns. (6)–(11), $T_m = 296$ K

Parameter	Value $\pm$ confidence limits
$\log K_{2,2,1,G}$	13.55 ± 0.04
$\log K_{2,2,1,M}$	14.56 ± 0.03
$pK_{2,G}$	3.62 ± 0.05
$pK_{2,M}$	3.46 ± 0.02

TABLE 3

Parameter estimates obtained by regressing the 1582 batch reactor data with rate eqn. (16), $T_m = 348$ K .

Parameter	Value $\pm$ confidence limits
ΔS_r° (J mol ⁻¹ K ⁻¹)	1.322 ± 0.009
ΔH_r° (kJ mol ⁻¹)	3.47 ± 1.09
A_o (10 ⁺¹⁷ s ⁻¹)	6.65 ± 0.52
E_a (kJ mol ⁻¹)	126.1 ± 1.4
$K_{3,2,1,M}/K_{3,2,1,G}$	26.8 ± 2.3
$pK_{2,G}$	4.11 ± 0.30
$pK_{2,M}$	3.81 ± 0.06
$pK_{1,G}$	1.82 ± 0.08
$pK_{1,M}$	0.49 ± 0.07

To facilitate the estimation of activation energies and/or heat of reaction, a re-parametrization was applied:

$$k = A_o \exp\left(-\frac{E}{RT}\right) = A'_o \exp\left[-\frac{E}{RT}\left(\frac{1}{T} - \frac{1}{T_m}\right)\right] \quad (5)$$

with T_m the average temperature of the experiments.

Equilibria in aqueous molybdate solutions

It is well known [15–21] that numerous polyanions are formed from molybdic acid in aqueous solutions. Sugars, moreover, form complexes with molybdates [22–31]. The relative stability of the different species depends on the pH, the monomolybdate and the sugar concentrations. This can be accounted for considering reactions of the type:

the equilibrium coefficient of which, $K_{p,q,r}$, being the stability constant for the $\text{S}_r \text{H}_{p-2n} \text{Mo}_q \text{O}_{4q-n}^{(2q-p)-}$ species. For dilute solutions the following relation holds at equilibrium

$$K_{p,q,r} = \frac{[\text{S}_r \text{H}_{p-2n} \text{Mo}_q \text{O}_{4q-n}^{(2q-p)-}]}{[\text{H}^+]^p [\text{MoO}_4^{2-}]^q [\text{S}]^r} \quad (6)$$

For sugar-free solutions, stability constants, $K_{p,q,0}$, have been reported at room temperature for anions containing up to 36 molybdenum atoms. Equilibrium calculations show that the hepta- and octamolybdate polyanions are the most abundant species at a pH and a monomolybdate concentration typical for molybdate-catalysed epimerization. At these conditions the dimolybdate concentration is at least two orders of magnitude lower.

Less is known about the relative stabilities of polymolybdate anions complexed with sugars. Potentiometric titrations and ^{95}Mo NMR led Verchere and Chapelle [22] to the conclusion that a single molecule of D-mannose forms an anionic complex with dimolybdate in acidic solutions at room temperature. To obtain more detailed information, potentiometric titrations have been performed close to epimerization conditions, *viz.* Table 1. Figure 1 shows two typical titration curves at room temperature, one for D-glucose and one for D-mannose. Apparently there is a first equivalence point for both D-glucose and D-mannose at which one mole of HCl per mole of monomolybdate has been added. A second equivalence point seems to be reached after adding three moles of HCl per two moles of monomolybdate. Thus the titration curves indicate that equilibria involving p/q ratios of 1 and 1.5 are important at the conditions investigated. This points to species such as $\text{SMo}_2\text{O}_7^{2-}$ and $\text{SHMo}_2\text{O}_7^-$ respectively, as shown in Fig. 2. The form of the titration curves clearly does not allow an accurate estimation of stability constants such as $K_{2,2,1}$ and $K_{3,2,1}$ based on the equivalence points of a single titration. Therefore a regression of all the titration data at room temperature, *i.e.* for different monomolybdate and sugar concentrations, both D-glucose and D-mannose, was performed to obtain these estimates. The most significant regression was obtained by taking into account the equilibria shown in Fig. 2, the equilibria describing the relative stabilities of the most important molybdate polyanions in sugar-free solutions, *i.e.* 20 equations similar to (6) with $r=0$, the Mo balance:

