Reaction Mechanisms

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Glucose Activation by Transient Cr^{2+} Dimers**

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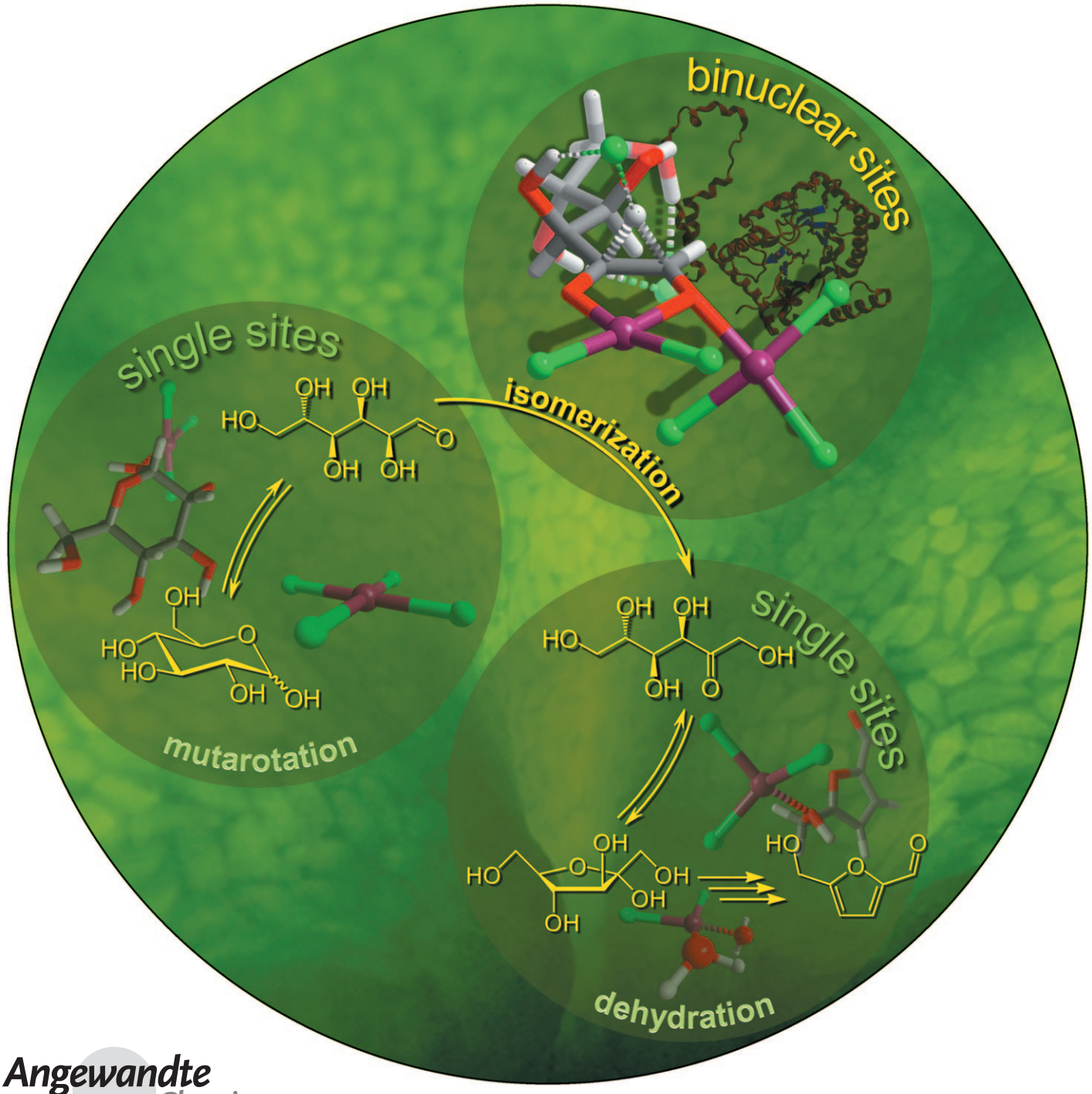

