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PAPER

Glucose and fructose to platform chemicals: understanding the thermodynamic landscapes of acid-catalysed reactions using high-level *ab initio* methods†

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Molecular level understanding of acid-catalysed conversion of sugar molecules to platform chemicals such as hydroxy-methyl furfural (HMF), furfuryl alcohol (FAL), and levulinic acid (LA) is essential for efficient biomass conversion. In this paper, the high-level G4MP2 method along with the SMD solvation model is employed to understand detailed reaction energetics of the acid-catalysed decomposition of glucose and fructose to HMF. Based on protonation free energies of various hydroxyl groups of the sugar molecule, the relative reactivity of gluco-pyranose, fructo-pyranose and fructo-furanose are predicted. Calculations suggest that, in addition to the protonated intermediates, a solvent assisted dehydration of one of the fructo-furanosyl intermediates is a competing mechanism, indicating the possibility of multiple reaction pathways for fructose to HMF conversion in aqueous acidic medium. Two reaction pathways were explored to understand the thermodynamics of glucose to HMF; the first one is initiated by the protonation of a C2–OH group and the second one through an enolate intermediate involving acyclic intermediates. Additionally, a pathway is proposed for the formation of furfuryl alcohol from glucose initiated by the protonation of a C2–OH position, which includes a C–C bond cleavage, and the formation of formic acid. The detailed free energy landscapes predicted in this study can be used as benchmarks for further exploring the sugar decomposition reactions, prediction of possible intermediates, and finally designing improved catalysts for biomass conversion chemistry in the future.

1 Introduction

Utilizing the biomass and wastes by converting them to useful chemicals for alternative fuel precursors or industrial chemicals is essential to a sustainable economy.[1,2] Recently, the conversion of biomass to platform chemicals such as hydroxy-methyl-furfural (HMF), furfuryl alcohol (FA), furfural (FF), levulinic acid (LA), and γ-valero-lactone (GVL) was proposed as one of many key reactions for producing 'green' chemicals.[3–11] One of the possible preliminary routes for decomposing cellulosic-biomass is through Brønsted acid hydrolysis to their monomers such as C6 sugars, C5 sugars, and subsequent selective dehydration/rehydration to make HMF, FA, and LA in aqueous media, as shown in Scheme 1. It is reported that many of these acid-hydrolysis products lack selectivity to produce the desired decomposition products in aqueous solution and produce undesired polymeric products called 'humins', especially when dealing with high concentration of cellulosic materials. For example, the conversion of cellulose to monomeric glucose units is hindered by the formation of oligomers of glucose or reversion products.[12] Additionally, platform chemicals such as HMF are predominantly obtained from the fructo-furanose with high selectivity than the naturally abundant glucose due to the high reactivity and the presence of a five-membered ring. Fructo-pyranose, a dominant form of fructose (68%) in aqueous solution, is less selective towards HMF and its acid-catalysed decomposition is not reported yet. Thus, it is inevitable to have catalysts that enable industrial level isomerization of naturally abundant pyranoses to furanoses and further selective dehydration to form HMF or FA in aqueous solution.[13,14]

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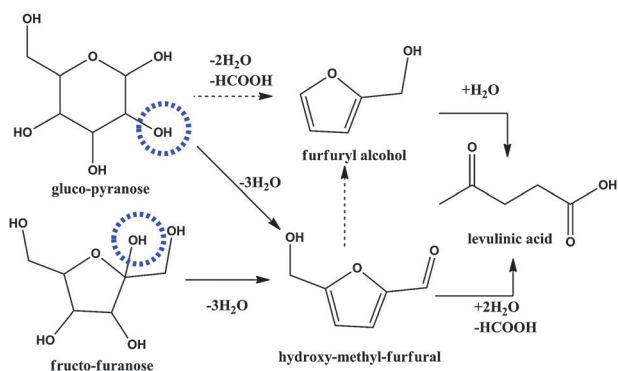
Scheme 1 Formation of hydroxy-methyl-furfural, furfuryl alcohol, and levulinic acid from glucose and fructose.

Recent experimental studies to address these isomerization and selective dehydration reactions in a 'one-pot' approach using large pore Sn-beta zeolites have been promising.[15]

However, at present, an economically viable option is the usage of a Brønsted acid in aqueous solution, where the understanding of structure and reaction energetics of acid-catalysed reactions of complex sugar molecules to form desired platform chemicals such as HMF, FA, FF, and LA is needed to compliment experimental efforts. In order to gain molecular level understanding of sugar decomposition reactions, previously we have reported an investigation of the detailed thermochemistry of the conversion of glucose to levulinic acid through fructo-furanosyl intermediates in neutral solution at the G4[16] level of theory. This enabled understanding of the thermodynamic landscapes of the reaction, effect of temperature on the free energy of reactions, and enthalpies of formation of various likely intermediates.[17] We have also investigated detailed reaction energies and reaction barriers for a likely pathway of acid catalysed conversion of fructose to HMF through cationic intermediates at the G4 level of theory.[18] This mechanistic study indicates that the acid catalysed mechanism starts with the protonation of a tertiary hydroxyl group and the rate-limiting steps are processes associated with the second dehydration of fructose molecules. Additionally, we have investigated the thermochemistry of various decomposition routes of hexoses to C2–C3 species and anhydrosugars[19–21] through retro-aldol, isomerisation, and dehydration reactions. The objective of this work is to explore the free energy landscapes of the fructose–HMF reaction pathway and glucose–HMF/FAL pathways under aqueous acidic reaction conditions using a simpler, yet more accurate approach. The aim is to provide an energy landscape of likely reaction pathways, thus providing a platform for the experimentalists to confirm the chemical nature of intermediates, kinetics and finally design more efficient catalysts to enable the conversion of sugar molecules to desired platform chemicals.

