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Catalytic Activity of Lanthanide(III) Ions for the Dehydration of Hexose to 5-Hydroxymethyl-2-furaldehyde in Water

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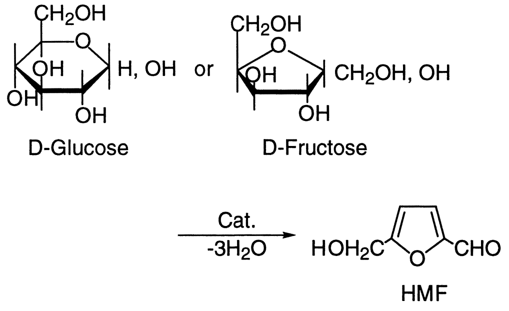
All of the lanthanide(III) (La^{3+}–Lu^{3+}) efficiently catalyzed the dehydration of hexose in water at 140 °C to produce 5-hydroxymethyl-2-furaldehyde (HMF) without accompanying further hydrolysis to levulinic acid, which is routinely obtained as a by-product in the conventional Brønsted acid-catalyzed reactions. The relationships between the catalytic activity and the ionic radius (r_i) of lanthanides(III) for the dehydration of D-fructose and D-glucose were found to have a double-peak profile maximizing at Pr or Nd (r_i 1.00 Å) and Er or Yb (r_i 0.87 Å) with a dip at Sm (r_i 0.96 Å). Kinetic analyses revealed that the rate-determining step is not the complex formation of lanthanide(III) ion with the saccharide molecule, but a subsequent reaction from the substrate-catalyst complex. Possible reasons why the catalytic activity–ionic radius relationships show a two-peak profile are discussed.

Saccharides, including cellulose, have recently attracted much attention as biomass for substituting petroleum resources, and their conversion to useful chemicals has actively been investigated as a promising route to a sustainable, versatile carbon source.[1] The dehydration of hexose, such as D-glucose[2–6] and D-fructose,[4,6–13] giving 5-hydroxymethyl-2-furaldehyde (HMF), has been known as a primary process for converting saccharides to a variety of chemicals (Eq. 1). This reaction is catalyzed by various acids. Thus, Brønsted acids[2–4,6–9,11,12,14,15] have been widely used, while the use of Lewis acids[5,7,10,13] is quite limited in number, probably because they are active as catalysts only in organic solvents. Although it is advantageous that the Brønsted acid-catalyzed dehydration proceeds in aqueous solution, the initial product HMF often suffers further hydration to levulinic acid under the same reaction condition (Eq. 2), and therefore control of the dehydration/hydration processes is difficult in general.[1] In our recent study in search of novel catalysts for converting saccharides to chemicals,[16,17] we found for the first time that lanthanide(III) ions can efficiently catalyze the conversion (dehydration) of saccharides to HMF in organic solvents, such as DMSO and DMF; e.g. D-fructose is converted to HMF in > 90% yield at 100 °C in 3.5 h.[17] More interestingly, this catalyzed dehydration proceeds even in aqueous solutions.[16]



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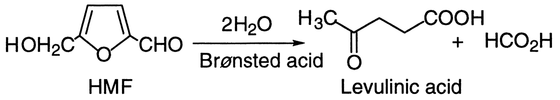


(2)

In this paper, we report on the catalytic activities of lanthanide(III) ions for the dehydration of D-glucose, D-fructose, D-galactose, and D-mannose to HMF in water. We elucidate the relationship between the catalytic activity and the ionic radius of lanthanide(III) for the dehydration reaction of D-glucose and D-fructose, and further discuss the possible factors and mechanisms controlling the activity through kinetic analyses.

