Cooperative Activation of Cellulose with Natural Calcium

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Abstract. Naturally occurring metals such as calcium catalytically activate the inter-monomer β-glycosidic bonds in long chains of cellulose initiating reactions to volatile oxygenates for renewable applications. In this work, the millisecond kinetics of calcium catalyzed reactions were measured via the method of pulse-heated analysis of solid/surface reactions (PHASR) at high temperature (370–430 °C) to reveal accelerated glycosidic ether scission with a second order rate dependence on Ca²⁺ ions. First principles density functional theory (DFT) calculations were used to identify stable binding configurations for two Ca²⁺ ions that demonstrated accelerated transglycosylation kinetics with an apparent activation barrier of 50 kcal mol⁻¹ for a cooperative calcium catalyzed cycle. The agreement of mechanism with calcium cooperativity to the experimental barrier (48.7 ± 2.8 kcal mol⁻¹) suggests that calcium enhances reactivity through a dual role of disrupting native H-bonding and stabilizing charged transition states.

Introduction. The thermochemical conversion of biopolymers such as cellulose renewably produces an array of five or six-carbon oxygenates that can be catalytically upgraded to fuels and chemicals.¹⁻³ The maximum yield of oxygenates including levoglucosan, furans, and pyrans is produced at temperatures between 400-600 °C, where cellulose activates to form volatile components sufficiently fast to evaporate organic compounds from reacting molten cellulose.⁴⁻⁷ While progress has been made to develop models of cellulose reaction kinetics, most notably by Broadbelt and co-workers,⁸,⁹ experimental kinetics to support cellulose fragmentation mechanisms have been difficult to obtain due to the challenges in quantifying hundreds of compounds forming over milliseconds from the complex, evolving macromolecular structure of reacting cellulose.¹⁰⁻¹² These experimental challenges have limited the development of a detailed understanding of the activation mechanisms of cellulose and the more complicated catalytic role of naturally occurring alkaline earth and alkali metals in lignocellulosic materials.¹⁰

High temperature cellulose activation occurs via inter-monomer scission of chains that are interconnected by a network of hydrogen bonds (H-bonds) as depicted in Figure 1A. Transglycosylation is widely believed to be the dominant one-chain scission mechanism which involves the nucleophilic attack of the C6 hydroxymethyl group of the cellulose monomer on the C1 carbon, thereby breaking the glycosidic ether bond and the cellulose chain with a calculated activation barrier of 50-53 kcal mol⁻¹ in the absence of intra-sheet H-bonding.⁹,¹³,¹⁴ By this mechanism, the C6 hydroxymethyl group must be free to rotate close to the C1 carbon; in the crystalline structure of cellulose Iβ, Hosoya et al. calculated that breaking the H-bonds connected to the C6 hydroxymethyl group can increase transglycosylation activation barriers by almost 10 kcal mol⁻¹.¹⁵ Westmoreland and co-workers, on the other hand, computed a lower activation energy for transglycosylation catalyzed by water and small oxygenates that are H-bonded to reacting carbohydrates, lowering the activation energy to around 36-40 kcal mol⁻¹.¹⁶ Auerbach and co-
workers similarly showed that pre-cursors to levoglucosan can be formed with free energy barriers ~36 kcal mol$^{-1}$ via transition states that are stabilized by H-bonding.\textsuperscript{17}

Recent experimental kinetics to characterize cellulose activation further revealed the role of the H-bonding network in cellulose chemistry.\textsuperscript{18,19} Experimental measurements indicated two kinetic regimes that transition at 467 °C.\textsuperscript{18} At high temperature, cellulose activates with an apparent energy of 53.7±1.1 kcal mol$^{-1}$, consistent with the uncatalyzed transglycosylation mechanism. However, below 467 °C the apparent activation energy of cellulose activation was measured to be significantly lower at 23.2±1.9 kcal mol$^{-1}$, indicating that reaction is driven via a catalytic mechanism that occurs within the cellulose molten phase. This lower apparent barrier was consistent with computed energies of a mechanism that suggested vicinal hydroxyl groups could promote facile proton transfer during transglycosylation.\textsuperscript{19} These studies indicate that H-bonding in the vicinity of the reaction center can increase or decrease the activation kinetics depending on the conditions, solid crystal versus reacting melt, as has been noted in a recent review by Westmoreland.\textsuperscript{20}