A remarkable difference between glucose and its highly reactive isomer fructose is its highly stable pyranose ring structure in aqueous solution and four almost equally reactive secondary hydroxyl groups. In this paper, we first compute the protonation free energy of various oxygen atoms of glucose and fructose to understand the relative reactivity of the sugar molecules. Protonation of each hydroxyl group and subsequent rearrangements/ dehydration routes to produce the platform chemicals and their

relative energetics were studied using the accurate G4MP2[22] level of theory, with the SMD solvation model.[23] The computational details are given in the next session and the details of our findings are presented in Results and discussions. Finally conclusions were drawn from our investigations.

2 Computational details

All calculations presented in this paper were performed using the highly accurate G4MP2 level of theory, which is less computational intensive than the very accurate G4 level of theory. This level of theory uses the B3LYP/6-31 G(2df,p) geometries, frequencies, and G4MP2 levels of theory previously reported to predict reaction energetics comparable with experimental results (within 1 kcal mol^{-1} accuracy) and reaction barriers compared to CCSD(T) with a quadruple zeta basis set. A limitation of the application of these methods in studying sugar molecule reactions is the inclusion of a large number of explicit solvent molecules. An alternative to this approach is to use density functional methods by including first or second layer solvent coordination shells explicitly. However, such modelling techniques have limitations due to the number of water molecules that can be treated, configurational problems of the solvent molecules, and computational difficulty to find transition states. An *ab initio* dynamics using Carr–Parnello methods (CPMD) study at the scale described in this paper requires a significant amount of computational effort and is beyond the scope of this present study. Also, it is worth noting that standard density functionals (B3LYP, PBE, PW91, BLYP) used in the *ab initio* dynamics slightly overestimate the protonation free energies and underestimate the reaction barriers.[24] Additionally, choosing collective variables for an *ab initio* dynamics study does require a significant understanding of chemistry. Therefore in this study, in order to address the aqueous medium, we have employed an implicit solvation model, SMD: a solute density based model, at the B3LYP/ 6-31G(2df,p) level of theory, which is adequate enough to describe the energetics and is computationally less demanding.[18,20]

We have also performed computations with some explicit water molecules (B3LYP/6-31+G*, water molecules placed in such a way that maximum hydrogen bonding is established) to make sure that the conclusions drawn from the high-level theory with the implicit solvent model are chemically correct. We note that, for predictions of reaction barriers for solvent assisted processes it is essential to include explicit solvent molecules.[20,25] The proton solvation energy in aqueous solution is taken to be -262.5 kcal mol^{-1} as indicated from recent high-level theoretical and experimental studies.[26,27] The lowest energy geometries were based on our previous theoretical studies and also based on the fact that stability of molecules depends on the maximum intra-molecular hydrogen bonding. All calculations presented in this study were performed using Gaussian09 software.[28]

3 Results and discussion

3.1 Thermodynamics of protonation of glucose and fructose

Acid catalysed decomposition of sugar molecules in aqueous medium is initiated by the protonation of the hydroxyl groups.

To understand the thermodynamics of protonation in an aqueous Brønsted acid medium, we have computed the free energy of protonation of various hydroxyl groups of gluco-pyranose, fructo-pyranose, and fructo-furanose at the G4MP2 levels of theory. All oxygen atoms were protonated and the computed free energies (298 K) of protonation of all the possible oxygen sites in aqueous medium are shown in Fig. 1.

The calculations suggest that the protonation of any sites of sugar molecules considered here is thermodynamically uphill by a range of 8 to 18 kcal mol^{-1} in aqueous medium. Based on the protonation free energy, the tertiary hydroxyl group of the fructo-furanose is found to be the most likely protonation site in fructo-furanoses (protonation is endergonic by 8 kcal mol^{-1}). For both gluco-pyranose and fructo-pyranose molecules, the free energy of protonation of any oxygen sites (secondary alcohol sites) is in the range of 14–18 kcal mol^{-1}. Also, it is seen that the protonation at the primary hydroxyl groups is stabilized by the presence of an adjacent ring oxygen atom. One important finding is that the model predicts that the protonation of tertiary hydroxyl sites of sugar molecules is more likely that secondary or primary hydroxyl sites based on reaction free energies. This indicates that fructo-furanose would be more reactive in aqueous acidic media than pyranoses. All the secondary hydroxyl groups of sugar molecules show similar protonation energetics indicating similar reactivity. Therefore, a selective dehydration at these secondary alcohol sites to produce platform chemicals is not efficient from pyranoses in aqueous solution, which suggests the need for efficient catalysts to convert pyranoses to furanoses in order to produce platform chemicals such as HMF or LA.[13,14,29]

Understanding the kinetics using the method adopted here is difficult, however reported previous studies[30] and our preliminary[31] *ab initio* molecular dynamics (glucose with 64 explicit water molecules and two H_2SO_4 molecules) studies suggest the kinetic preference of the O1 sites of glucose and fructose molecules over the other possible sites. For glucose, upon protonation of its hydroxyl groups (sites 1 to 5, Fig. 1), the protonated hydroxyl groups become good leaving groups and the stability of the resulting positive charge is one of the key factors in determining the initial protonation site and the other being the kinetics of dehydration. Protonation and

subsequent dehydration of the C1–OH site of the glucose result in the formation of carbocation which is stabilized by the presence of adjacent pyranose oxygen atom and leads to the formation of a stable oxonium ion. This explains the reason for the kinetic preference of the C1–OH site.[31] Also of great importance, this oxonium cation can react with glucose molecules to form reversion products such as dimers, especially at high concentration.[12,30] This reaction is believed to effect the conversion of glucose to platform chemicals significantly.

