RESEARCH ARTICLE

The Effect of Dicarboxylic Acid Catalyst Structure on Hydrolysis of Cellulose Model Compound D-Cellobiose in Water

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Abstract: ***Background*:** Polycarboxylic acids are of interest as simple mimics for cellulase enzyme-catalyzed depolymerization of cellulose. In this study, DFT calculations were used to investigate the effect of structure on dicarboxylic acid organo-catalyzed hydrolysis of cellulose model compound D-cellobiose to D-glucose.

***Methods*:** Binding energy of the complex formed between D-cellobiose and acid (E_{bind}), as well as glycosidic oxygen to dicarboxylic acid closest acidic H distance, were studied as key parameters affecting the turn over frequency of hydrolysis in water.

***Result*:** α-D-cellobiose - dicarboxylic acid catalyst down face approach showed high E_{bind} values for five of the six acids studied, indicating the favorability of the down face approach. Maleic, *cis*-1,2-cyclohexane dicarboxylic, and phthalic acids with the highest catalytic activities showed glycosidic oxygen to dicarboxylic acid acidic H distances 3.5-3.6 Å in the preferred configuration.

***Conclusion*:** The high catalytic activities of these acids may be due to the rigid structure, where acid groups are held in a fixed geometry.

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1. INTRODUCTION

Cellulose is the most abundant renewable carbon form on earth and is produced as a result of carbon dioxide sequestration by photosynthesis. The resourceful utilization of this complex natural biopolymer is a principal challenge in achieving a sustainable carbon-based future. Current efforts in this direction can be grouped into three fundamental approaches: pyrolysis to bio-oil [1], conversion to syngas [2], and depolymerization to sugars [3] for further processing into fuels and feedstock chemicals. Even with numerous challenges, the third approach involving hydrolysis of cellulose to glucose can lead to a broader range of possibilities. This will include the fermentation to ethanol [4], conversion to drop-in hydrocarbon fuels by carbon number upgrading followed by deoxygenation techniques [5], as well as dehydration to promising key feedstock 5-hydroxymethylfurfural (HMF) with a vast array of possibilities to convert into monomers for sustainable carbon-based polymer industry [6, 7]. However, the crucial cellulose hydrolysis step is a difficult task, and the currently used method is the high temperature-pressure dilute acid or steam pretreatment followed by the use of a cellulase enzyme cocktail in a biochemical process [4, 8]. Nevertheless, definite deficiencies in the present biochemical technologies like the energy-intensive pretreatment requirement, cellulase enzyme costs, and the inability to recycle the expensive enzymes have motivated the research into alternative, more efficient catalytic methods such as simple enzyme mimics for the hydrolysis of cellulose to glucose. The extensively studied non enzymatic approaches include the use of dilute aqueous acids [9], concentrated acids [10], solid acids [11-13], mineral acid in neutral ionic liquids [14], acidic ionic liquids [15, 16] metal salts in mineral acid solutions and ionic liquid solutions [17, 18]. While this non-enzymatic cellulose hydrolysis can produce glucose in relatively low yields, often contaminated with by-products like HMF and levulinic acid, further improvements in the cellulose hydrolysis process require a thorough understanding of the catalysis mechanisms. Although the active site of the cellulase enzyme contains a carboxylic acid functional group for the key proton transfer step in the enzymatic hydrolysis, there are only a handful of reported studies on the use of carboxylic acids as homogeneous catalysts for cellulose hydrolysis [19-21]. In one of the pioneering studies in this area, Mosier and co-workers compared the catalytic activities of acetic, succinic, and maleic acids and found that maleic acid is the most effective of the three carboxylic acids in cellulose hydrolysis in water [21]. In comparison with mineral acids, they have shown that the rate of Avicel cellulose hydrolysis is almost identical for both 5 x 10^{-2} M maleic and sulfuric acids. In addition, glucose degradation to secondary products such as HMF, levulinic acid, and hu-

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min formation was much lower in maleic acid when compared with aqueous sulfuric acid [21]. Additionally, the understanding of carboxylic acid-catalyzed cellulose hydrolysis is important in the high temperature hot water pretreatment of cellulosic biomass for cellulosic ethanol process as well, since low concentrations of acetic, formic, levulinic, and lactic acid are formed as cellulose degradation products during the pretreatment process causing some depolymerization as well [4].