Alternatively, the vicinal hydroxyl reaction environment in cellulose can also be modified by the presence of natural metal impurities. Lignocellulosic feedstocks have varying amounts of alkaline earth (Mg$^{2+}$ and Ca$^{2+}$) and alkali (Na$^+$ and K$^+$) metals which chemically influence both the composition of the final product yields and the overall rate of cellulose breakdown.\textsuperscript{21–26} Cellulose breakdown studies using thermal analysis techniques such as TGA and DSC showed that these metals reduce the onset temperature where cellulose degradation occurs.\textsuperscript{26} In homogeneous catalysis for biomass upgrading, metal ions are known to significantly re-orient solvent H-bonding in their vicinity.\textsuperscript{27} Similarly, metal cations with +1 or +2 oxidation state are expected to selectively bind to different regions of the cellulose matrix and disrupt the H-bonding environment in a manner similar to homogeneous catalysis carried out in metal salt solutions. In addition, the Lewis acid character of these metals can stabilize oxygenated transition states.\textsuperscript{28–30}

In this work, the mechanism of calcium-promoted cellulose activation is evaluated by combined experimental reaction kinetic studies and first principles density functional theory (DFT) calculations to identify favorable metal binding positions and elucidate the catalytic activation mechanism. Activation kinetics of calcium catalysis were measured by the method of pulse-heated analysis of solid/surface reactions (PHASR) by rapidly heating and cooling a film of cellulose at

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**Figure 1.**\ A. Cellulose consists of long chains of β(1–4) linked D-glucose units that are hydrogen-bonded into stackable sheets.  
B. Introduction of calcium ions (depicted here as red spheres) into cellulose matrix disrupts the native hydrogen-bonding network leading to increased reactivity of cellulose chains.  
C. Higher loadings of calcium produce neighboring calcium binding sites capable of cooperatively catalyzing the scission of inter-monomer glycosidic bonds.
a temporal resolution as small as 20 milliseconds. As shown by previous experiments, PHASR provides temporally resolved reaction kinetic data in the absence of heat and diffusion transport artefacts, thereby facilitating reliable comparisons between experimental kinetic data and ab initio calculated activation barriers. The activation mechanism was characterized by the reaction of calcium-impregnated α-cyclodextrin (CD). CD is a known cellulose kinetic surrogate of cellulose that is readily quantified and exhibits similar computed barriers for activation as with cellulose despite different C1 stereochemistry. Experimental kinetics were measured at varying temperatures (370-430 °C) and calcium concentrations (0.1-0.5 mmol Ca²⁺/g CD). The experimental results were used along with DFT studies to elucidate the primary catalytic role of calcium in aiding C-O bond scission as well as a secondary role that calcium contributes in disrupting H-bonding networks (Figure 1B-1C). This work presents the first such study on intrinsic cellulose activation kinetics in the presence of metal salts and highlights the unique roles that metal ions can play in enhancing reactivity.

**Results and Discussion.**

**Experimental reaction kinetics.** The temporal extent of conversion of α-cyclodextrin was measured for thermal pulses of 20-2000 milliseconds (ms), temperatures of 370-430 °C, and calcium concentrations of 0.1-0.5 mmol Ca²⁺/g α-CD as depicted in Figure 2. Each data point is comprised of at least three independent experimental trials, and the error bars associated with each point represent a 95% confidence interval. Conversion of α-cyclodextrin exhibited apparent first order kinetic behavior with respect to α-cyclodextrin mass among all temperatures and calcium concentrations. For each temperature and concentration series, a first order kinetic model was fit to the experimental data and found to pass through all the experimental confidence intervals. At 415 °C, pure α-cyclodextrin only achieved...
~75% conversion after 2000 ms of reaction duration. In contrast, when α-cyclodextrin was doped with 0.5 mmol Ca\textsuperscript{2+}/g α-CD at 415 °C, a similar conversion was achieved within 100 ms and exceeded a conversion of 90% within 200 ms. (See Table S1A-M)