Results and Discussion

Catalytic Conversion of Monosaccharides to HMF by Lanthanide(III) Ions. The dehydration of D-glucose, D-fructose, D-galactose, and D-mannose in the presence of a catalytic amount of lanthanide(III) salt was carried out in water at 140 °C in an autoclave. The major product, HMF, was isolated by extraction with benzene, and identified by NMR and mass spectroscopy.[16] The yields of HMF, obtained after heating aqueous solutions of hexoses (0.30 mol dm^{-3}) and lanthanide(III) salts (2.0 mmol dm^{-3}) for 1 h in water at 140 °C, are listed in Table 1. Although practically no HMF was produced in the absence of the lanthanide(III) catalysts, except for the D-fructose case, a catalytic amount of lanthanide(III) dramatically enhanced the rate of HMF production in all cases, as can be seen from Table 1. It is interesting to note that the formation rate of HMF increases with increasing atomic number, or decreasing ionic radius, of lanthanide(III). Among the hexoses used, D-fructose is most efficiently dehydrated to HMF both in the presence and in the absence of lanthanide(III) ions, giving the highest product yields and catalytic enhancements.

Table 1. Yields (in μmol) of 5-Hydroxymethyl-2-furaldehyde (HMF) Produced in the Ln(III)-Catalyzed Reaction of Hexose in Water (15 cm^3) at 140 °C for 1 h

	Catalyst[a]					
Substrate[b]	None	$LaCl_3$	$NdCl_3$	$EuCl_3$	$DyCl_3$	$YbCl_3$
D-Fructose	198	707	741	788	773	831
D-Glucose	trace	125	219	252	333	363
D-Mannose	trace	152	164	234	255	264
D-Galactose	trace	180	182	210	243	222

a) 2.0 mmol dm^{-3}. b) 0.30 mol dm^{-3}.

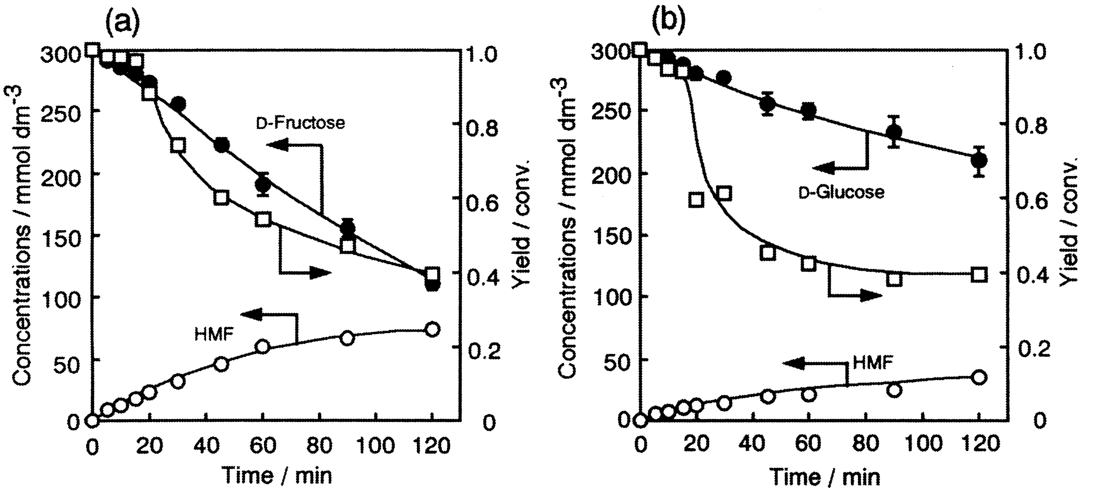
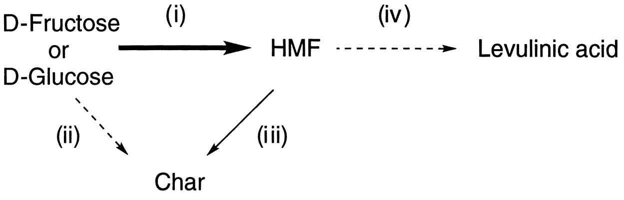


Fig. 1. HMF and substrate concentrations employed in the dehydration reactions of (a) D-fructose and (b) D-glucose catalyzed by $DyCl_3$ (2.0 mmol dm^{-3}) at 140 °C in water: the amounts of substrate (closed circle) and HMF (open circle) and the yield based on consumed substrate (square).