$$\begin{aligned} \text{Mo}_t = 2 & ([\text{SMo}_2\text{O}_7^{2-}] + [\text{SHMo}_2\text{O}_7^-] + [\text{SH}_2\text{Mo}_2\text{O}_7]) \\ & + \sum_k q_k [\text{MoO}_4^{2-}]^{q_k} [\text{H}^+]^{p_k} K_{p,q,0} + [\text{MoO}_4^{2-}] \end{aligned} \quad (7)$$

Fig. 1. Titration curves at room temperature, $[\text{S}] = 1.3 \text{ kmol m}^{-3}$, $\text{Mo}_t = 20 \text{ mol m}^{-3}$. Points (experimental values): D-glucose (■), D-mannose (●). (—) calculated from eqns. (6)–(11) with estimates from Table 2.

and, finally, the charge balance:

$$[\text{Na}^+] + [\text{H}^+] = [\text{Cl}^-] + 2 [\text{SMo}_2\text{O}_7^{2-}] + [\text{SHMo}_2\text{O}_7^-] + \sum_k (p_k - 2q_k) [\text{H}^+]^{p_k} [\text{MoO}_4^{2-}]^{q_k} K_{p,q,o} + 2[\text{MoO}_4^{2-}] \quad (8)$$

Table 2 gives the obtained estimates for the sugar complexation constants, $K_{2,2,1}$, and for the proton dissociation constant, K_2 .

Note that:

$$\log K_{3,2,1} = \log K_{2,2,1} + \text{p}K_2 \quad (9)$$

As at equilibrium:

$$K_2 = \frac{[\text{H}^+] [\text{SMo}_2\text{O}_7^{2-}]}{[\text{SHMo}_2\text{O}_7^-]} \quad (10)$$

The estimates for the equilibria involving D-mannose agree with the values reported by Verchere and Chapelle [22]. The third equilibrium, shown in Fig. 2, must be included to describe adequately the titration curves at pH values lower than 3:

$$K_1 = \frac{[\text{H}^+] [\text{SHMo}_2\text{O}_7^-]}{[\text{SH}_2\text{Mo}_2\text{O}_7]} \quad (11)$$

The corresponding $\text{p}K_1$ estimates, amounting to 0.85 for D-glucose and 1.54 for D-mannose, are less accurate. Possibly this is caused by the decomposition of the uncharged complex into polymolybdates and sugar or by the formation of higher polymolybdate sugar complexes at these low pH values. The largest binary correlation coefficient amounts to 0.35. Figure 3 shows a parity diagram for the titrations with D-mannose. The parity diagram for D-glucose is similar. Clearly, it is sufficient to consider the species and equilibria shown in Fig. 2 to describe adequately the titration experiments at room temperature. Equilibria involving hepta- or octamolybdates did not allow such a description. The obtained estimates for the equilibrium constants corresponding to Fig. 2 allow, together with the $K_{p,q,o}$ constants from the literature, calculation of the equilibrium concentrations of the free molybdates and the sugar molybdate complexes. At sugar/molybdenum ratios and pH values typical for the molybdate-catalysed epimerization, more than 97% of the molybdate is present

Fig. 2. Main species and equilibria in aqueous solutions of D-glucose or D-mannose, S, and molybdate. [S] 0.1–4 kmol m⁻³, Mo₆ 20–70 mol m⁻³, pH 7.7–1.5 and T 298–343 K.

Fig. 3. Parity diagram for the titrations with D-mannose at room temperature.

in the form of the sugar complexes shown in Fig. 2. Free molybdate anions become only significant at pH values higher than 5. Hence, the molybdenum balance at pH values lower than 5 reduces to:

$$\text{Mo}_t = 2 ([\text{SMo}_2\text{O}_7^{2-}] + [\text{SHMo}_2\text{O}_7^-] + [\text{SH}_2\text{Mo}_2\text{O}_7]) \quad (12)$$

and the concentrations for the sugar complexes depend only on the total molybdenum concentration and the equilibrium constants of the protonation steps, *e.g.* for $[\text{SHMo}_2\text{O}_7^-]$:

$$[\text{SHMo}_2\text{O}_7^-] = \frac{\frac{1}{2} \text{Mo}_t}{1 + [\text{H}^+]/K_{1,S} + K_{2,S}/[\text{H}^+]} \quad (13)$$