The experimental data presented in Figure 2 show that calcium significantly increased the overall decomposition kinetics of cyclodextrin. To ensure that Ca\textsuperscript{2+} was the catalytic material, experiments were also conducted with different calcium salts, Ca(NO\textsubscript{3})\textsubscript{2} and CaCl\textsubscript{2} (Figure S3-1); these experiments indicated that the overall measured kinetics were independent of the identity of the counter-ion (NO\textsubscript{3}\textsuperscript{-} or Cl\textsuperscript{-}). This was further evaluated by thermogravimetric analysis with mass spectrometry, where these anions were shown to volatilize out of the cellulose matrix at temperatures lower than the reaction temperature (Figure S3-2). This agrees with other recent studies that suggest that anions are not present in the reaction melt at reaction conditions.\textsuperscript{35}

To characterize the effect of the calcium catalyst, the experimental conversion data of Figure 2 were fit to a first-order kinetic model with apparent rate parameters, \( k_{\text{app}} \) (see Eq. 1), for each temperature and calcium concentration. The first order rate parameters were then plotted against the varying integer powers of calcium concentration to determine the dependence of calcium concentration on the rate of activation. The apparent rate parameters exhibited an almost linear fit with respect to the square of calcium concentration as shown in Figure 3A, indicating second order rate dependence in the catalyst concentration. It must be noted that while a non-first-order dependence on catalyst concentration is typically not measured in heterogeneous catalysis, such rate orders are found in homogenous systems. For example, Bures discussed case studies where the participation of reactant-metal complexes in bimolecular reactions resulted in second order rate dependence in catalyst concentration\textsuperscript{36}. As shown, the rate coefficient was non-zero at zero calcium concentration, consistent with uncatalyzed cellulose chemistry, as previously measured.\textsuperscript{28} For comparison, other rate expressions were evaluated as shown in Figure S4-1 of the supporting information.

From a mechanistic standpoint, the second order rate dependence in calcium concentration suggests a catalytic mechanism that proceeds via two calcium ions in the elementary steps. The rate of activation can then be described as:

\[
rate of reaction (g_{CD}, s^{-1}) = k_{\text{app}} * M_{CD} = (k_H + k_C[Ca^{2+}]^2) * M_{CD}
\]
where $k_H$ is a homogeneous or non-catalyzed rate constant, $k_C$ is a catalyzed rate constant, and $M_{CD}$ is the mass of $\alpha$-cyclodextrin. Mass is chosen instead of concentration because $\alpha$-CD is a kinetic surrogate for cellulose, and it is difficult to characterize concentration of cellulose. This model was selected to incorporate the first order kinetic behavior with respect to $\alpha$-cyclodextrin mass at all calcium concentrations (Figure 2), the second order dependence on calcium, and the non-zero rate of reaction when calcium is not present with the homogenous rate constant term. The catalyzed rate constant, $k_C$, was determined by fitting to the model described above and is presented in Arrhenius form in Figure 3B. The first-order kinetic catalytic rate constant exhibits a high activation energy, $E_a = 48.7 \pm 2.8$ kcal mol$^{-1}$, and a pre-exponential factor, $k_0 = 1.28 \times 10^{17}$ (mmol Ca/g CD)$^{-1}$s$^{-1}$ (1.35 x $10^{17}$ (mol Ca/mol CD)$^{-1}$s$^{-1}$ on a mol/mol basis). It must also be noted that in the presence of salts, use of activities is more appropriate than concentrations. While models exist for the prediction of activity coefficients of salts in electrolyte or aqueous solutions, predictive models are not currently available for polymer solids/melts.

Previous work utilizing PHASR considered activation of pure cellulose by measuring the conversion of $\alpha$-cyclodextrin between 385-505 °C, which indicated a drastic change in the rate of activation occurs above 467 °C. This two-regime behavior motivated plotting of the total reaction rate constant at different calcium concentrations along with the non-catalyzed rate constant on an Arrhenius plot, shown in Figure 4. The dashed color lines in Figure 4 represent a fit line for the rate constants by combining contributions from the non-catalyzed and catalyzed activation using the measured activation energies and associated Arrhenius pre-exponential factors. The absence of any sharp transition with increasing concentration of calcium indicates that a higher fraction of glycosidic activation occurs through the catalyzed pathway which has only one kinetic regime. In addition, it is also observed that the slope of the dashed curves tends towards that of the high temperature, non-catalyzed regime albeit at significantly lower temperatures. This is further experimental validation that the degradation onset temperature decreases in the presence of metal ions.