Protonation and subsequent removal of water molecule at positions 2, 3, and 4 of a glucose molecule could lead to the rearrangement of the six-membered ring to five membered rings (depending on the stability of carbo-cation).The nature of the rearrangement depends on temperature, water density, and the hydrogen bonding between the sugar and the surrounding water molecules.[32,33] Protonation at position 2 (C2–OH, Fig. 1) is speculated[34] to form a likely precursor of HMF, and detailed thermochemistry of this reaction pathway is described later in this paper. Protonation of the ring oxygen of glucose leads to opening of the six-membered ring and this acyclic glucose can undergo further dehydration or deprotonation. In aqueous solution this appears to be a minor decomposition pathway due to the stability of the ring structure over the acyclic structures, however these pathways are suggested to be key pathways in heterogeneous catalysis due to the stabilization of acyclic intermediates.[35] Therefore, this pathway and a detailed energetics were subjected to quantum chemical study (Section 3.4).

Initial protonation and subsequent dehydration of various hydroxyl group sites result in the formation of positive charge at the carbon atoms. These cationic species can undergo three possible reactions, such as (1) losing the positive charge to the aqueous medium through deprotonation, (2) internal rearrangements to stabilize the carbocation and (3) reversion reactions with the unreacted glucose molecule. At higher temperature in aqueous medium deprotonation is less likely due to the fact that the protonation free energy of water decreases due to the weakening of its hydrogen bonding networks.[36] Both at low and high temperatures internal rearrangements to reduce the energy of the molecular system
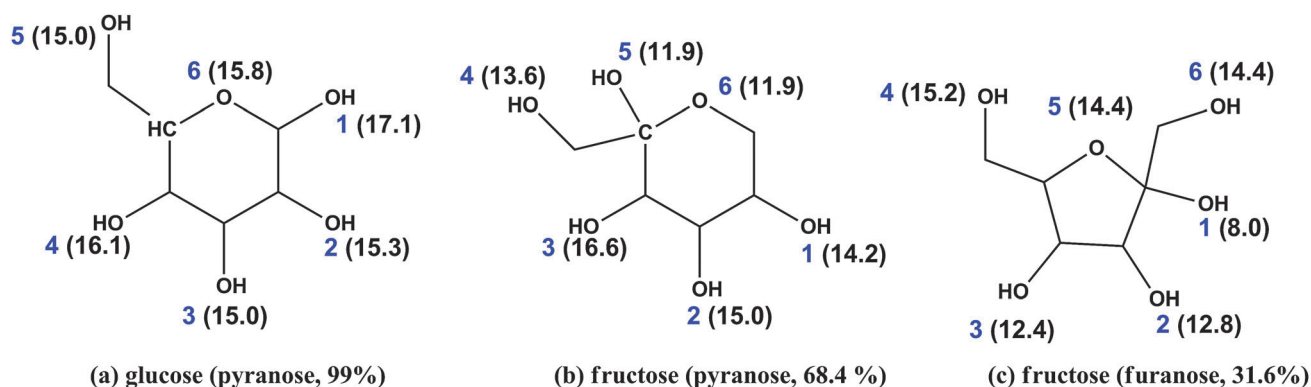
Fig. 1 Predicted Gibbs free energy (298 K) required to protonate various oxygen sites of glucose, fructo-pyranose, and fructo-furanose at the G4MP2 level of theory in water dielectric. An experimental proton solvation free energy of −262.5 kcal mol^{-1} is included to assess the Gibbs free energy of protonation. The solvation free energies are calculated using the SMD solvation model at the B3LYP/6-31 + G(2 df,p) level of theory. All values are reported in kcal mol^{-1}.

are preferred, often due to the preference of kinetics over oligomerisation.

3.2 Fructose to HMF

Acid-catalysed dehydration of fructose to HMF was previously studied using protonated intermediates and the high-level G4[18] and QM/MM methods.[37,38] Here, the reaction mechanism and energetics were investigated by computing the structures and free energies of all likely intermediates assuming that protonation, subsequent removal of water, and deprotonation of the cation in aqueous medium occur in a sequential manner. A detailed free energy profile for the acid-catalysed conversion of fructose (F1) to HMF in aqueous solution at 298 K using the G4MP2 level of theory is shown in Fig. 2. Note that, all energies are wrt the free energy of neutral fructo-furanose in aqueous dielectric medium. The acid-catalysed reaction is initiated by the protonation of the tertiary hydroxyl group (F1 → F2) and this process is endergonic by 8 kcal mol^{-1}. Upon protonation, the hydroxyl group becomes a good leaving group, and leads to the breaking of C1–OH2 bond forming an oxonium ion (F3, 5.4 kcal mol^{-1}) and a water molecule. The oxonium ion is slightly more stable than the protonated precursor (F2, 8.0 kcal mol^{-1}).

A hydride shift or deprotonation from F3 results in the formation of species F4 and F5 respectively. Previously, it has been reported that the hydride shift requires a reaction barrier

of 23–25 kcal mol^{-1}.[18,38] In terms of Gibbs free energy, deprotonation to form F3-A or F5 is preferred, where the hydride shift (F3 → F4) is thermodynamically uphill. The formation of anhydro-fructo-pyranose (F3-A) from F3 is thermodynamically more favourable than the direct deprotonation to form F5. Formation of F3-A occurs through the formation of bond between carbon (of the oxo-carbonium ion) and the primary hydroxyl group at the 4th position (Fig. 1b, fructo-furanose) and subsequent deprotonation. The Gibbs free energy of F3-A wrt F1 is −4.0 kcal mol^{-1}, indicating the stability of this intermediate and this intermediate has been experimentally characterized by Horvath and co-workers very recently.[39] The likelihood of the alternative deprotonation of F3 to F5 by aqueous medium is also suggested from the molecular dynamics simulation performed at 500 K using Car–Parinello simulation, where the species F3 is found to be stable only for 150 fs[31] indicating F3 may undergo deprotonation (to F3-A or F5) to reduce the free energy.