The carboxylic acid group catalyzed cellulose hydrolysis is known in solid acid catalysis as well, and in these instances, heterogeneous catalysts with multiple carboxylic acid groups attached to a solid surface have shown promising results [22-25]. For example, graphene-type materials bearing carboxylic acid groups as well as -OH on the surface have been shown to produce up to 88% glucose yield in cellulose hydrolysis at relatively mild conditions in aqueous mediums [23, 26]. In addition, cellulose nanocrystals with di and tricarboxylic acids grafted on the surface have also shown excellent yields in cellulose hydrolysis [27]. This type of facile cellulose hydrolysis with the use of catalysts with multiple -COOH and -OH groups in proximity have been explained as a result of multiple hydrogen bonding type interactions between carboxylic acid and the carbohydrate -OH groups [23, 26]. This synergistic effect of vicinal oxygenated groups to the active carboxylic acid group is known as homogeneous phase cellulose hydrolysis as well. For example, Fukuoka and co-workers studied the catalytic activities of a series of substituted aromatic carboxylic acids with and without phenolic -OH groups and found that *o*-hydroxybenzoic and phthalic acids show higher activities than other substituted benzoic acids [28]. Furthermore, they have noted that their turnover frequencies are larger than those of *o*-chlorobenzoic acid and *o*-triflurobenzoic acid, despite their lower acid strength. The same research group later suggested a mechanism of cellobiose hydrolysis by vicinal oxygenated aromatic carboxylic acids based on a density functional theory energy calculation study [29]. Three substitute acids, *o*-hydroxybenzoic, *o*-chlorobenzoic, and phthalic were compared with benzoic acid in this study. Most importantly, the calculated binding energies of the acids followed the experimental turnover numbers of cellobiose hydrolysis, suggesting that the formation and the stability of the cellobiose-carboxylic acid adduct complex are imperative for catalysis [29]. In addition to this, glycosidic oxygen protonated system effectively modeled the experimental activation energy, implying that a hydronium ion participates in the reaction [29].

Our interest in the development of cellulase enzyme mimicking catalysts for depolymerization of cellulose has led us to study a series of eight common polycarboxylic acids in an aqueous medium using 0.500 mmol -COOH/L at 170 °C [30]. In these experiments, maleic acid showed the highest catalytic activity with a turnover frequency (TOF) of 29.5 h^{-1}. In addition, we have studied the interaction of carboxylic acids with D-cellobiose by measuring the rate constant k_H of anomeric -OH exchange rate in cellobiose using ^{1}H NMR spectroscopy as well. The maleic, oxalic, and citric acids showed infinitely large k_H values indicating very strong interactions with D-cellobiose [30]. The next highest interactions were found with phthalic acid (k_H = 248.8 Hz). Furthermore, we have explored the use of C=O stretching frequency shifts ($\Delta\nu_{C=O}$) in FT-IR spectra of D-cellobiose - polycarboxylic acid mixtures to evaluate the role of hydrogen bonding type interactions on carboxylic acid-catalyzed cellulose hydrolysis [30]. In continuation of these efforts, we have studied the dicarboxylic acid-catalyzed hydrolysis of cellulose model compound D-cellobiose to D-glucose as shown in Fig. (**1**) using density functional theory methods. Six dicarboxylic acids with -COOH groups in close proximity were chosen for the study such that both -COOH groups are sufficiently close enough to have intermolecular interactions with multiple -OH groups on D-cellobiose. In this publication, we present the co-relation between hydrogen bonding type cellobiose-carboxylic acid intermolecular interactions as well as the structure of the dicarboxylic acid on the turnover frequencies (TOFs) of the carboxylic acid-catalyzed D-cellobiose hydrolysis reaction.

2. MATERIAL AND METHODS

2.1. Computational Methods

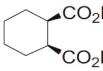
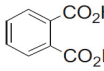
The geometries of α and β D-cellobiose (Fig. **1**), individual dicarboxylic acids (Table **1**), and approach of the dicarboxylic acids from up and down faces of α and β D-cellobiose anomers are illustrated in Fig. (**2**); these structures were drawn using Avogadro software for optimizations. Initially, geometries were optimized using the same program to obtain the preliminary Z-matrix coordinates. The z-matrix was further optimized using Gaussian 09 program on the computational cluster at the Department of Physics, Tennessee State University, TN. The optimization of structures was performed by DFT calculations using the B3LYP exchange-correlation function method [31-33]. The 6-31g* basis set was used for all atoms [34, 35]. The solvation effect was taken into consideration by using the self-consistent reaction field method (SCRF) with a polarized continuum model [36-38]. The optimized structures are shown in the supplementary information. The charge distribution of the atoms was obtained using the Mulliken population analysis.