Concerns about global warming and energy security have led to the exploration of alternatives to fossil hydrocarbon resources to supply chemicals and energy.[1] Biomass is a promising renewable feedstock. Efficient routes are required for the conversion of carbohydrates, the main constituents of biomass, into fuels and chemicals.[2,3] 5-Hydroxymethylfurfural (HMF) is considered a key biorenewable platform molecule.[3,4] Although HMF can be obtained from fructose in high yield by using Brønsted and Lewis acid catalysts,[5,6] the selective transformation of glucose, the dominant sugar in cellulosic biomass, remains a challenge. Only recently, unprecedented HMF yields were reported for glucose dehydration by chromium(II) chloride in the ionic liquid (IL) 1-ethyl-3-methylimidazolium chloride (EMIMCl).[6]

Lewis acid catalyzed transformations in ionic liquids are thought to involve mononuclear metal complexes.[6–9] For the dehydration of glucose to HMF, a $CrCl_3^-$ anion was proposed to coordinate an enediolate intermediate, which undergoes the hydrogen transfer (H shift) required for the isomerization of glucose to fructose.[6,8] Usually, it is assumed that the role of the ionic-liquid medium is to provide a noncoordinating polar environment to stabilize catalytically active low-coordinate metal species.[7] The direct involvement of the organic cations of the ionic liquid in the catalytically active complex has also been mentioned;[8] however, evidence of the formation of metal–carbon bonds is lacking. Besides this chemocatalytic system, some enzymes readily promote glucose conversion. Typical enzymes capable of isomerizing glucose to fructose with high selectivity contain an active site involving two metal centers.[10–14]

In this study, we combined kinetic experiments, in situ X-ray absorption spectroscopy (XAS), and density functional theory (DFT) calculations to unravel the molecular-level details of the unique reactivity of chromium(II) chloride towards selective glucose dehydration in an ionic-liquid medium. As a starting point, we investigated the kinetics of glucose dehydration by $CrCl_2$ in EMIMCl at 100 °C. The reaction proceeds through glucose isomerization to fructose, followed by dehydration to give HMF (Figure 1). The HMF yield after a reaction time of 3 hours is 62 %. An experiment with fructose gave HMF in 59 % yield under identical conditions. In both cases, the starting sugar underwent almost complete conversion. Thus, the $CrCl_2$/EMIMCl catalyst converts glucose into fructose with high selectivity, and then catalyzes the dehydration of fructose to give HMF.[6] The poorly characterized humin-type side products are due to condensation reactions of intermediates formed during fructose dehydration.[6]