This is consistent with the observations reported for other acid-catalyzed dehydration reactions that ketohexoses, such as D-fructose, afford HMF in better yields than aldohexoses, such as D-glucose, D-galactose, and D-mannose.[8,10,18]

The time profiles of the dehydration of D-fructose and D-glucose catalyzed by $DyCl_3$ in water at 140 °C are shown in Fig. 1, where the amounts of substrate and product, as well as the yield of HMF based on the consumed substrate, are plotted as functions of the reaction time. As can be seen from Fig. 1, both D-fructose and D-glucose are smoothly dehydrated to give HMF catalytically and the product yields based on conversion are higher than 95%, at least in the initial stages of the reaction (< 15 min). However, the material balance gradually decreases after 20 min in both cases, reaching the ultimate product yield of ca. 40% attained at 120 min.[19]

In the elucidation of possible mechanism(s) for the gradually decreasing HMF yield based on the consumed saccharide, we first examine the mechanism of a Brønsted acid-catalyzed reaction of hexoses proposed by Kuster et al. (Scheme 1).[12] There are four successive/competing processes in the Scheme: i.e. (i) production of HMF from hexose, (ii) direct formation of char, a polymeric material insoluble in both water and organic solvents, (iii) indirect formation of char via HMF, and (iv) further hydration of HMF to levulinic acid. In the present case using the lanthanides(III) as catalysts, path (i) is obviously the major process throughout the reaction. The direct path to char (ii) from saccharides does not appear to be catalyzed by lanthanide ions, because the substrate consumption matches to the HMF production, and no appreciable side reaction is seen at the initial stages of the reaction. In order to evaluate the possible intervention of the indirect path (iii), HMF was subjected to catalytic dehydration under the same conditions. Thus, aqueous solutions of HMF (300 mmol dm^{-3}) were heated to 140 °C in the presence and absence of $LaCl_3$ (2.0 mmol dm^{-3}). After 120 min of heating, the amounts of recovered HMF were 219 and 205 mmol dm^{-3} in the presence and absence of the lanthanide catalyst, respectively. Although ca. 30% of HMF was certainly consumed in both cases, the presence of the catalyst did not affect the rate of consumption. These results clear-



Scheme 1. Reaction scheme for acid-catalyzed dehydration of D-fructose or D-glucose, proposed by Kuster et al.[12]; the thick solid line (arrow) (i) denotes the lanthanide catalyzed path, the thin solid line (iii) indicates the non-catalyzed path, and the dashed lines ((ii) and (iv)) denote the steps which were not observed in the lanthanide-catalyzed reactions.

ly indicate that the non-catalytic, indirect char formation, path (iii), occurs in the dehydration of saccharides, consuming the product HMF. Significantly, levulinic acid was not detected in the reaction mixture, even after 120 min, which rules out the possible decomposition of HMF through path (iv) in the present dehydration catalyzed by lanthanides. In summary, we have revealed that the lanthanide-catalyzed dehydration of hexoses preferentially affords HMF in > 95% yield at the initial stages, but unfortunately the product HMF is not stable under the reaction conditions and suffers non-catalytic secondary char formation without accompanying the decomposition to levulinic acid. Since the material balance is excellent and no serious decomposition of HMF to char is observed during the initial stages of the reaction, all of the following discussion is made based on the initial rates.

Catalytic Activity and Ionic Radius of Lanthanide(III). In order to elucidate the relationships between the catalytic activity and the ionic radius of lanthanide(III), the initial rates of catalyzed dehydration were measured for D-fructose and D-glucose in the presence of various lanthanides(III) under comparable conditions. The initial rates are plotted against the ionic radius of lanthanides in Fig. 2,[20] where the net rates for D-fructose were calculated by subtracting the blank rates (obtained in the absence of catalyst) from the observed initial rates in the presence of catalysts. Although the reaction rate (v_0) shows a global increasing tendency with decreasing ionic radius (r_i) from La to Lu, closer examinations of the relationships obtained for both D-fructose and D-glucose exhibit the characteristic two-peak profiles, where the v_0 value maximizes at Pr or Nd (r_i 1.00 Å) and Er or Yb (r_i 0.87 Å) with a drop at Sm (r_i 0.96 Å).