The binding energy of the complex was calculated using the following equations [29].

$$\Delta E = E_{\text{cellobiose-catalyst}} - [E_{\text{cellobiose}} + E_{\text{catalyst}}] \text{ and } E_{\text{bind}} = -\Delta E$$

All energies used to calculate the binding energy were obtained using the data from calculations performed in an aqueous environment. The α and β D-cellobiose glycosidic oxygen to closest acidic hydrogen of the dicarboxylic acid was obtained from energy-optimized configurations of up and down approaches of dicarboxylic acids, as shown in Fig. (**2**).

Table 1. The turnover frequency (TOF) data for dicarboxylic acid-catalyzed hydrolysis of D-cellobiose in water at 170 °C and pKa's of carboxylic acids.

Entry	Dicarboxylic Acid HO_2C-R-CO_2H	TOF (h^{-1})	pKa
1	Oxalic (O) 	14.7	1.25, 4.14
2	Malonic (MO) 	11.6	2.83, 5.69
3	Succinic (S) 	14.8	4.2, 5.6
4	Maleic (ME) 	29.5	1.9, 6.07
5	*cis*-Cyclohexane-1,2- dicarboxylic (C) 	15.4	4.21
6	*o*-Phthalic (P) 	19.6	2.89, 5.51

TOF = [(mole of glucose produced in catalytic reaction) - (mole of glucose produced in blank test)]/ (mole of catalyst) / time (h).

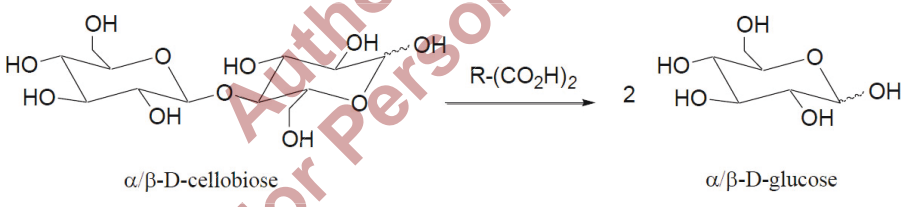


Fig. (1). Dicarboxylic acid-catalyzed hydrolysis of D-cellobiose to D-glucose in water.

3. RESULTS AND DISCUSSION

The present interest in cellulose depolymerization reaction inspired us to perform this computational study on carboxylic acid-catalyzed hydrolysis of model compound D-cellobiose, as shown in Fig. (**1**), with the aim of understanding the structural and thermodynamic factors affecting this important reaction. Six common dicarboxylic acids were selected for this study, and the turnover frequency (TOF) values for dicarboxylic acid-catalyzed hydrolysis of D-cellobiose in water at 170 °C from our previous work was used as experimental kinetic data for this study. The turnover frequency (TOF) data for dicarboxylic acid-catalyzed hydrolysis of D-cellobiose in water at 170 °C and pKa's of carboxylic acids are shown in Table **1**. According to these acidity data, oxalic acid with pKa values 1.25 and 4.14 is the strongest acid in the group; however oxalic acid showed the second-lowest TOF in the D-cellobiose hydrolysis, indicating that the acidity of the carboxylic acid is not the primary factor determining the catalytic activity of dicarboxylic acids in this hydrolysis reaction. The cellulose model compound D-cellobiose exists as two anomers α and β. The β form is the more favorable anomer by a ratio of about 9:1 in water at room temperature, as we have shown in our earlier work [30]. However, this anomeric composition can be disturbed by the addition of the dicarboxylic acid, and the acid-catalyzed hydrolysis can occur in both α and β anomeric forms of D-cellobiose. In addition, the dicarboxylic acid can approach the α and β forms of D-cellobiose from up and down faces of the molecule for the crucial glycosidic oxygen protonation step during the hydrolysis, as shown in Fig. (**2**). Therefore, in this computational study on model compound, we have considered D-cellobiose - dicarboxylic acid interactions in all four configurations.