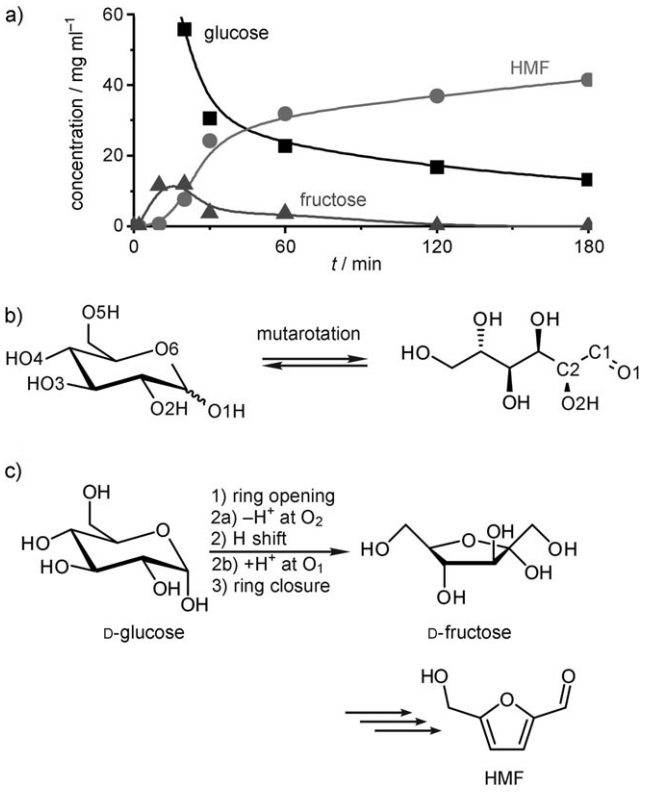

Figure 1. a) Concentration of the reactant and of the fructose and HMF products during glucose dehydration catalyzed by $CrCl_2$ in EMIMCl at 100 °C. b) Ring opening and mutarotation of α-D-glucopyranose. c) Isomerization and dehydration of α-D-glucopyranose.

X-ray absorption spectroscopy at the Cr K edge was used to resolve the nature and coordination properties of Cr species involved in the conversion of glucose. We used an in situ cell for liquid-phase experiments (see the Supporting Information). Absorption spectra in the $CrCl_2$/EMIMCl/glucose system were recorded at 80 °C, as glucose is not converted under these conditions. Spectra were recorded before reaction, after reaction at 100 °C for 10 minutes, and after reaction at 100 °C for 180 minutes (the fit results are given in Table 1 and spectra in the Supporting Information).

The reference spectrum of $CrCl_2$ dissolved in EMIMCl at 80 °C showed that Cr^{2+} is coordinated by four chlorine atoms at an average bond length of 2.39 Å. This distance is typical for four-coordinate chlorine-containing Cr^{II} complexes.[15] Cr–Cr coordination, as present in solid $CrCl_2$ and in a mixed crystal of $CrCl_2$ and EMIMCl,[16] is absent. DFT calculations confirmed the structure of chromium(II) chloride in EMIMCl. Geometry optimization of a cluster model containing two $CrCl_2$ units and five ion pairs of the ionic liquid (a model constructed from X-ray diffraction data[16]) led to two noninteracting square-planar $CrCl_4^{2-}$ units. This geometry is typical for four-coordinate Cr^{II} complexes.[15] The average

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Table 1: EXAFS fit parameters of the $CrCl_2$/EMIMCl system.

Backscatter	N[a]	R [Å][b]	$\Delta\sigma^2$ [Å^2][c]	ΔE_0 [eV][d]
$CrCl_2$/EMIMCl, 80 °C				
Cr–Cl	3.9	2.39	0.008	−8.4
$CrCl_2$/EMIMCl/glucose, 80 °C				
Cr–Cl	2.9	2.38	0.007	−3.4
Cr–O	1.0	2.13	0.015	
$CrCl_2$/EMIMCl/glucose, 100 °C, 10 min				
Cr–Cl	2.4	2.36	0.004	−7.4
Cr–O	2.0	2.04	0.004	
Cr–Cr	0.6	3.45	0.006	
$CrCl_2$/EMIMCl/glucose, 100 °C, 180 min				
Cr–Cl	2.4	2.35	0.005	−5.2
Cr–O	1.4	2.02	0.003	

[a] Coordination number (±20%). [b] Coordination distance (±0.02 Å). [c] Debye–Waller factor (±10%). [d] Inner potential.

computed Cr–Cl bond length of 2.39 Å agrees with the experimental values.