It follows from eqn. (13) that $[\text{SHMo}_2\text{O}_7^-]$ reaches a maximum for:

$$\text{pH}_{\max} = \frac{1}{2} (\text{p}K_{1,S} + \text{p}K_{2,S}) \quad (14)$$

Obviously, there are no maxima for $[\text{SMo}_2\text{O}_7^{2-}]$, nor for $[\text{SH}_2\text{Mo}_2\text{O}_7]$ at pH values lower than 5.

Some titrations were performed at temperatures above ambient in order to investigate the temperature dependence of the equilibria shown in Fig. 2. Interference of epimerization while titrating inhibited quantification of the latter. The heat of complexation lies between 20 and 40 kJ mol⁻¹, which is low enough to extrapolate the conclusions derived from the titrations at room temperature to typical epimerization temperatures.

Kinetics of epimerization

Influence of the reaction conditions on the initial rate of epimerization

Figure 4 shows typical conversion *versus* time curves obtained in the batch reactor. The rate of epimerization of D-glucose to D-mannose is much

Fig. 4. X/X_E vs. time curve for D-glucose (■) and D-mannose (●), 346 K, pH=2.50, $[S]_0=1.2$ kmol m⁻³, $Mo_0=10$ mol m⁻³, batch reactor. (—) Calculated from integration of eqn. (2) with rate eqn. (16) and the parameter estimates from Table 3.

Fig. 5. Initial rate of D-glucose epimerization vs. molybdenum concentration, 248 K, pH=2.67±0.14, $[G]_0=1.2$ kmol m⁻³.

higher than the rate of epimerization of D-mannose to D-glucose. Equation (3) applies to the linear part of such curves and allows calculation of the initial rates of epimerization from them.

Figure 5 shows a linear dependence of the initial rate on the molybdenum concentration. The influence of the sugar concentration is shown in Fig. 6 to be absent. Both of these observations can be explained by eqn. (13) if it is assumed that there exists a rate-determining step involving $SHMo_2O_7^-$.

The influence of the pH on the initial rate of epimerization is shown in Fig. 7. The initial rate reaches a maximum at a pH of ~2.5 for both D-glucose and D-mannose, which is close to the values of pH_{max} calculated from eqn. (14) and the estimates for $pK_{1,s}$ and $pK_{2,s}$ reported in the previous section. This agreement can be understood if $SHMo_2O_7^-$ is the only species involved in the rate-determining step of the epimerization.

Fig. 6. Initial rate of D-glucose epimerization *vs.* sugar concentration, 348 K, $\text{pH} = 2.70 \pm 0.03$, $\text{Mo}_t = 10 \text{ mol m}^{-3}$.

Fig. 7. Initial rate of epimerization *vs.* pH. D-glucose (●), D-mannose (■), 348 K, $\text{Mo}_t = 10 \text{ mol m}^{-3}$, $[\text{S}]_0 = 1.2 \text{ kmol m}^{-3}$.

D-Glucose and D-mannose are present in the form of α - and β -pyranose anomers in aqueous solutions. The so-called mutarotation from one anomer to the other occurs through the relatively unstable aldehyde form at rates which can be estimated to be at least two orders of magnitude higher than the rate of epimerization [32]. Hence, it can be expected that the initial rate of epimerization of D-glucose or D-mannose will not be affected by the initial ratio of the anomers. Replicate experiments were performed in the continuous flow stirred tank reactor set-up, *viz.* Table 1. One set of these experiments was performed with a feed containing mainly α -D-glucose, another set with a feed containing mainly β -D-glucose. There was no statistically significant difference in the initial rate of epimerization between the α -D-glucose-rich feed and β -D-glucose-rich feed. Hence, the kinetics of epimerization can be based on the combined, *i.e.* without distinguishing between the anomers, concentrations of D-glucose and D-mannose.