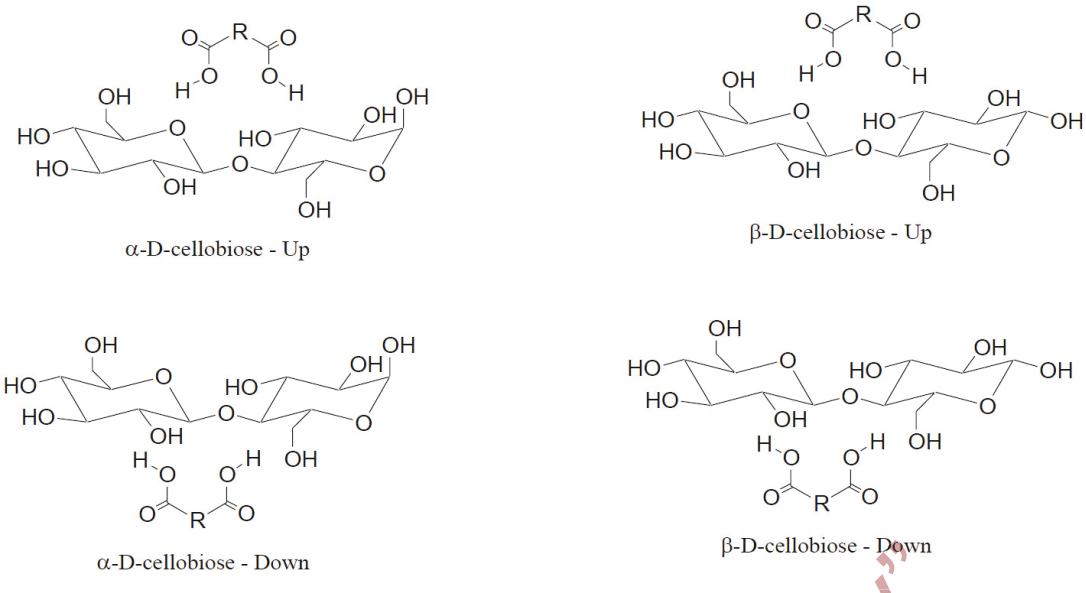


Fig. (2). The up and down approaches of dicarboxylic acid towards α-D-cellobiose and β-D-cellobiose anomers

Table 2. Optimized energies of α/β-D-cellobiose and dicarboxylic acids calculated using the B3LYP method

Molecule	Optimized Energy (Hartree)
α-D-Cellobiose	-1297.900238
β-D-Cellobiose	-1297.903116
Oxalic acid	-378.326000
Malonic acid	-417.653714
Succinic acid	-456.970822
Maleic acid	-455.732889
cis-1,2-Cyclohexane dicarboxylic acid	-613.024331
o-Phthalic acid	-609.393819

The optimized energies of α/β-D-cellobiose and dicarboxylic acids are shown in Table **2**. Similarly, optimized energies of dicarboxylic acid - α/β-D-cellobiose complexes in up and down orientations are shown in Table **3**. Furthermore, the optimized energy change (ΔE) during the complex formation of a dicarboxylic acid and α/β-D-cellobiose in up and down orientations as well as cellobiose glycosidic O - dicarboxylic acid acidic H distances are shown in Table **4**. The binding energy of the complex formed between D-cellobiose (E_{bind}) and the distance between D-cellobiose glycosidic oxygen and dicarboxylic acid acidic H in the energy minimized complex were selected as key parameters for the present study. The plots of Turn Over Frequency (TOF) of dicarboxylic acid-catalyzed D-cellobiose to glucose hydrolysis versus D-cellobiose - dicarboxylic acid-binding energy (E_{bind}) for α/β-D-cellobiose - dicarboxylic acid Up/Down approaches are shown in Fig. (**3**). Secondly, plots of Turn Over Frequency (TOF) of dicarboxylic acid-catalyzed D-cellobiose to glucose hydrolysis versus distance between D-cellobiose glycosidic oxygen and dicarboxylic acid acidic H for α/β-D-cellobiose - dicarboxylic acid Up/Down approaches are shown in Fig. (**4**).

The plots in Figs. (**3** and **4**) do not indicate simple relationships between TOF and binding energy (E_{bind}) as well as TOF and distance between D-cellobiose glycosidic oxygen and dicarboxylic acid acidic H for all configurations studied. However, these complex plots indicate the following factors related to the effects of the structure of the series of dicarboxylic acids studied on the catalytic activity in D-cellobiose hydrolysis reaction.

1. The binding energy for the maleic acid (ME) with the highest catalytic activity is relatively high in three out of the four configurations: α-D-cellobiose - dicarboxylic acid Up/-Down, and β-D-cellobiose - dicarboxylic acid Up. This result may indicate that the strong binding of maleic acid (ME) to D-cellobiose is an important factor contributing to its high catalytic activity.

Table 3. Optimized energies of dicarboxylic acid - α/β-D-cellobiose complexes in up and down orientations, calculated using the B3-LYP method.