EXAFS data recorded at 80 °C in the presence of glucose provided evidence for the coordination of glucose to Cr through one of its hydroxy groups. One of the chlorine ligands was replaced with an oxygen ligand. The Cr–O and Cr–Cl bond lengths were 2.13 and 2.38 Å, respectively. The relatively long Cr–O distance indicates coordination of Cr^{II} to a hydroxy group of the sugar.[15,17] The fructose concentration was highest after a reaction time of 10 minutes at 100 °C (Figure 1a). At this stage, the coordination environment of Cr had changed substantially. Chromium coordinated two oxygen atoms at a distance of 2.04 Å and two chlorine atoms at 2.36 Å. The decrease in the Cr–O distance is due to deprotonation of the sugar hydroxy groups coordinated to Cr.[15] The fit of this spectrum also contains a Cr–Cr shell with a coordination number of 0.6 at a distance of 3.45 Å which points to the presence of O- or Cl-bridged Cr dimers.[15] When nearly all the glucose had been converted, this Cr–Cr coordination was no longer observed. The coordination environment of Cr contained on average 1.4 oxygen ligands at a distance of 2.02 Å and 2.4 chlorine ligands at 2.35 Å.

The exceptional catalytic performance of the $CrCl_2$/EMIMCl system is directly related to its ability to promote the isomerization of glucose to fructose. The EXAFS results imply dynamic evolution of the catalytic Cr^{II} species during the course of the reaction. DFT calculations were carried out to unravel the molecular mechanism of the chromium(II)-catalyzed glucose isomerization. On the basis of a mechanism similar to that proposed for enzymes,[10] we considered three steps in the conversion of glucose into fructose: 1) ring opening, 2) H transfer between C2 and C1, and 3) ring closure (Figure 1c). The replacement of a Cl^- ligand and coordination of α-D-glucopyranose (α-D-GP) to Cr through the O1 atom (Figure 2c) is favorable ($\Delta G^{o,IL}_{100^\circ C} = -10$ kJ mol^{-1}). Such a coordination mode of glucose to the Cr center was considered because it enables the opening of the glucopyranose ring through H^+ transfer from O1 to O6. This choice is supported by the observation that the mutarotation of α-D-glucose to β-D-glucose occurs in the presence of a Cr^{II} catalyst even under conditions (80 °C) that do not promote its conversion into fructose or HMF. Mutarotation requires opening of the glucopyranose ring. The DFT-computed bonding parameters of the respective complexes correspond well with the structural parameters determined by EXAFS (see the Supporting Information). The coordination of a second Cr center at this step of the reaction is unfavorable.

In the enzyme-catalyzed process, the initial proton transfer is catalyzed by a basic histidine moiety (His53) located in the cavity of the enzyme active site (Figure 2a).[10,11] In the chemocatalytic system, the mobile chloride anions of the ionic liquid play the role of basic mediators. The chloride anions