An explanation for the observed second order dependence of calcium concentration is provided via theoretical analysis of the calcium-catalyzed activation mechanisms using cellulose. In previous studies, it was shown that the C$_1$ stereocchemistry of glycosidic bonds (C$_1$-O-C$_6$) does not influence the kinetics of activation$^{34}$ or the distribution of decomposition products$^{33}$; cycloextrin (alpha glycosidic bonds) and cellulose (beta glycosidic bonds) both produced the same chemical products at the same rate. Comparable behavior resulted from the similar mechanisms of nucleophilic attack of hydroxyl groups in activating glycosidic bonds$^{35}$. As such, computed mechanisms evaluating calcium-catalyzed activation considered the cellulose beta glycosidic bonds.

**Nature of calcium active sites.** Prior studies have suggested that metal ions can form chelated complexes with the hydroxyl groups of cellulose chains, which could be active sites for catalysis.$^{28-30}$ While these proposed sites/complexes may be the stable binding sites for metal ions at ambient conditions, the experiments reported here (Supplemental Note S3, Figure S3-1 & 2) suggest that the anions leave the polymer melt as volatile acids at reaction conditions. This indicates that the

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source providing protons to leave with anions is likely hydroxyl groups of cellulose chains. In the absence of these protons, the deprotonated hydroxyl groups would likely be stabilized by calcium ions leading to Lewis acid (LA) – Lewis base (LB) site pair comprised of the calcium cation (LA), and the oxygen anion (LB) of the deprotonated hydroxyl.

A suitable model that represents the cellulose Iβ crystal (Figure 5A) was used to identify stable binding positions for metals. A single calcium ion in this system corresponds to ~1.0 wt%, which is within the experimental range for calcium concentration. Various different binding sites were examined within the cellulose matrix as outlined in the SI. The most stable binding site (based on electronic energies) for calcium, also the resting state of the catalyst, is a site that sits between the deprotonated states of C6 and C3 hydroxyl groups of two adjacent chains thus forming a stable O-Ca-O bridge; this binding site is more stable than any other binding site by 2-8 kcal mol⁻¹ (structures of other sites are shown in S6) The bond lengths for Ca-O shown in Figure 5B are in good agreement with XRD studies of calcium-impregnated sugar crystals.³⁷,³⁸

To evaluate the mobility of calcium ions and address the mechanism for calcium ion diffusion, a mechanism was first developed wherein a hydroxyl group from a vicinal sugar transfers its proton to a deprotonated bridging O anion and binds to the calcium ion. Through this mechanism, calcium ions can move from site to site via small molecules that contain hydroxyl groups. We verified this using a simple model of glucose molecules interacting with an O-Ca-O bridged site and calculated a very low barrier of 2.5 kcal mol⁻¹ which suggests facile diffusion. It is expected that such hydroxyl group interactions with calcium binding sites would be easier in a melt phase as small molecules in the melt can interact and move around more freely. Therefore, a periodic model was also used that consisted of two cellulose sheets containing the impregnated calcium with glucose and water molecules being used to fill the space in between to signify trapped melting regions. Ab initio
molecular dynamics simulations on these prototypical models showed that the calcium ions can indeed easily move out from bridged sites and into the melt phase in short timescales of 15 ps. (Further details in Supplemental Note S7)

A rate order dependence on calcium concentration that is nearly second order suggests that two possible catalytic cycles can operate under reaction conditions. The first catalytic cycle involves the participation of a single calcium ion,

\[
Ca + Cell \xrightleftharpoons[K_1]{k} Ca - Cell
\]  

(2)

\[
Ca - Cell \xrightarrow{k} Ca - Int
\]  

(3)

\[
Ca - Int \xrightleftharpoons[K_2]{k} Ca + Int
\]  

(4)

where Cell is the neat cellulose chain, Int is the post cleavage intermediate, Ca is the calcium catalyst, Ca-Cell is the calcium bound intermediate. The constants k, K_1 and K_2 refer to the intrinsic rate constant for glycosidic bond cleavage of the cellulose, adsorption of cellulose to the Ca, and the desorption of the intermediate from the Ca. The rate which is thought to be controlled by glycosidic cleavage can be written as:

\[
rate = \frac{kK_1[Cell][Ca_{initial}]}{(1+K_1[Cell])}
\]  