It is well documented that several properties of lanthanide(III) ions are not simple, but discontinuous, functions of the ionic radius, often displaying a break somewhere in the middle of the lanthanide series, most at Gd. For instance, the stability constants of the lanthanide(III) complexes of ethylendiaminetetraacetic acid (EDTA),[21] 1,2-diaminocyclohexane-*N,N,N′,N′*-tetraacetic acid (DCTA),[22] and diethylenetriamine-*N,N,N′,N″,N″*-pentaacetic acid (DTPA),[23] display sudden changes at Gd. However, the break in the rate of dehydration occurs not at Gd, but at Sm, in the present cases. This rather unusual break at Sm may be related to a change in the hydration number. Hydration energy calculations[24] indicate that lanthanide(III) ions lighter than Sm are most stabilized as nonahydrates, while heavier ones are stable as octahydrates. Indeed, the hydration numbers of lanthanide(III) ions in water are reported to be 9 for La to Nd, 8 or 9 for Nd to Tb, and 8 for Tb to Lu.[25–27] Hence, it is not unreasonable to attribute the Sm-break observed for the catalytic activity to the hydration number change somewhere between Nd and Tb. We further discuss the plausibility of this hypothesis later.

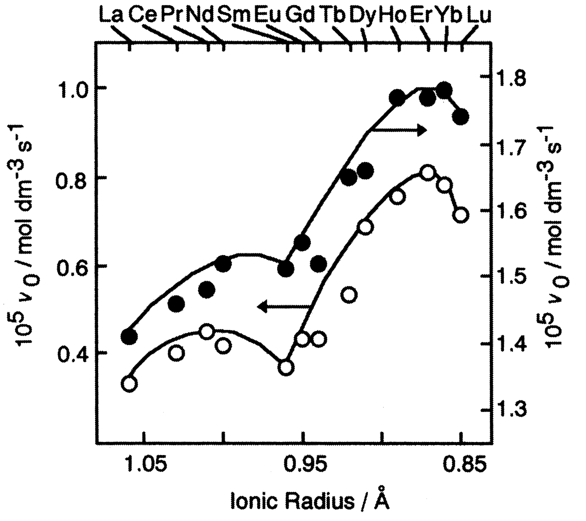
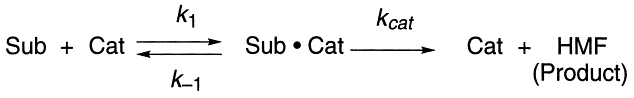


Fig. 2. Relationship between the initial rate (in $\mathrm{dm^3\ mol^{-1}\ s^{-1}}$) and the ionic radius of lanthanides(III) for HMF production from D-fructose (closed circle) and D-glucose (open circle); the catalyst concentration: 2.0 mmol $\mathrm{dm^{-3}}$.

Kinetic Analysis. To effect catalytic dehydration, lanthanide(III) ions have to interact with the saccharide substrates. In order to elucidate the lanthanide(III)–substrate interaction, we first performed NMR measurements with mixtures of several lanthanide ions and hexoses in $\mathrm{D_2O}$. However, no appreciable spectral changes were observed in the shape and chemical shifts of saccharide proton signals. Previous NMR[28] and calorimetric[29] studies also indicate that the interactions between lanthanide(III) ions and neutral saccharides are extremely weak.



Scheme 2. Michaelis–Menten mechanism applied to the lanthanide(III)-catalyzed dehydration of saccharides, where $K_\mathrm{d} = (k_{-1} + k_\mathrm{cat})/k_1$.

In order to gain insights into the nature of lanthanide(III)–saccharide complexes and the subsequent reaction rates, we performed a kinetic analysis based on the Michaelis–Menten-type mechanism, shown in Scheme 2, and the Michaelis–Menten Eqs. 3 and 4. The initial rates of dehydration were measured for D-fructose and D-glucose at varying concentrations of 0.10–0.50 mol $\mathrm{dm^{-3}}$ in the presence of $\mathrm{LaCl_3}$, $\mathrm{NdCl_3}$, $\mathrm{EuCl_3}$, $\mathrm{DyCl_3}$, or $\mathrm{YbCl_3}$ at a fixed concentration of 2.0 mmol $\mathrm{dm^{-3}}$. Plots of the inverse reaction rates against the reciprocal substrate concentrations gave the good straight lines shown in Fig. 3. From the slopes and intercepts of the regression lines, the dissociation constants (K_d) and the catalytic reaction rate constants (k_cat) were calculated (see experimental section for detail). The K_d values obtained are 0.2–0.3 mol $\mathrm{dm^{-3}}$ for D-fructose and 0.2–0.4 mol $\mathrm{dm^{-3}}$ for D-glucose. These large dissociation constants mean weak interaction between the lanthanide(III) ions and the saccharides, which is in good agreement with the results of NMR and calorimetric studies.[28,29]