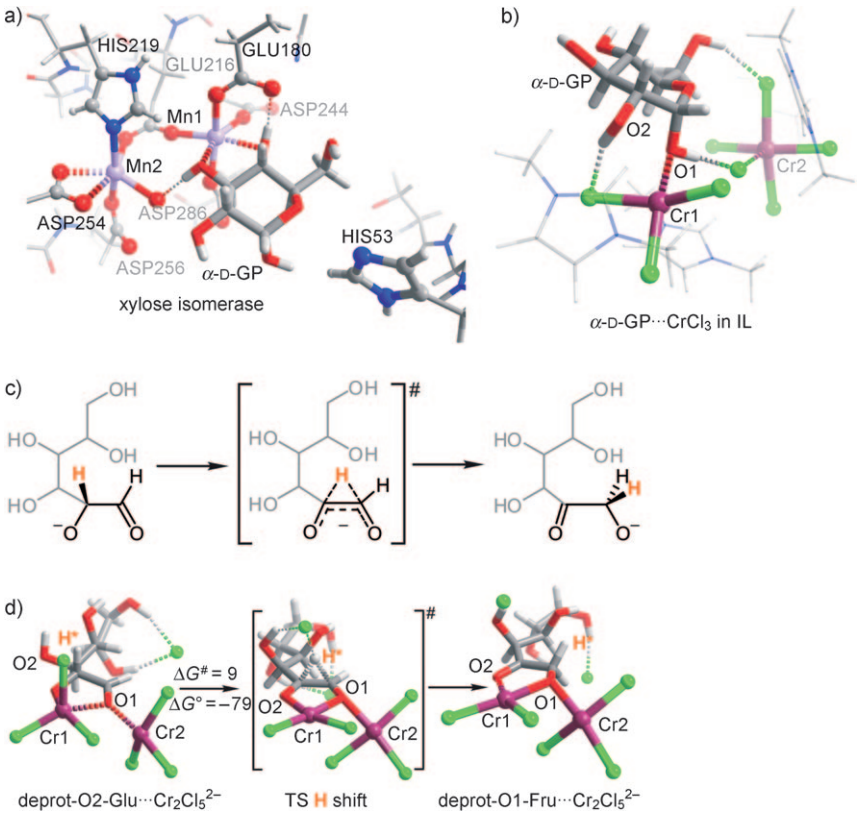

Figure 2. a) Atomic-resolution XRD structure of glucose interacting with the binuclear active site of a xylose isomerase enzyme.[10] b) DFT-optimized structure of the initial coordination complex between glucose and chromium(II) chloride. c) Scheme showing the H shift that takes place during glucose isomerization. d) DFT-computed binuclear Cr^{II} complexes with the deprotonated sugar intermediates shown in (c). ΔG values are given in kJ mol^{-1}. TS = transition state.

form a hydrogen-bonding network with the hydroxy groups of the carbohydrate. This proposition is supported by the absence of fructose and HMF formation when the anion of the ionic liquid is replaced with nonbasic PF_6^- (see the Supporting Information).

Figure 3 shows the computed free-energy diagram for glucose isomerization involving mono- and binuclear Cr complexes. The free-energy barrier to the formation of the open form of D-glucose is low and does not depend on the nuclearity of the Cr complex. The free-energy change for the ring opening of D-glucose coordinated to a single Cr center compares favorably to that of the noncatalytic ring opening; the difference in the free-energy change for these processes is in line with optical-rotation results (see the Supporting Information). The resulting complex of the open form of D-glucose with Cr is the precursor to the following transformation. The isomerization of glucose to fructose requires an H shift between C2 and C1 of the open form of the sugar (Figure 2c). This step is thought to involve an enediolate intermediate.[6,8] Prior to the H shift, deprotonation of the O2–H group is required. This step is strongly endothermic (+68 kJ mol^{-1}) when the open form is stabilized by one Cr center. The energy cost of the subsequent H shift is 51 kJ mol^{-1}. The overall free-energy barrier to the H shift is 120 kJ mol^{-1}. The O2-deprotonated glucose intermediate is stabilized considerably when a second Cr center becomes involved (Figure 3). In the resulting binuclear complex, O1 bridges the two Cr centers (Figure 2d). One of the chromium ions also coordinates to O2. In this case, the free energy required for the deprotonation of O2 is lowered by 15 kJ mol^{-1}. More importantly, the energy barrier to the direct H shift from C2 to C1 in this complex is negligible (9 kJ mol^{-1}). The product is also a Cr dimer, which now contains the open form of D-fructose deprotonated at O1 (Figure 2d). This complex is much more stable than its mononuclear counterpart. Thus, the isomerization of glucose proceeds by the coordination of a second Cr center during the deprotonation of O2, followed by a rapid H shift.

The overall activation free-energy barrier of only 63 kJ mol^{-1} for the binuclear pathway compares favorably to the barrier of the mononuclear pathway. The Cr–Cr distances observed in the optimized structures of the stable Cr dimer complexes of the O1-deprotonated and neutral open forms of fructose agree well with the Cr–Cr distance determined by EXAFS analysis (see the Supporting Information). The transition state of the direct H shift is stabilized by delocalization of the electron density in the conjugated π system. During the H shift, negative charge develops on the O1 atom. The coordination of O1 to two Lewis acidic Cr centers stabilizes this negative charge better than coordination to a single Cr center and results in a substantial decrease of the free-energy barrier. Analysis of the computational results showed that the transferred H atom has a positive charge of +0.34e$^-$. The high concentration of the free basic Cl^- ions of the ionic liquid should facilitate proton transfer. The formation of fructose from the binuclear complex with the open form of fructose involves the protonation of C1, followed by ring closure. The DFT-optimized structures of Cr^{2+} complexes with the products of glucose dehydration, namely HMF and H_2O, are also in close agreement with