Of the two secondary hydroxyl groups of species F5, the C2–OH has higher proton affinity (12 kcal mol^{-1} higher proton affinity than C3–OH), suggesting that the protonation of that hydroxyl group occurs, resulting in the formation of species F6. The initial protonation of F5 (F5 → F6) is endergonic by 11.9 kcal mol^{-1} and subsequent removal of the water to form F7 is exergonic (F6 → F7, −10.8 kcal mol^{-1}). Deprotonation of F7 results in the formation of thermodynamically stable aldehyde (4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde),
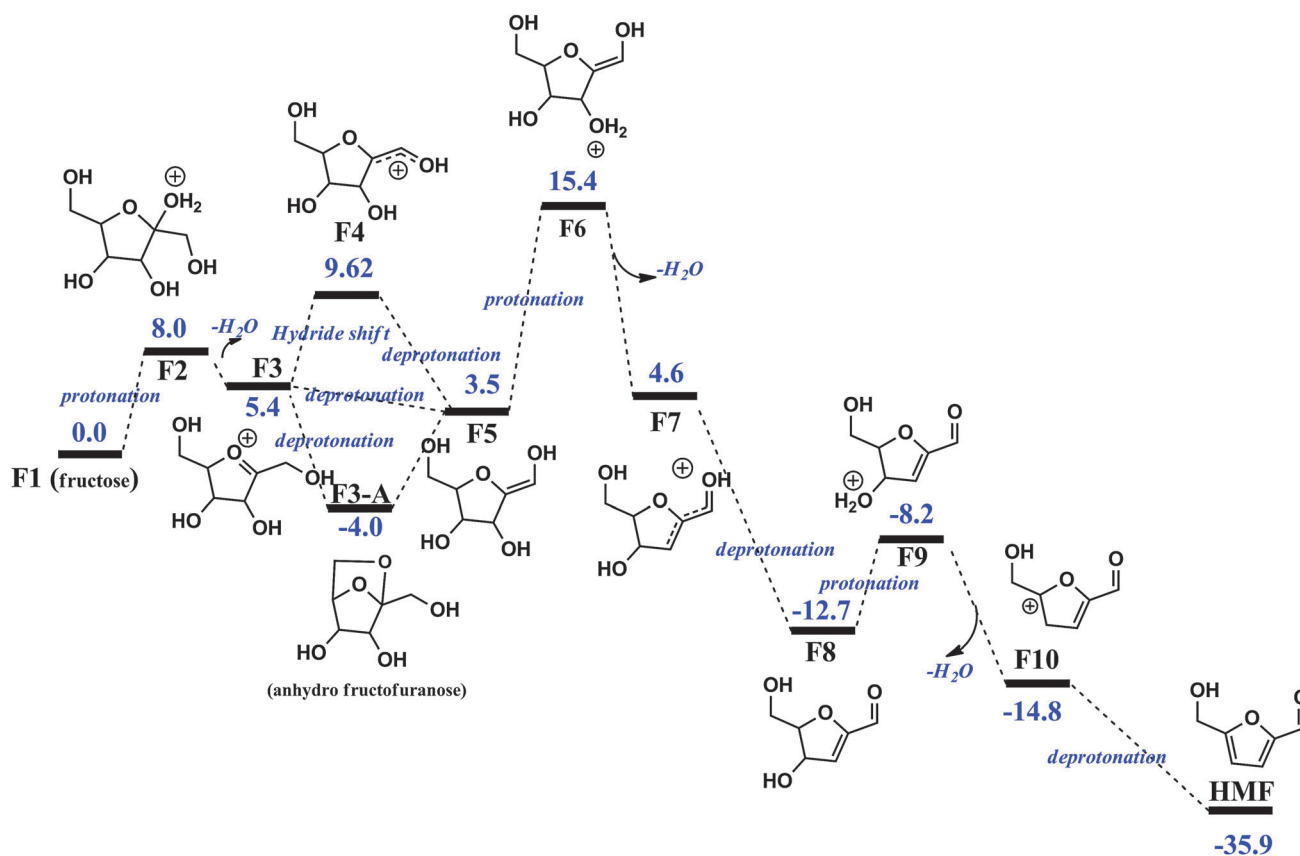
Fig. 2 Predicted free energy profile (298 K) of the decomposition of fructose (F1) to hydroxy-methyl-furfural (HMF) at the G4MP2 level of theory in water dielectric medium. Contributions from the water dielectric medium is calculated at the B3LYP/6-31 G(2 df,p) level of theory using the SMD solvation model. All values are reported in kcal mol^{-1}.
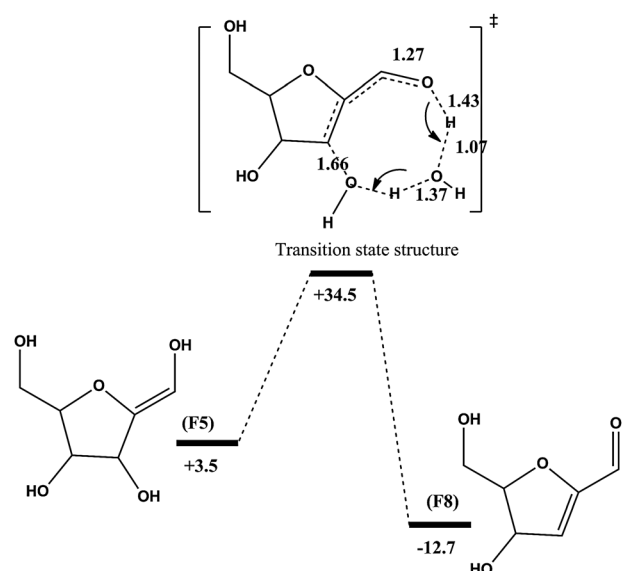
Scheme 2 Predicted solvent assisted dehydration of F5 to F8 (see Fig. 2) through an eight-membered transition state. All of the energies (kcal mol^{-1}, 298 K) are computed using the G4MP2 level of theory and are wrt fructo-furanose in water dielectric.