Dicarboxylic Acid -Cellobiose Complex	Optimized Energy (Hartree)			
	α-Up	α-Down	β-Up	β-Down
Oxalic acid	-1676. 244664	-1676. 237337	-1676.236612	-1676.251126
Malonic acid	-1715. 572270	-1715. 578143	-1715.577585	-1715.576285
Succinic acid	-1754. 891469	-1754. 895259	-1754.903893	-1754.885611
Maleic acid	-1753. 654232	-1753. 658495	-1753.645030	-1753.652537
cis-1,2-Cyclohexane dicarboxylic acid	-1910. 948153	-1910. 951912	-1910.943331	-1910.936543
o-Phthalic acid	-1907. 303162	-1907. 319300	-1907.320531	-1907.313587

Table 4. Optimized energy change (ΔE) during the complex formation of dicarboxylic acid -α/β-D-cellobiose in up and down orientations. α/β-D-Cellobiose glycosidic O - dicarboxylic acid acidic H distances.

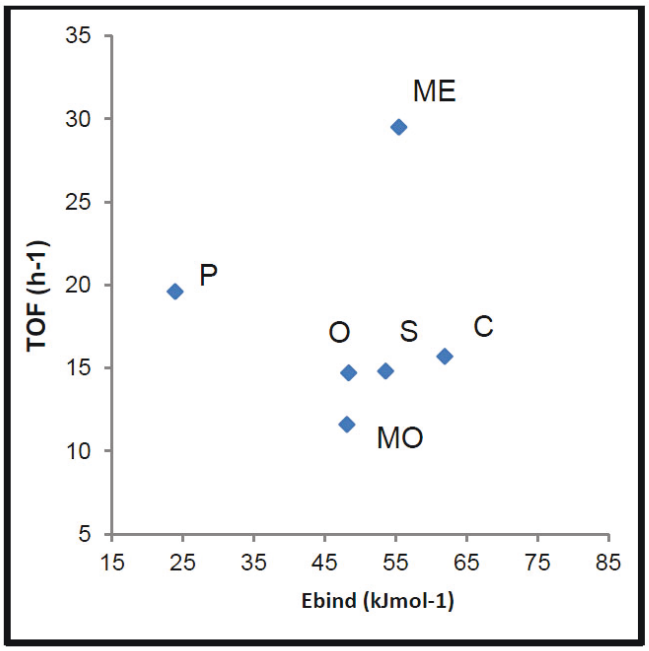
Dicarboxylic Acid - Cellobiose Complex	ΔE Complex formation (kJ/mol)				Cellobiose Glycosidic O - Dicarboxylic Acid Acidic H Distance (Å)			
	α-Up	α-Down	β-Up	β-Down	α-Up	α-Down	β-Up	β-Down
Oxalic acid	-48.378	-29.1412	-19.6823	-57.7878	2.783	5.506	5.423	5.639
Malonic acid	-48.0939	-63.5129	-54.492	-51.0807	3.355	2.816	2.707	2.90
Succinic acid	-53.5864	-63.5366	-78.6468	-30.6493	3.788	3.227	3.888	4.665
Maleic acid	-55.4099	-66.6018	-43.404	-23.6946	4.823	3.488	3.921	3.921
cis-1,2-Cyclohexane dicarboxylic acid	-61.9206	-71.7888	-41.7042	-23.8831	3.851	3.599	2.694	5.791
o-Phthalic acid	-23.9041	-66.2736	-61.9513	-43.7188	4.94	3.518	3.056	2.871

2. The binding energy for the malonic acid (MO) with the lowest catalytic activity is moderately high in all four configurations α-D-cellobiose - dicarboxylic acid Up/Down, and β-D-cellobiose - dicarboxylic acid Up/Down. This could indicate that binding energy for the malonic acid (MO) - D-cellobiose complex is not the most important factor in determining the catalytic activity as there are other structural factors in this 1,1-dicarboxylic acid: malonic acid (MO) contributing to its poor catalytic activity.