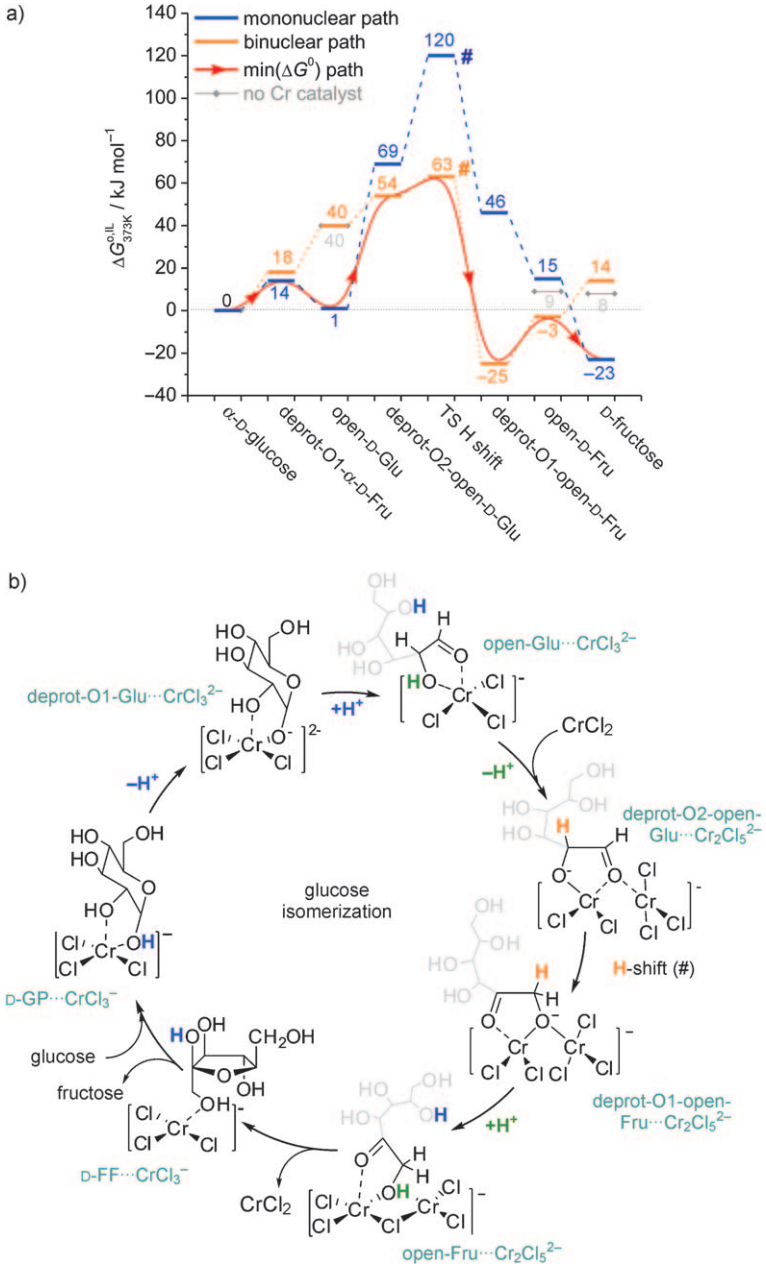

Figure 3. a) DFT-computed free-energy ($\Delta G^{\circ,IL}_{100^\circ C}$) diagrams for glucose isomerization involving mono- (blue) and binuclear (orange) Cr^{II} complexes with the carbohydrate in a model MMIM ionic-liquid medium. The red line highlights the path of lowest free energy (the corresponding catalytic cycle is shown in (b)). b) Catalytic cycle for the isomerization of glucose in the presence of $CrCl_2$ in a model MMIM ionic-liquid medium. D-FF = D-fructofuranose, D-GP = D-glucopyranose.

the EXAFS results after completion of the reaction (see the Supporting Information).