F8 (−12.7 kcal mol^{-1}). Considering the protonation of F5 (F5 → F6) is significantly uphill (15.4 kcal mol^{-1} wrt F1), it is likely that the enol could undergo a solvent assisted (water) dehydration to form F8, which is shown in Scheme 2. The dehydration (F5 → F7 + H$_2$O) is thermodynamically favoured by 16.2 kcal mol^{-1} due to the formation of a conjugated double bond with the aldehyde group and an increase in entropy. The solvent-assisted dehydration reaction proceeds *via* an eight-membered transition state, where the water molecule participates as the proton mediator and as a catalyst, as shown in Scheme 2. The computed apparent activation free energy and enthalpy of activation of this reaction is 34.5, 34.3 kcal mol^{-1} respectively.

Due to the thermodynamic stability of this intermediate F8 (−12.7 kcal mol^{-1}), this would be a very likely species[40,41] that one should observe in an experimental study and in fact this (4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbal-dehyde) is the major intermediate observed in acid-catalysed dehydration of fructose in aqueous medium. A protonated form of this intermediate was recently calculated in a mecha-nistic study by Vlachos and co-worker.[37] Protonation of F8 occurs at the C3–OH position and this process (F8 → F9) is endergonic by 4.5 kcal mol^{-1}, where the proton affinity of the secondary hydroxyl group is clearly enhanced by the presence of a conjugated double bond. The removal of water from F9 results in the formation of F10 and a subsequent deprotona-tion (F9 → HMF) results in the formation of the final product HMF. Based on the pathway computed here, this model clearly explains the formation of experimentally identified intermediates (F3-A and F8) and the computed activation barriers are consistent with recent experimental (30 to 36 kcal mol^{-1}) and theoretical studies.[37,42,43] In terms of the influence of the fructo-pyranose form, in contributing to the conversion of fructose to the HMF pathway in acidic medium, the Gibbs free energy of protonation suggests that protonation at the furan oxygen and ring opening could lead to epimerization. Due to higher reactivity of the fructo-furanose, the conversion to HMF pushes the equilibrium shift more towards the furanose from the pyranose. A computational study to under-stand the likely reactions of fructo-pyranose in acid medium is currently underway. Additionally, HMF can further undergo acid-catalysed decomposition or polymerization which has recently been the subject of a combined experimental and theoretical study.[44]

3.3 Glucose to HMF

Experimental studies show that direct conversion of gluco-pyranose to HMF is relatively poor unless a catalyst that can isomerize glucose to fructose is used. Recent computational studies
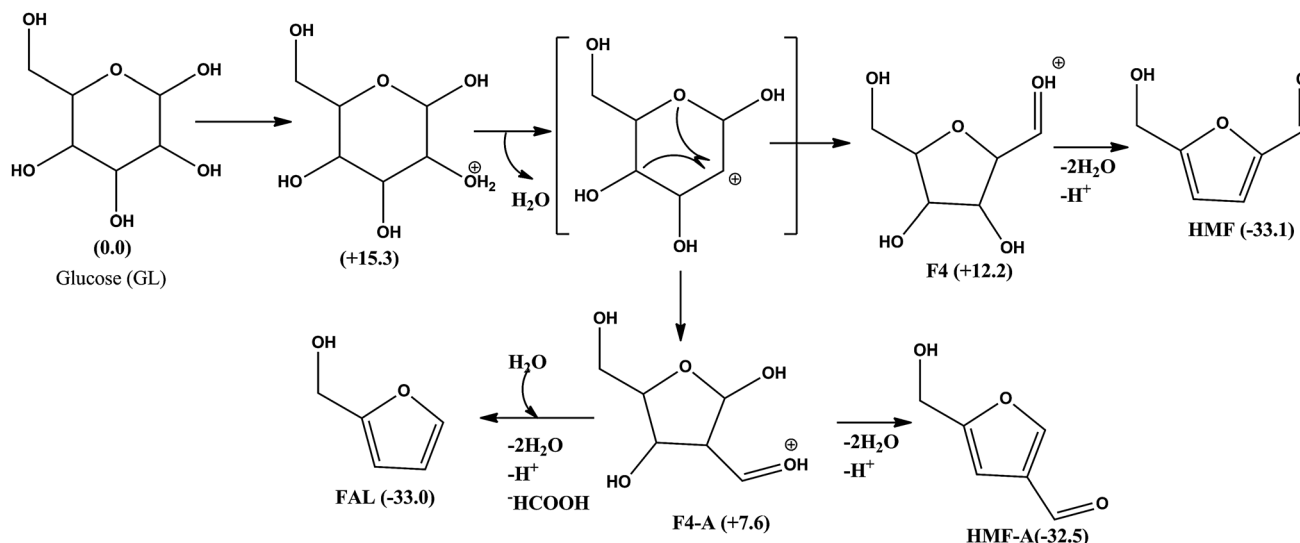
Scheme 3 Formation of two types of intermediates up on the protonation and subsequent dehydration of C2–OH of glucose. The relative free energies (kcal mol^{-1}, 298 K) at the G4MP2 level of theory in a water dielectric medium are also shown.