Reaction sequence for epimerization

The observations reported in the two previous sections lead to the reaction sequence for epimerization shown in Fig. 8. It features a rate-determining step consisting of the monomolecular transformation of a molybdate complex of glucose into a molybdate complex of mannose. These complexes are in a dynamic equilibrium with the free molybdate anion and sugar, the equilibrium being strongly towards to complexed side. The complexation equilibria shown in Fig. 8 are obviously not elementary reactions. The details of these reactions are not kinetically significant as long as the carbon skeleton rearrangement step is rate-determining. It is postulated that the complex is formed with a dimolybdate anion in analogy with the existing equilibria in the absence of epimerization, *viz.* Fig. 2. Finally, the pH dependence of the rate of epimerization requires that the complex involved in the rate-determining step can dissociate a proton and can be protonated. Hence, $\text{SHMo}_2\text{O}_7^-$, which also features in the reactions describing the equilibria in the absence of epimerization, is proposed as the reaction intermediate involved in the rate-determining step.

Rate equation for epimerization

If it is assumed that the reaction sequence shown in Fig. 8 is the only significant one, the rate of epimerization follows from the application of the law of mass action on the carbon skeleton rearrangement step:

$$r = k_G[\text{GHMo}_2\text{O}_7^-] - k_M[\text{MHMo}_2\text{O}_7^-] \quad (15)$$

Taking into account the equilibria of the other reactions shown in Figs. 2 and 8, eqns. (6), (10) and (11) as well as the absence of uncomplexed molybdate anions, eqns. (12) and (13), leads to a rate equation featuring only observable process variables and thermodynamic and kinetic parameters:

$$r = \frac{\frac{1}{2} k_G K_{3,2,1,G} \text{Mo}_i ([G] - [M]/K)}{(1 + [\text{H}^+]/K_{1,G} + K_{2,G}/[\text{H}^+]) K_{3,2,1,G} [G] + (1 + [\text{H}^+]/K_{1,M} + K_{2,M}/[\text{H}^+]) K_{3,2,1,M} [M]} \quad (16)$$

Fig. 8. Reaction sequence for the epimerization of D-glucose, G, into D-mannose, M, in aqueous molybdate solutions. [S] 0.3–3.0 kmol m⁻³, Mo_i 0.30–40 mol m⁻³, pH 1.9–3.2 and T 325–386 K.

Analogous rate expressions are well known in enzyme catalysis [33]. Rate eqn. (16), far from equilibrium, yields expressions completely consistent with the observed dependencies of the initial rate of epimerization on the reaction conditions. It predicts in particular a maximal initial rate at a pH given by eqn. (14) and this pH is also characteristic for the maximum concentration of $\text{SHMo}_2\text{O}_7^-$. Note that a reaction sequence for epimerization involving $\text{SMo}_2\text{O}_7^{2-}$ or $\text{SH}_2\text{Mo}_2\text{O}_7$ in the carbon skeleton rearrangement step would not lead to a rate equation in agreement with the observed pH dependency. A reaction sequence with another complexed molybdate, *e.g.* $\text{SHMo}_7\text{O}_{24}^{5-}$, would lead to a rate equation analogous to eqn. (16), however. The only difference would be the physical meaning of the parameters and the substitution of the factor of 1/2 by a factor of 1/7.

If the temperature dependence of the protonation–deprotonation equilibria, eqns. (10) and (11), and of $K_{3,2,1,M}/K_{3,2,1,G}$ is neglected over the investigated range, rate eqn. (16) contains 9 independent parameters which are listed in Table 3. The available literature data on the standard enthalpies and entropies of formation of D-glucose and D-mannose [34] were not considered accurate enough to allow a reliable *a priori* calculation of the standard enthalpy and entropy of epimerization. Table 3 also shows the parameter estimates obtained by regression of the experimental data obtained in the batch reactor.

The maximum linear correlation occurs between E_a and both ΔS° , and ΔH° , and leads to a binary correlation coefficient of 0.88. The ratio of the mean regression sum of squares to the mean residual sum of squares amounts to more than 100,000. The solid lines in Fig. 4 are obtained by integration of the continuity equation for D-glucose (2) with rate eqn. (16) and with the parameter estimates reported in Table 3. The parity diagram shown in Fig. 9 shows the adequacy of the proposed rate equation. A further validation of rate eqn. (16) and the parameter estimates listed in Table 3 follows from

Fig. 9. Calculated *vs.* experimental conversions. The calculated values are obtained from integration of eqn. (2) with rate eqn. (16) and the parameter estimates from Table 3. Batch reactor.