Catalysis by chromium usually involves highly complex redox and coordination chemistry of the metal center. In the case of heterogeneous catalytic ethylene oligomerization, a single-site Cr^{II} species has been accepted as the active site.[18] Examples of homogeneous catalysis involve both mono- and binuclear Cr^{II} complexes.[15,19] We are unaware of prior observations of the transient self-organization of mononuclear Cr species into a binuclear complex with a reactant in a chemocatalytic system. Our results show that the facile reactions of sugar ring opening and closure involve coordination to a single Cr center. The rate-controlling H-shift reaction of the open form of the carbohydrate is facilitated by the transient self-organization of the Lewis acidic Cr^{2+} centers into a binuclear complex with the open form of glucose. The active site for this step resembles the active site of hexose isomerase enzymes.[11] The exact role of the second metal site in biological systems is still under debate. In the $CrCl_2$/EMIMCl system, the second Cr center stabilizes the reaction intermediates involved in the H shift. The moderate basicity and the high concentration and mobility of the chlorine ions of the ionic-liquid reaction medium promote the various (de)protonation reactions. In enzymes, such reactions are catalyzed by basic amino acid residues at the active site. The unique transient self-organization of Cr^{2+} dimers to facilitate the rate-controlling H shift in glucose isomerization is possible as a result of the dynamic nature of the Cr complexes and the presence of moderately basic sites in the ionic liquid.

Experimental Section

Dehydration procedure: Glucose or fructose (50 mg) and the ionic liquid EMIMCl (500 mg) were placed in a glass reaction vial (15 × 45 mm), and $CrCl_2$ (2 mg, 6 mol% with respect to the sugar) was added. The vial was closed under an inert atmosphere and then heated at 80 or 100 °C in an oil bath. The reaction was quenched at 0 °C, and the product mixture was analyzed by HPLC analysis.

X-ray absorption spectroscopy (XAS): XAS spectra were recorded in a home-built transmission cell for liquid samples. In a typical experiment, hexose (50 mg), EMIMCl (500 mg), and $CrCl_2$ (8 mg) were mixed at 60 °C. A 3 mL sample of this mixture was transferred into the XAS cell. XAS spectra at the Cr K edge were recorded in fluorescence mode at DUBBLE of the European Synchrotron Radiation Facility (ESRF, Grenoble, France).

DFT calculations: Electronic energies of the ground and transition states were calculated at the PBE0/Tζ//PBE0/Dζ level of theory by using Gaussian 03.[20] Dζ denotes the basis-set combination, whereby the 6-31 + G(d) basis set was used for Cr, Cl, and O atoms, and C, N, and H atoms were treated with the 6-31G(d) basis set. In an extended Tζ combination, the 6-31 + G(d) basis set was used for Cr, 6-311 + + G(d,p) for Cl and the C, H, and O atoms of the carbohydrate molecule and its derivatives, and 6-311G(d,p) for the remaining C, H, and N atoms of the 1,3-dimethylimidazolium (MMIM) cations of the model ionic-liquid solvent. At least two MMIMCl ion pairs per Cr atom were explicitly added to describe the reaction environment. The polarizable continuum model (PCM) was used to approximate the medium. Zero-point, finite-temperature, and entropic (*TS*) energy contributions were computed by normal-mode analysis at the PBE0/Dζ level. The reported Gibbs free energy differences, $\Delta G^{o,IL}_{100^\circ C}$, include solvation, thermal, entropic, and zero-point energy contributions. Extended computational and experimental details can be found in the Supporting Information.

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