suggest that protonation of C2–OH (Fig. 1, 15.3 kcal mol^{-1}) leads to the formation of HMF through the fructose intermediates.[32,34] The formation of a HMF precursor from glucose is shown in Scheme 3. Upon protonation and subsequent dehydration at the C2–OH position of the glucopyranose, the C1–O6 bond (furan oxygen) cleaves and the six-membered ring rearranges to a five-membered intermediate F4 (+ 12.2 kcal mol^{-1} wrt. glucose). Subsequent removal of two water molecules results in the formation of HMF. Due to a similar bond strength of the C1–O6 and the C3–C4 bond, formation of an analogous intermediate is also likely. Formation of such an intermediate, F4-A (Scheme 3), is thermodynamically favourable than F4 (+7.6 kcal mol^{-1}), however kinetic preference is not explored in this study.

In the presence of water the hydroxyl groups at the C3 and C4 positions would be hydrogen bonded with the solvent molecules. A recent computational study by Qian[34] describes the formation of F4 using *ab initio* dynamics simulation using metadynamics, however the collective variables are chosen to establish the formation of this particular intermediate. It would be valuable to perform such studies using another set of collective variables to understand the kinetics for the formation of the intermediate F4-A. Understanding the kinetic preference of the formation of intermediates F4-A and F4 from glucose requires calculations with a large number of explicit solvent molecules, as this is a solvent assisted rearrangement, which is beyond the scope of this manuscript.

Subsequent dehydration (removal of two water molecules) of FA-4 would result in the formation of an isomer of HMF, denoted as 'HMF-A', and the relative energy of this species (–32.5 kcal mol^{-1}) is almost identical to the HMF (–33.1 kcal mol^{-1}). An alternative is the cleavage of the C═O moiety of FA-A to form furfuryl alcohol and this pathway is explored and discussed in Section 3.4.

Recent experimental studies using sulfonic acid resins and solid acids show significantly high conversion of glucose to HMF and levulinic acid.[35,45] It is speculated that the reaction may proceed *via* acyclic intermediates due to the stabilization of these species on the surface of the catalysts compared to that in the aqueous solution. In order to understand the thermodynamics of such a likely pathway of HMF formation from glucose, we have computed the free energetics of a likely pathway through an acyclic pathway. The predicted free energy profile in aqueous solution is given in Fig. 3. The protonation of the ether oxygen (G3, 15 kcal mol^{-1}) of the pyranose (G1, neutral) ring initiates the ring opening to form acyclic glucose, G2 (9.1 kcal mol^{-1}). The enthalpy of activation of solvent assisted ring opening of glucose in neutral aqueous medium was computed previously as 28 kcal mol^{-1}.[20] Therefore the ring opening can be catalysed by a solvent (water, methanol *etc.*) or protons from mineral acids.

Acyclic glucose can be protonated (G3, + 15.8 kcal mol^{-1}) at the aldehyde position, due to the higher proton affinity of the aldehyde group than the hydroxyl groups, further
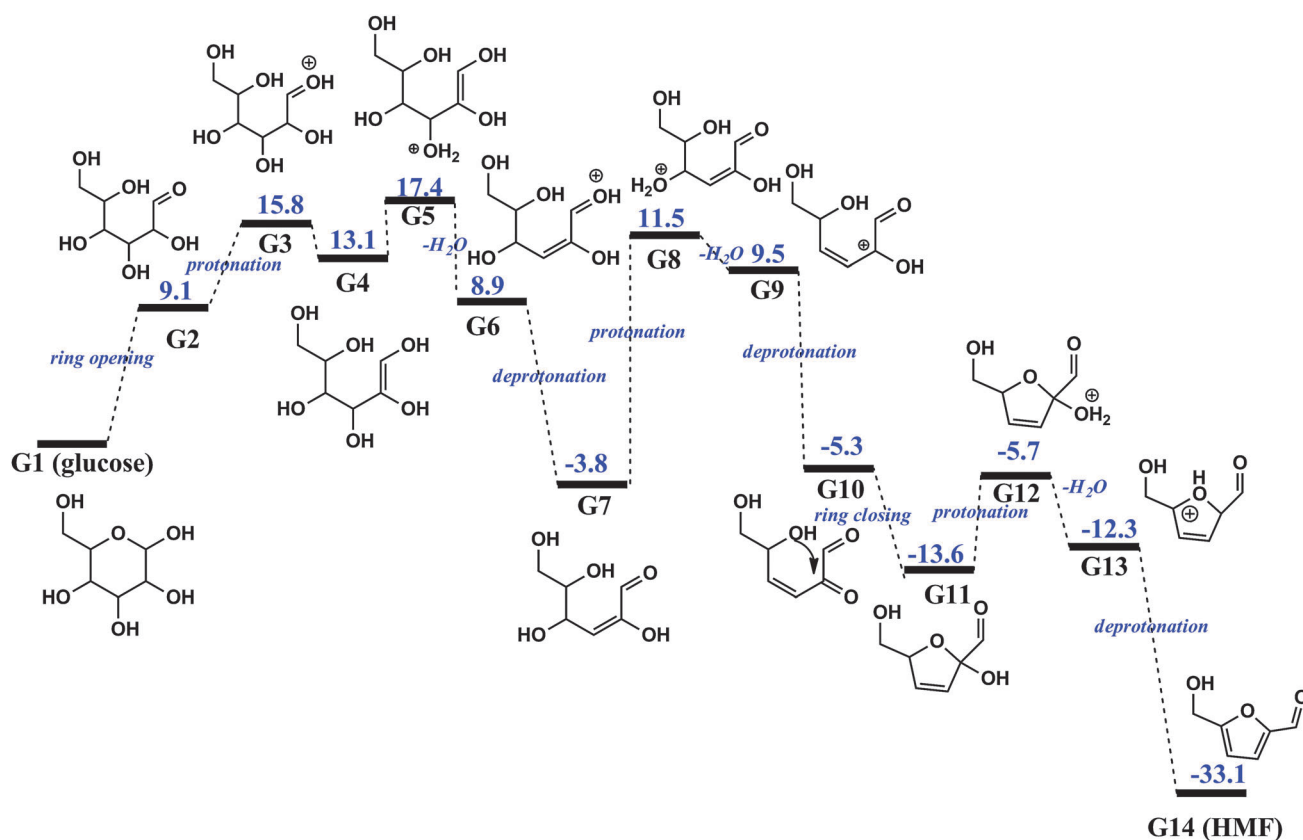
Fig. 3 Predicted free energy profile (298 K) of decomposition of glucose (G1, neutral) to hydroxy-methyl-furfural (HMF,G14) through acyclic pathways at the G4MP2 level of theory in water dielectric medium. Contributions from water dielectric medium is calculated at the B3LYP/6-31 G(2df,p) level of theory using the SMD solvation model. All values are reported in kcal mol^{-1}.