(5)

where the rate dependence of calcium will be first order if the first term in the denominator is dominant (i.e., the unbound cellulose state is dominant). Figure 5C & 5D show the front and zoomed-in top view of bound Ca-Cell intermediate wherein the calcium ion closely interacts with the hydroxymethyl group and the glycosidic oxygen. In such a configuration, calcium can stabilize the transition state and catalyze the transglycosylation reaction (Scheme 1), believed to be a dominant initiation mechanism, thus leading to a levoglucosan chain end intermediate, the product in Scheme 1 (Int).^9,13,14

Looking more closely at Figure 5D, the rotation of C6 hydroxymethyl group to interact with the glycosidic bond (circled blue), which is critical for transglycosylation, requires breaking multiple intra-sheet H-bonds leading to an energy penalty. This penalty has been shown to increase the activation barriers of transglycosylation from 51-53 kcal mol\(^{-1}\) in simple gas phase models to ~59 kcal mol\(^{-1}\) for such crystal models.\(^{15}\) Similarly, there exists a strong intra-molecular H-bond that needs to be stretched/broken during the course of reaction (circled green in Figure 5D). It is possible for an additional calcium ion to bind in configurations such as those shown in Figure 5E and 5F, respectively, and disrupt native H-bonding networks leading to potentially lower barriers. The two configurations for cooperative calcium catalysis shown in Figure 5E and 5F are referred to as configurations 1 and 2, respectively. In these scenarios an alternative catalytic cycle can be proposed as follows,

\[
Ca + Cell \xrightleftharpoons[K_1]{k} Ca - Cell
\]  

(6)

\[
Ca + Ca - Cell \xrightleftharpoons[K_2]{k} Ca - Cell - Ca
\]  

(7)

\[
Ca - Cell \xrightarrow{k} Ca - Int - Ca
\]  

(8)

\[
Ca - Int \xrightleftharpoons[K_3]{k} Ca + Ca - Int
\]  

(9)

\[
Ca - Int \xrightleftharpoons[K_4]{k} Ca + Int
\]  

(10)

where Ca-(X) and Ca-(X)-Ca are the single and double bound calcium intermediates, respectively.

Scheme 1. Mechanism for glycosidic bond cleavage by transglycosylation catalyzed by a single calcium ion. Monomers shown in red correspond to monomers connected by glycosidic bond that undergoes catalytic cleavage.
This model yields a rate expression for the slowest step as follows,

$$rate = \frac{kK_1K_2^*[\text{Cell}][\text{Ca}_{\text{initial}}]^2}{(1+K_1[\text{Cell}])^2}$$  \hspace{1cm} (11)$$

The proposed catalytic cycle would lead to second order rate dependence of calcium in the rate of activation when concentrations of Ca-bound species are low. Detailed derivations of the above rate expressions as well as concentration balances on Ca are provided in Supplemental Note S8.

DFT calculated energetics for calcium catalytic cycles. Considering the energetics of the single calcium catalytic cycle in Figure S9-1, it is shown that the binding of Ca to form the Ca-Cell reactant in the boat conformer (necessary to carry out transglycosylation) is 17 kcal mol\(^{-1}\) uphill in energy. This uphill energetic penalty derives from two sources – (1) a penalty exists to move the calcium ion from its most favorable binding site to the site where it carries out catalysis, and (2) an energetic penalty is required to break intra-sheet H-bonds to rotate the hydroxymethyl group to drive transglycosylation. At low concentrations of Ca bound to the active site, the apparent rate constant for transglycosylation from cycle 1 is \(k_{\text{app}}=kK_1\). This results in a calculated apparent activation energy of 53 kcal mol\(^{-1}\) which is lower than the barrier for carrying out transglycosylation in a neat cellulose crystal (59 kcal mol\(^{-1}\)).\(^{19}\) This leads to the observation that one of the primary roles of calcium in this chemistry is to stabilize the negatively charged hydroxymethyl O6 atom in the transition state. This cycle would result in a rate order dependence of one and activation barrier of 53 kcal mol\(^{-1}\).