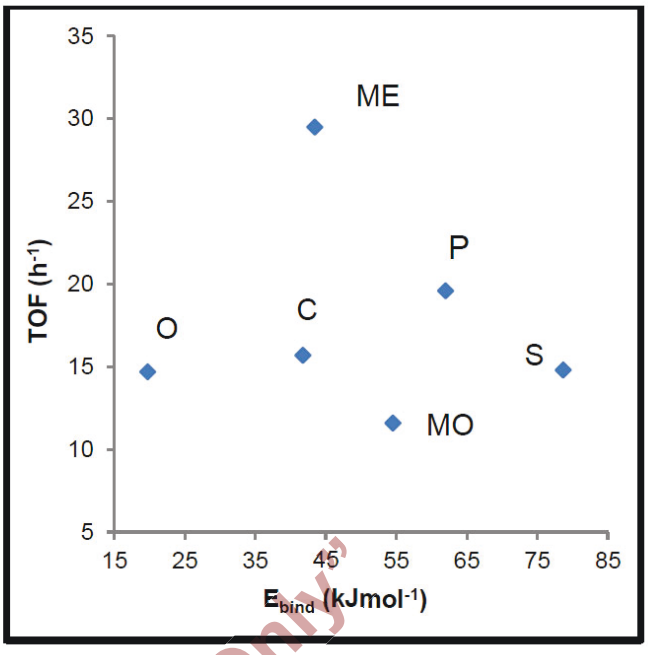
3. The α-D-cellobiose - dicarboxylic acid - Down configuration shows high binding energies in five of the six acids studied. Apparently, α-D-cellobiose is the most favorable anomeric form for the reaction, and the down approach is the preferred approach for the reaction. This argument can be further supported by the fact that the same five dicarboxylic acids show relatively short distances between D-cellobiose glycosidic oxygen and dicarboxylic acid closest acidic H for α-D-cellobiose - dicarboxylic acid - Down configuration, as shown in the bottom left plot of Fig. (**4**).

4. All three dicarboxylic acids, maleic (ME), *cis*-1,2-cyclohexane dicarboxylic (C), and phthalic (P), with the highest catalytic acclivities, show very similar and relatively short distances between 3.5-3.6 Å for glycosidic oxygen and dicarboxylic acid acidic H for α-D-cellobiose - dicarboxylic acid - Down configuration as shown in the bottom left plot of Fig. (**4**). Interestingly, the least active malonic (MO) and succinic (S) acids show even shorter D-cellobiose glycosidic oxygen - dicarboxylic acid acidic H distances of 2.816 and 3.227 Å, respectively, as shown in the same plot in Fig. (**4**). This is probably due to the fact that a much closer approach of acidic hydrogen to the glycosidic oxygen can also negatively affect the catalytic activity of the D-cellobiose hydrolysis reaction.

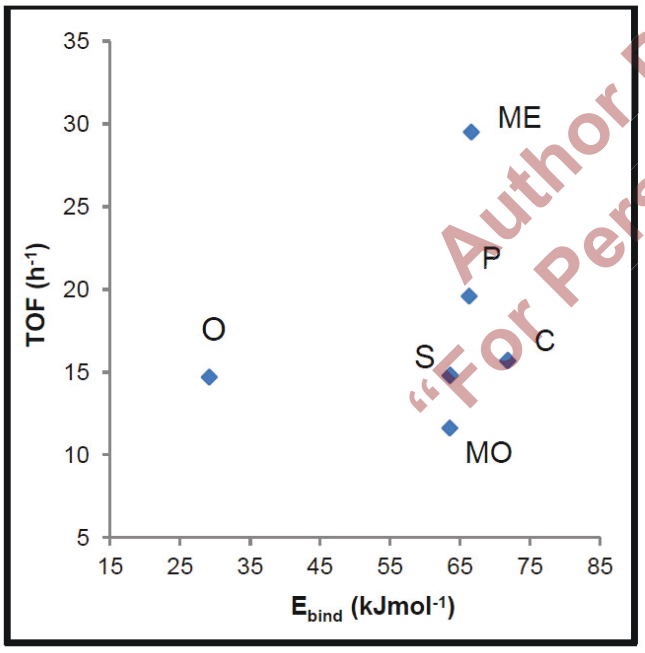
5. The common feature of the three dicarboxylic acids, maleic (ME), *cis*-1,2-cyclohexane dicarboxylic (C), and phthalic (P), with the highest catalytic activities, is a rigid structure, where acid groups are held in a fixed geometry with limited flexibility by C=C bond(s) or a ring structure. These three acids are most likely to catalyze the D-cellobiose hydrolysis reaction by a similar mechanism in the preferred α-D-cellobiose anomeric form with a more energetically favorable down approach of the dicarboxylic acids.