leading to the formation of an enol form of the glucose (G4, +13.1 kcal mol^{-1}) upon deprotonation at the C2 position (G2 → G3 → G4). Subsequent protonation at the C3–OH (G5, +17.4 kcal mol^{-1}) and the C3–O bond cleavage results in the formation of a protonated dienol (G6, +8.9 kcal mol^{-1}). Deprotonation of G6 results in the formation of a conjugated aldehyde (G7, −3.8 kcal mol^{-1}). Protonation of the C4–OH (G7 → G8) is endergonic by 15.3 kcal mol^{-1} to form the intermediate G8. Subsequent removal of water and deprotonation leads to the formation of a diketone (G10, −5.3 kcal mol^{-1}). The diketone (G10) undergoes ring closure to give a five-membered HMF precursor (G11, −13.6 kcal mol^{-1}). Protonation of the tertiary hydroxyl group of G11 results in the formation of G12 (−5.7 kcal mol^{-1}), subsequent elimination of a water molecule (G13, −12.3 kcal mol^{-1}), and deprotonation finally gives HMF (−33.1 kcal mol^{-1}).

The HMF can further react with water to produce levulinic acid and formic acid and the detailed mechanism of that reaction is beyond the scope of this manuscript.

Considering the free energy profile in the aqueous medium, it is evident that the initial steps of ring opening and subsequent protonation are the most endergonic (G1 → G3 → G5). Catalysts that can stabilize the acyclic glucose and their enol form are essential for this pathway to occur. The highest point in free energy corresponds to the protonation of

the enol (G5, 17.4) and is quantitatively similar to that is seen in the case of the fructose-HMF pathway. The initial dehydration leads to formation of a relatively stable conjugated aldehyde (G7) and the second dehydration leads to the formation of a diketone (G10). Both of these species are thermodynamically stable wrt glucose in aqueous medium and therefore they could be potential intermediates that can be observed using spectroscopic techniques. Similar to that of Scheme 2, a solvent assisted dehydration of G4 to G7 and G7 to G10 is likely and the enthalpy of activation required for these processes are 40.8 kcal mol^{-1} and 33.2 kcal mol^{-1} respectively. Therefore, it is likely that the first process (G4 → G7) is catalysed by the acid (protons) and the second process (G7 → G10) is either solvent or acid-catalysed. We note that both intermediates G7 and G10 can potentially polymerize and this could lead to insoluble humins, which require another comprehensive study and the consideration of reaction conditions.