Moving on to the catalytic cycle for two calcium ions in configuration 1 (Figure 6A), the energy diagram indicates an energetic penalty (+7 kcal mol\(^{-1}\)) to move a calcium ion from its most favorable binding site (Figure 5B) to the site in Figure 5E. However, the introduction of the primary, catalytic calcium ion leads to a stable chair conformer Ca-Cell-Ca species that is 7 kcal mol\(^{-1}\) lower in energy than the unbound cellulose state (Cell + 2Ca). In this conformation, the calcium ion (circled in blue) frees up the hydroxymethyl group to rotate and form a highly stable chair conformer where the OH strongly binds to the primary catalytic calcium ion near the glycosidic bond reaction center. Just as in the previous catalytic cycle, at low concentration of the Ca-bound species, the rates are measured with respect to the unbound state thus resulting in an apparent rate constant of \(kK_1K_2 \) and apparent activation energy of 41 kcal mol\(^{-1}\). The observed rate order in this cycle would be second order in Ca and first order in Cell, in agreement with the experiments.
In configuration 2 (Figure 6B), the Ca-Cell-Ca boat conformer reactant is 15 kcal mol\(^{-1}\) uphill in energy versus 17 kcal mol\(^{-1}\) for the boat conformer intermediate in the single calcium case (not shown). As shown in Figure 5F, the secondary calcium ion breaks a strong intramolecular H-bond (circled green in Figure 5D), which promotes the conformational change from chair to boat structure and, in addition, the facile cleavage of the glycosidic bond. This is visible in the calculated activation barrier which is ~3 kcal mol\(^{-1}\) lower than the calculated barrier for the single calcium case (50 versus 53 kcal mol\(^{-1}\)). The calculated barrier for this cooperative cycle of 50 kcal mol\(^{-1}\) also agrees well with the experimentally measured barrier of 48.7 ± 2.8 kcal mol\(^{-1}\) for the calcium catalyzed CD breakdown reported in the earlier section.

The structure of the optimized transition state in Figure 7A for the single calcium catalytic cycle has geometrical features (bond distances) near the reaction center that are similar to those observed for the optimized transition states in the cooperative calcium catalytic cycles shown in Figures 7B and 7C. This suggests that the additional Ca ion plays only a secondary role in lowering the activation barriers. It must be noted that at low concentrations of calcium, the concentration of species such as Ca-Cell-Ca is possibly not high enough for most of calcium catalysis to occur through the cooperative catalytic cycle. At higher concentrations, the contribution of the cooperative cycle would likely increase. This dual catalytic mechanism would also suggest that the rate expression should include three parallel pathways resulting in one uncatalyzed and two catalyzed terms as shown below:

\[
\text{rate of reaction}(g_{CD} \text{ s}^{-1}) = (k_H + k_{C1}[Ca^{2+}] + k_{C2}[Ca^{2+}]^2) \times M_{CD}
\]

(12)

While an integer fit to the reaction kinetics was shown in Figure 3A, a non-integer fit of the rate expression shown in supplementary Figure S5-1 indicated a rate order in calcium of 1.71 ± 0.09, suggesting that the cooperative calcium catalytic mechanism dominates over the single calcium catalytic pathway at the chosen reaction conditions and calcium dopant levels.

Conclusions. Millisecond reaction kinetics together with first principle density function theory calculations indicate that cellulose activation can proceed via a mechanism involving single and cooperative calcium-catalyzed glycosidic bond activation. Temporally resolved conversion data of the cellulose surrogate, \(\alpha\)-cyclodextrin, revealed a catalyzed acceleration of cellulose activation in the presence of calcium with observed second order rate dependence of calcium ion. Experiments also indicated a lower activation energy barrier for calcium-catalyzed glycosidic bond activation of 48.7 ± 2.8 kcal mol\(^{-1}\). The second order catalytic kinetics of calcium were evaluated using explicit cellulose crystal models and DFT calculations. DFT results suggest that calcium ions play a primary catalytic role of stabilizing charged transition states along with a secondary role of disrupting the native H-bonding networks to enhance reactivity. This cooperative catalytic mechanism serves to significantly lower the temperature at which lignocellulosic materials become chemically accessible either in nature or through engineered renewable energy systems.
Methods. Cyclodextrin sample preparation. Thin films of α-cyclodextrin samples were prepared via evaporative deposition on passivated carbon steel heating elements. Heating elements were cleaned and passivated using a butane torch before cooling back to ambient conditions. A 1.0 wt% solution of α-cyclodextrin in HPLC-grade water was prepared, and the corresponding amount of Ca(NO₃)₂$\cdot$4H₂O (0.1-0.5 mmol Ca(NO₃)₂/g α-CD) was added to the solution and thoroughly mixed to dope α-cyclodextrin with calcium. A 5.0 μL aliquot of the solution was pipetted onto the center of the cleaned heating element, corresponding to 50 μg of α-cyclodextrin. Samples were then placed under vacuum at 25 in. Hg and 40 °C until the water had been evaporated and the film was formed. This deposition and drying technique were performed twice sequentially to generate 100 μg samples that were uniform circular films, <20 μm in thickness and 3.0 mm in diameter.