$$\frac{1}{v_0} = \frac{K_d}{k_{cat}[Cat]_0} \bullet \frac{1}{[Sub]} + \frac{1}{k_{cat}[Cat]_0} \tag{3}$$

$$K_d = \frac{k_{-1} + k_{cat}}{k_1} \tag{4}$$

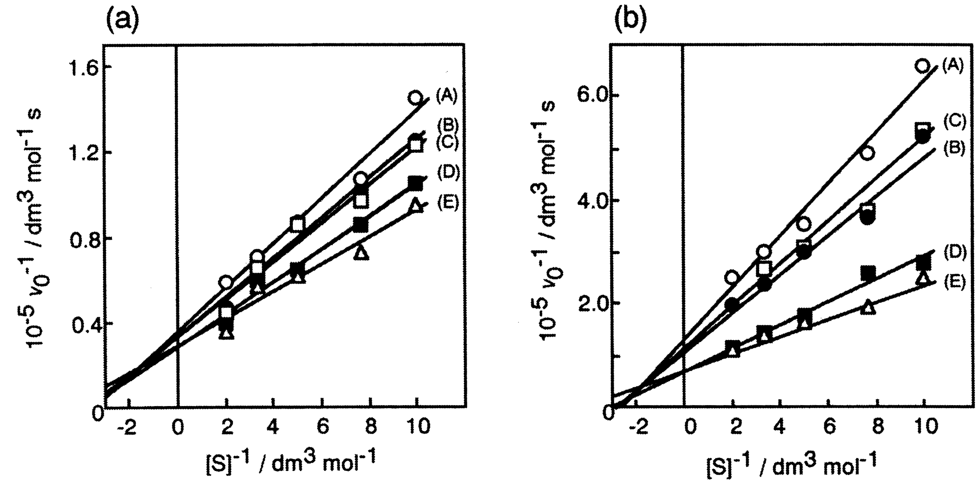


Fig. 3. Plots of v_0^{-1} vs $[S]^{-1}$ for dehydration of (a) D-fructose and (b) D-glucose catalyzed by lanthanide(III) ions (2.0 mmol dm^{-3}): (A) $LaCl_3$, (B) $NdCl_3$, (C) $SmCl_3$, (D) $DyCl_3$, and (E) $LuCl_3$.

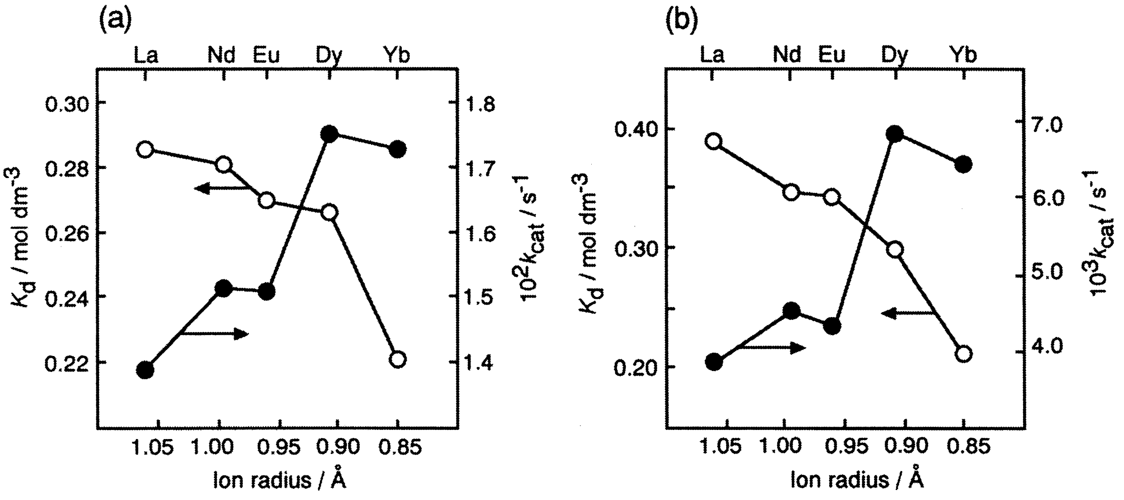


Fig. 4. Kinetic parameters (K_d (open circle) and k_{cat} (closed circle)) as functions of the ionic radii of lanthanides(III) for catalytic dehydration of (a) D-fructose and (b) D-glucose.