Fig. 10. Calculated vs. experimental conversions. The calculated values are obtained from eqn. (4) with rate eqn. (16) and the parameter estimates from Table 3. Continuous flow stirred tank reactor.

the comparison of the conversions calculated using eqn. (4) with the conversions observed in the continuous flow stirred tank reactor set-up, see Fig. 10. No regression was involved in this case. Finally, it should be mentioned that several other rate equations have been tested. Rate eqn. (16) gives by far the best description of the experimental observations.

Equilibrium coefficient for epimerization

The estimates for the standard reaction enthalpy and entropy reported in Table 3 lead to an equilibrium coefficient, K , of 0.35 and an equilibrium conversion, X_E , of 0.26 at 348 K in reasonable agreement with the value given in the literature [1,4,5,8,12]. As the rate eqn. (16) describes the combined kinetics of epimerization, this holds also for the above values. It is possible to calculate the equilibrium coefficient of a reaction between combined components assuming internal equilibrium in each component [35]. Assuming equilibrium among the anomers of D-glucose and D-mannose and using the available thermodynamic literature data for each of them [34], a value is obtained for the equilibrium coefficient, K , in accordance with the value based on Table 3. This is in line with the process observations mentioned earlier and validates the description of the epimerization based on combined kinetics.

Rate coefficients for epimerization

Based on Table 3, eqn. (5) and:

$$k_M = \frac{k_G K_{3,2,1,G}}{K K_{3,2,1,M}} \quad (17)$$

lead to values for the rate coefficient of the rate-determining step ranging from 0.01 to 0.5 s⁻¹. The rate coefficient k_M is an order of magnitude smaller than k_G , which explains the observations shown in Fig. 4. A typical initial

TABLE 4

Standard activation enthalpies and entropies for the rate-determining step in the epimerization, $T_m = 358$ K

	G → M	M → G
$\Delta^\# H^\circ$ (kJ mol ⁻¹)	123	129
$\Delta^\# S^\circ$ (J mol ⁻¹ K ⁻¹)	87	58

turnover frequency of D-glucose, *i.e.* the initial rate per mole of molybdenum, amounts to 0.3 s⁻¹ at 348 K.

The high value for the frequency factor, A_o , can only be understood if degrees of freedom other than the translational one can help to overcome the activation barrier. Experimental evidence for the importance of activation in many degrees of freedom indeed mainly concerns unimolecular reactions [36]. Note that a rate equation based on a rate-determining step involving complexed heptamolybdate would have given rise to an even higher frequency factor.

The high frequency factor corresponds to high standard activation entropies, as indicated in Table 4, which shows the standard activation enthalpies and entropies for the rate-determining step based on Table 3 and:

$$E_a = \Delta^\# H^\circ + RT \quad (18)$$

$$A_o = \frac{e RT_m}{N_A h} \exp(\Delta^\# S^\circ / R) \quad (19)$$

The obtained standard activation entropies are approximately 40 J mol⁻¹ K⁻¹ higher than those reported by Sankovič *et al.* [12] at a pH ~5.5, whose values are close to those listed in Table 4. Hence, the higher pH seems to impose some steric requirements on the rate-determining step. It should be noted that, according to the data presented in Table 2, $\text{SMo}_2\text{O}_7^{2-}$ is the most abundant molybdate complex at a pH of 5.5. This suggests that an epimerization route involving $\text{SMo}_2\text{O}_7^{2-}$ in the rate-determining step is slower than the route prevailing at the conditions investigated in the present work. Finally, it follows from Table 4 that the difference between k_G and k_M is caused by the standard activation entropy differences.

Complexation and ionization coefficients

Table 3 shows that the dimolybdate mannose complex is much more stable than the dimolybdate glucose complex. If the $K_{3,2,1,M}/K_{3,2,1,G}$ ratio is calculated from the titration experiments using the data in Table 2 and eqn. (9), a value of 7.1 is obtained. This corresponds to a complexation of D-glucose which is slightly more exothermic than that of D-mannose. The titration results indicated heats of complexation between 20 and 40 kJ mol⁻¹.