Reaction experiments. Reaction of α-cyclodextrin films was performed using the method of ‘pulse-heated analysis of solid/surface reactions’ (PHASR) by which reactant samples were subjected to rapid thermal pulses for prescribed temperatures and time intervals. A detailed design and description of reactor performance has been previously described. Sample were placed in a sealed reactor chamber between two stainless steel custom machined reactor housings (an upper heating housing and a lower cooling housing). The upper reactor housing contained two electrical leads that contacted the heating element to transfer uniform electrical current and heat the sample. A 1000 Hz optical pyrometer measured the temperature of the sample and was integrated with a 2000 Hz PID controller to precisely control the reaction temperature.

Chemical product analysis. Quantification of remaining α-cyclodextrin reactant after a thermal PHASR pulse was conducted via solvent extraction and liquid chromatography with light scattering detection. Heating elements containing partially reacted samples were removed from the PHASR reactor and cut into a small circle containing only the sample film. The smaller heating element was then placed into a 1.5 mL PTFE filter vial, after which 350 μL of HPLC grade water was pipetted into each vial. Vials were shaken for about one minute to ensure complete dissolution of α-cyclodextrin. The remaining heating element was then removed from the vial and the filter plunger was depressed to remove any remaining particulate. 100 μL of filtered sample was injected into a high-performance liquid chromatograph (HPLC, Shimadzu Prominence) with a carbohydrate separation column (Agilent Na Hi-Plex, PN: 1171-6140), light scattering detector (ELSD-LTII), and water mobile phase. Quantification of the α-cyclodextrin peak from the ELSD for PHASR pulses of increasing length yielded the consumption of reactant with time.

Computational methods. All of the calculations reported herein were carried out using periodic plane-wave density functional theory in the Vienna Ab-initio Simulation Program (VASP) along with generalized gradient approximation (GGA) functional developed by Perdew, Burke and Ernzerhof (PBE). The D2 method developed by Grimme, which can account for two-body dispersive interactions, was applied in all calculations. Plane waves with an energy cutoff of 396 eV were used based on projector augmented wave potentials (PAW). A 1x1x1 k-points grid was found to be sufficient for the system based on energy convergence calculations. The calculations were performed until self-consistent field calculations and geometric optimization converged to $10^{-6}$ eV and force of 0.05 eV/Å. To evaluate barriers for a mechanism, the climbing NEB method was used to generate intermediate images for the pathway and subsequently optimize the pathway with a force tolerance of 0.2 eV/Å. The transition state was then obtained using the dimer method, as developed by Henkelman, with a force tolerance of 0.05 eV/Å. NVT AIMD simulations were performed with the same functionals and dispersion corrections. Time step for the AIMD simulations was 1 fs. Temperature was maintained at 700K using a Nose–Hoover thermostat.

Computational model. A 1x2x2 supercell of the cellulose Iβ crystal was used to examine the most stable binding sites for calcium ions. The model was slightly modified to simulate reactions such that it consisted of a cellulose sheet with degree of polymerization of three sandwiched between two periodically extending cellulose sheets to reproduce the environment in a cellulose Iβ crystal. This modification of the reaction sheet was carried out because in periodic model it is not
possible cleave cellulose chain unless it is clipped to have a finite degree of polymerization. The lattice parameters were \( a = 16.352 \, \text{Å}, \, b = 32.804 \, \text{Å} \) and \( c = 20.760 \, \text{Å} \) with \( \gamma = 96.55^\circ \) to closely match the parameters observed in experimental XRD studies.\(^{52,53}\)

**Supporting Information.** The supporting information provides the raw tabulated conversion data for calcium incorporated samples of α-cyclodextrin. Validation of the second order dependence with calcium is shown and experimental evidence confirming the nitrate counterion has little effect on activation is shown. A derivation for the rate expressions of catalytic cycles introduced in the manuscript is also provided in the supporting information. Lastly, additional structures of intermediate species and calcium binding sites which are not shown in the manuscript are provided in the supporting information.

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**Keywords.** Activation, Cellulose, Calcium, Hydrogen Bond, Glycosidic Bond, Cyclodextrin

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