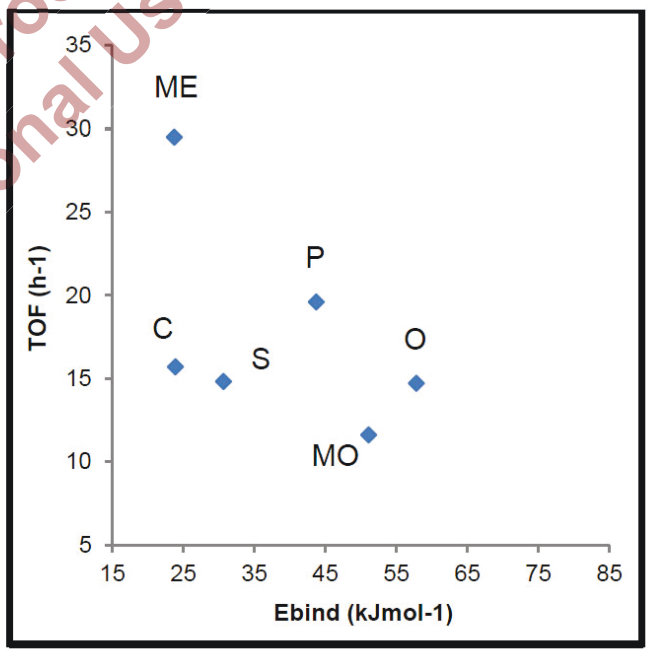
α-D-cellobiose - dicarboxylic acid Up



β-D-cellobiose - dicarboxylic acid Up



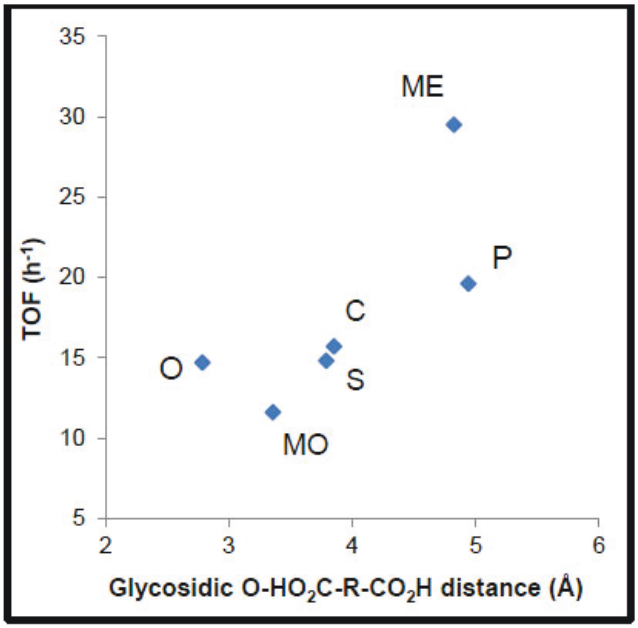
α-D-cellobiose - dicarboxylic acid Down



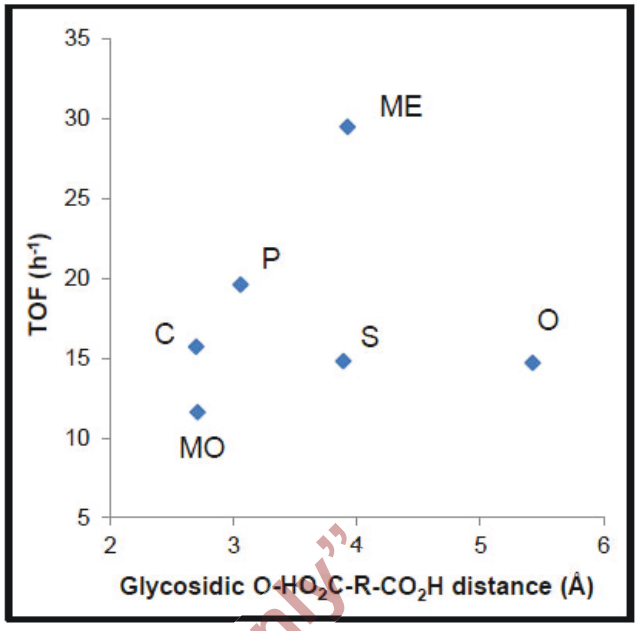
β-D-cellobiose - dicarboxylic acid Down

Fig. (3). Plots of Turn Over Frequency (TOF) of dicarboxylic acid-catalyzed D-cellobiose to glucose hydrolysis reaction versus D-cellobiose - dicarboxylic acid-binding energy (E_{bind}) for α-D-cellobiose - dicarboxylic acid Up/Down, and β-D-cellobiose - dicarboxylic acid Up/Down approaches. The D-cellobiose - dicarboxylic acid-binding energy (E_{bind}) values were obtained using DFT calculations using the B3LYP method.