3.4 Glucose to furfural alcohol

In addition to the formation of intermediate F4 (in Scheme 3), it is thermodynamically equally likely to form intermediate F4-A, where the protonated aldehyde group is at the C2 position of the five–membered ring. From this intermediate, we have proposed a pathway to form furfuryl alcohol.
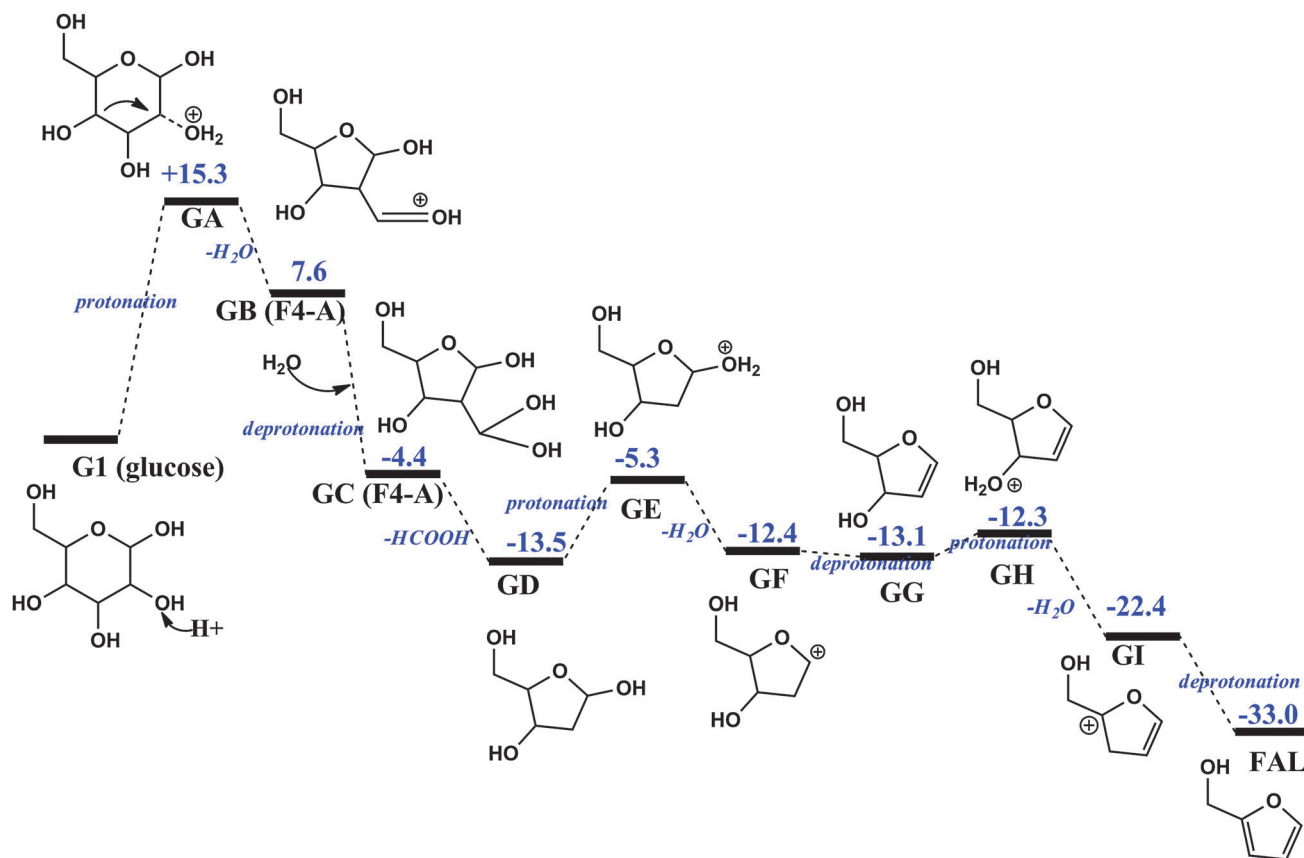
Fig. 4 Predicted free energy profile (298 K) of decomposition of glucose (G1) to furfuryl alcohol (FAL) at the G4MP2 level of theory in water dielctric medium. Contributions from water dielctric medium is calculated at the B3LYP/6-31 G(2df,p) level of theory using the SMD solvation model. All values are reported in kcal mol^{-1}.

The computed free energy profile for the formation of furfuryl alcohol from glucose in aqueous solution is shown in Fig. 4. We note that such a pathway is possible from the intermediate F4 as well. The reaction sequence is initiated by the protonation at the C2–OH group and subsequent removal of water to form GB (F4-A, $+7.6$ kcal mol^{-1}). Addition of water to the aldehyde group and deprotonation produces a gem diol, GC (-4.4 kcal mol^{-1}). Formation of such gem-diols in aqueous solutions is observed in our previous experimental study.[46] The gem-diol undergoes C–C scission to release formic acid and a thermodynamically stable intermediate GD (-13.5 kcal mol^{-1}). Similar C–C bond cleavage is shown to occur during the acid-catalysed rehydration of HMF, where levulinic acid and formic acid are formed. Protonation of the C1–OH hydroxyl group and subsequent dehydration leads to the formation of GE (-5.3 kcal mol^{-1}) and GF (-12.4 kcal mol^{-1}) respectively. A deprotonation of GF result in the formation of GG (-13.1 kcal mol^{-1}). Further, protonation, removal of water, and deprotonation result in the formation of GH (-12.3 kcal mol^{-1}), GI (-22.4 kcal mol^{-1}), and FAL (-33.0 kcal mol^{-1}), respectively. Interestingly, under acidic conditions FAL is significantly more reactive than HMF and forms levulinic acid[46] by rehydration reaction. At high concentrations FAL was shown to form a polymeric furfuryl alcohol[47,48] and hence limiting the yield of levulinic acid. Both of the reactions are found to be exothermic under acidic conditions and occur through multiple reaction pathways.

4 Conclusions

In this paper, we report on a high-level, CCSD(T)-based G4MP2 quantum chemical investigation of the energetics and important reaction barriers for the acid-catalysed reactions of glucose and fructose to platform chemicals such as hydroxymethyl furfural and furfuryl alcohol. The following conclusions can be drawn from this investigation.

Based on the protonation free energies of various hydroxyl groups of sugar molecules, the relative reactivity of sugar molecules can be predicted. The fructo-furanose is more reactive towards the acid-catalysed decomposition, predominantly due to the presence of tertiary group with high proton affinity and this explains the high-selectivity of HMF formation from fructose. A detailed free energy profile is computed and the intermediate predicted from the computations are consistent with the experimental studies.

In addition to the previously reported acid-catalysed fructose-HMF reaction pathway, a solvent-mediated dehydration pathway is also thermodynamically and kinetically feasible. The computed apparent enthalpy of activation of this pathway is $+34.3$ kcal mol^{-1}, suggesting that multiple reaction pathways are likely to exist for the fructose to HMF reaction.

Two pathways were proposed for the formation of HMF from glucose. One pathway is initiated by the protonation of the C2–OH group of the pyranose ring and dehydration leading to a carbo-cation rearrangement to form a furanose ring. This pathway is very similar to the fructose–HMF reaction pathway. A second possibility is through acyclic intermediates, where ring opening and enolization is essential.

Calculations indicate that the stabilization of enol and acyclic intermediates is essential for this pathway to occur.

The energy and structures of likely pathways for the formation of furfuryl alcohol from glucose are proposed and this reaction pathway is parallel to the formation of HMF from glucose.

The results from these studies can be used as a benchmark for detailed *ab initio* molecular dynamics studies using various solvents to elucidate key kinetics and thermodynamics of sugar decomposition reactions.

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