The K_d and k_{cat} values are plotted against the ionic radius of lanthanide(III) in Fig. 4. The dissociation constants (K_d), which monotonically decrease with decreasing ionic radius, are fairly large and no significant differences in the magnitude or tendency were observed between the two substrates. Notwithstanding the large dissociation constants, more than 50% of the lanthanide ion existing in the system can form a catalyst–substrate complex under the reaction condition, as the substrate concentration is very high (0.30 mol dm^{-3}). This means that changes in the K_d values do not significantly affect the initial reaction rate, and that the rate-determining step is not the complex formation process, but a subsequent reaction from the complex. In contrast, the k_{cat} value differs for each substrate and shows a sudden jump at Eu in both cases. Thus, the consistently faster reaction rates (v_0) for D-fructose and the discontinuous change around Sm in the catalytic activity are reasonably attributed to the k_{cat} value.

Interaction and Reaction Mechanisms. As can be recognized from the monotonically decreasing dissociation constant (K_d) with increasing atomic number of lanthanide(III), the lanthanide(III)–saccharide interaction becomes stronger as the ionic radius decreases and the surface charge increases. This tendency clearly indicates that the complexation of lanthanide(III) ion with hexose is primarily driven by the electrostatic interaction. Similarly, the catalytic reaction rate constant (k_{cat}) also increases with decreasing ionic radius, accompanying a break at Eu, probably due to a change in the hydration number. The enhanced reactivities observed for the heavier lanthanides are also rationalized by the increased electrostatic interactions. It is therefore evident that the nature and structure of the lanthanide-saccharide complex are the keys to this lanthanide(III)-catalyzed dehydration of saccharides in aqueous solution. However, such complexes are not stable in neutral aqueous solution, and the structures of such complexes have rarely been elucidated in detail. It has been suggested that the lanthanide(III) complex of saccharide is stabilized when three adjacent hydroxy groups on the pyranose ring are in the *axial*, *equatorial*, *axial* conformations.[28,30] However, D-

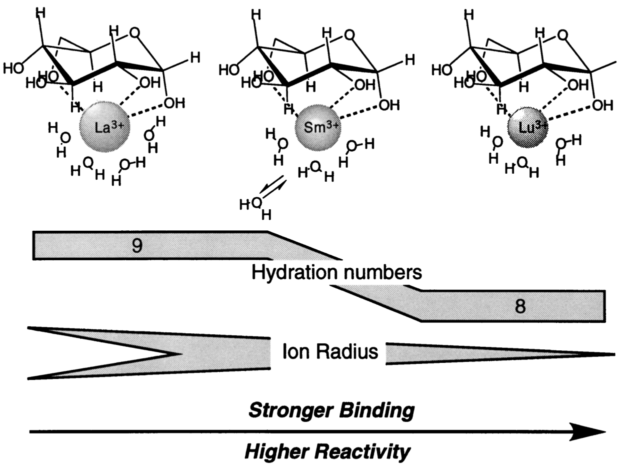


Fig. 5. Schematic drawing of the proposed lanthanide(III) ion–D-glucose complexes.

glucose does not exactly meet this condition. Hence, we speculate that the conformationally flexible 6-hydroxy group of D-glucose, as well as the 1-*axial*- and 2-*equatorial*-hydroxys, coordinate to the lanthanide ion to form the lanthanide–glucose complex shown in Fig. 5.

Although the detailed mechanism of the dehydration process is not clear for the lanthanide-catalyzed dehydration of saccharides, the Brønsted acid-catalyzed dehydration is believed to be initiated by removal of the 2-hydroxy of D-glucose or D-fructose.[10] In this context, it seems reasonable to conclude that the markedly enhanced reactivities upon lanthanide-catalyzed dehydration with Dy–Lu (Figs. 2 and 4) are correlated to the stronger and closer contacts with the less-hydrated, smaller-sized, heavier lanthanide ions.