A comparison of the values of the second ionization coefficients, $K_{2,S}$, reported in Tables 2 and 3 indicates an even smaller temperature dependency

for the ionization steps. The above comparisons justify *a posteriori* the neglect of the mentioned temperature dependencies during the regression of the batch epimerization data.

The differences between the first and the second ionization coefficients are typical for weak acids with two ionizable protons.

Discussion of the epimerization mechanism

Two points are debated in the literature on the molybdate-catalysed epimerization: the nature of the catalytically active molybdate anion and the form in which the monosaccharide interacts with the former.

Sanković and Sunjić [11, 12] suggested on the basis of a kinetic study that heptamolybdate anions are responsible for the epimerization through an oxo-allylic transition state involving d- π interaction between the aldehyde form of the monosaccharide and the central Mo(VI) atom of the anion.

The aldehyde form had been proposed already by Hayes *et al.* [9, 10] as ligand, but with a dimolybdate as anion. It was proposed that the complexation with the molybdate anion induced a rehybridization so that in the transition state C-1 and C-2 have the same hybridization and form a tricentric bond with C-3. The configuration at C-3 is maintained, while bond breaking and bond formation occur on the same face of this carbon. The hypothesis of a dimolybdate as major anion was confirmed by Verchere and Chapelle [22] who excluded the aldehyde form of the monosaccharides on the basis of ^{13}C NMR, however.

The results reported here favor the hypothesis that a dimolybdate anion is catalytically active in the epimerization. No conclusions can be drawn concerning the form of the monosaccharide involved in the reactive complex, however. The degree of protonation of the reactive complex could be important in that respect. It can be envisaged that a double negative ion is formed from a pyranose form and $\text{Mo}_2\text{O}_7^{2-}$, whereas upon protonation this complex could give an open chain form similar to the structure proposed by Hayes *et al.* [9, 10].

Conclusions

The kinetics of the molybdate-catalysed epimerization of D-glucose and D-mannose can be described adequately over a broad range of reaction conditions by a relatively simple rate equation. This rate equation is based on a reaction sequence with a monomolecular rate-determining step consisting of the carbon skeleton rearrangement. The latter is facilitated by the complexation of the reactant with a dimolybdate anion. The strength of the complexation is such that at the conditions investigated the presence of free molybdates can be neglected. The dependence of the epimerization rate on

the pH can be accounted for by ionization equilibria of the complexes considered as weak acids with two ionizable protons.

List of symbols

A_o	preexponential factor, eqn. (5) s^{-1}
e	Euler number, eqn. (19)
E	subscript, equilibrium value
E_a	activation energy, eqn. (5) $J\ mol^{-1}$
F	volumetric flow rate, eqn. (4) $m^3\ s^{-1}$
G	glucose
$[G]_0$	initial glucose concentration $kmol\ m^{-3}$
h	Planck constant, eqn. (19) Js
k_G, k_M	forward and reverse rate constants, eqns. (15), (16) s^{-1}
K	equilibrium constant for epimerization, eqns. (16),(17) dimensionless
K_1, K_2	equilibrium constants for protonation, eqns. (10), (11) $kmol\ m^{-3}$
$K_{p,q,r}$	stability constant for combined complexation and protonation, eqn. (6) $(kmol/m^3)^{1-p-q-r}$
M	mannose
$[M]_0$	initial mannose concentration $kmol\ m^{-3}$
Mo_t	total molybdenum concentration $kmol\ Mo\ m^{-3}$ or $kmol\ Mo$ -complexed m^{-3}
N_A	Avogadro constant, eqn. (19) mol^{-1}
$n_{p,q,r}$	stoichiometric coefficients, eqn. (6)
r	epimerization rate, eqns. (2), (15), (16) $kmol\ m^{-3}\ s^{-1}$
R	gas constant ($=8.3144$) $J\ mol^{-1}\ K^{-1}$
S	sugar, being G or M
t	time s
T	temperature K
T_m	average temperature K
V_r	reactor's liquid volume, eqn. (4) m^3
X	conversion, eqns. (2), (3), (4)

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