Conclusion

The catalytic activity of lanthanide(III) ions for the dehydration of hexoses, particularly D-glucose and D-fructose, yielding HMF has been investigated. The lanthanide(III) ions are excellent Lewis acid catalysts giving HMF without accompanying an undesirable further decomposition to levulinic acid, a process which is often observed upon dehydration with conventional Brønsted acids. The relationship between the catalytic activity and the ionic radius displays the characteristic two-peak profile maximizing at Pr (or Nd) and Er (or Yb) with a break at Sm. A kinetic analysis using the Michaelis–Menten model clearly demonstrated that the rate-determining step is not complex formation, but a subsequent dehydration reaction. Although the binding ability ($1/K_d$) of the lanthanide(III) ions towards the saccharides monotonically increases with decreasing ionic radius as a consequence of the smaller catalyst–substrate distance in the complex, the reactivity (k_{cat}) shows an abrupt jump between Eu and Dy for both D-glucose and D-fructose. Thus, the characteristic two-peak profile observed for the reaction rate (v_0) is attributable to the change in the hydration number of lanthanide ions around Sm.

This paper not only reports on the novel catalytic activity of lanthanide(III) ions, but also provides information through a kinetic analysis about the reactivity of lanthanide(III) complex with D-fructose or D-glucose in aqueous solutions, which has scarcely been elucidated so far because such complexes are hardly isolated due to the very weak interaction. The lanthanide-catalyzed dehydration of saccharides in organic solvents is currently under investigation for significantly different catalysis profiles. Further application of the present catalytic reaction to a process that directly transforms biomass, such as oligosaccharides, starch and cellulose, to some useful chemicals is also a future task.

Experimental

Materials. Lanthanide(III) chlorides and saccharides of the highest available grade were purchased from Wako Pure Chemical Industries, Ltd. and used without further purification.

Catalytic Reactions. An aqueous solution (15 cm^3) of monosaccharides (0.30 mol dm^{-3}) and lanthanide(III) chloride (1.0–5.0 mmol dm^{-3}) was charged in a glass tube (25 mmϕ × 165 mm) which was placed in an autoclave (Taiatsu Techno Corporation, TVS-N2 (100 cm^3)), and the whole system was heated to 140 °C under a nitrogen atmosphere at a 10 bar pressure. The temperature was kept constant at 140 °C for a given period of time by a heater equipped with a digital thermometer (CT-700S). After cooling the autoclave to room temperature, the resultant mixture was subjected to a gas chromatographic analysis on a Shimadzu GC-9A instrument equipped with an FID detector and a glass column (3.2 mmϕ × 1.6 m) packed with polyethylene glycol 20 M (10% (w/w) supported on acid-washed Chromosorb W); N_2 was used as a carrier gas. The chromatograms were recorded and integrated by a Shimadzu C-R6A integrator. The decrease in the substrate was analyzed by HPLC, using a Waters LC Module 1 plus equipped with a differential refractometer, Waters 410. A Sugar-Pak Ca column (7.8 mmϕ × 300 mm) was used with a guard column (6 mmϕ × 50 mm). Degassed water was used as the eluent. The chromatographs were monitored and recorded by using software, Waters Chromatograph Manager, Millennium 2010J, working on a computer, Digital VENTRIUS 4100.

Kinetic Analysis. The initial rates (v_0) of the dehydration of D-fructose and D-glucose (0.10–0.50 mol dm^{-3}) catalyzed by lanthanide(III) ions (2.0 mmol dm^{-3}) were analyzed by using the Michaelis–Menten model (Scheme 2). In the D-fructose case, the net rates were corrected for the appreciable dehydration which occurred in the absence of lanthanide, by subtracting the blank rate from the observed rates. According to Eqs. 3 and 4, the inverse initial rates were plotted against the corresponding inverse substrate concentrations, as shown in Fig. 3. The dissociation constants (K_d) and catalytic reaction rate constants (k_{cat}) were calculated from the slopes and y-intercepts of the plots.

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