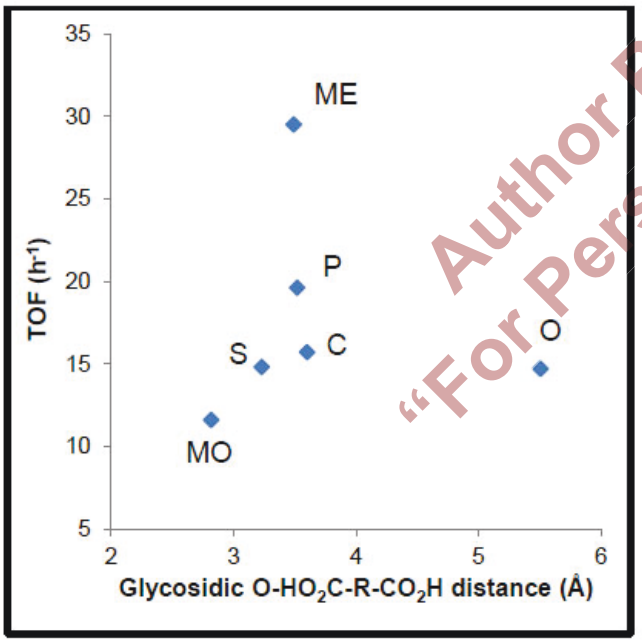
O - Oxalic Acid; MO - Malonic Acid; S - Succinic Acid; ME - Maleic Acid; C - *cis*-1,2-Cyclohexane Dicarboxylic Acid; P - Phthalic Acid. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



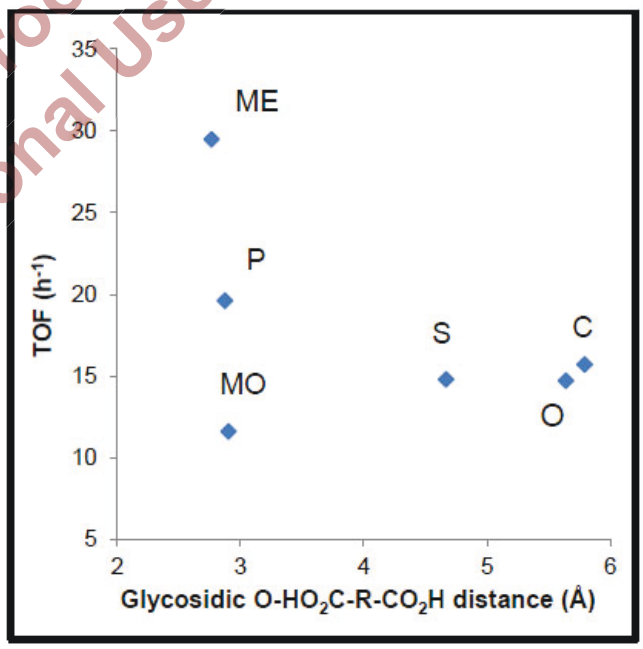
α-D-cellobiose - dicarboxylic acid Up



α-D-cellobiose - dicarboxylic acid Up



β-D-cellobiose - dicarboxylic acid Down



β-D-cellobiose - dicarboxylic acid Down

Fig. (4). Plots of Turn Over Frequency (TOF) of dicarboxylic acid-catalyzed D-cellobiose to glucose hydrolysis reaction versus distance between D-cellobiose glycosidic oxygen and dicarboxylic acid acidic H for α-D-cellobiose - dicarboxylic acid Up/Down, and β-D-cellobiose - dicarboxylic acid Up/Down approaches. The D-cellobiose - dicarboxylic acid-binding energy (E_{bind}) values were obtained using DFT calculations using the B3LYP method.
O - oxalic acid; MO - malonic acid; S - succinic acid; ME - maleic acid; C - *cis*-1,2-cyclohexane dicarboxylic acid; P - phthalic acid. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CONCLUSION

The binding energies and D-cellobiose glycosidic oxygen - dicarboxylic acid closest acidic H distances were studied in an attempt to elucidate the structural factors affecting the dicarboxylic acid-catalyzed hydrolysis of D-cellobiose to D-glucose in water. Out of the four configurations of α/β -D-cellobiose and dicarboxylic acid approaching from Up/ Down, α-D-cellobiose with dicarboxylic acid approaching from Down face (Fig. **3**), lower left plot) appears to be the most energetically favorable configuration for five out of six dicarboxylic acids studied. The three dicarboxylic acids with the highest Turn Over Frequency (TOF) numbers, maleic (ME), *cis*-1,2-cyclohexane dicarboxylic (C), and phthalic (P), have a common feature of rigid structure, where acid groups are held together in a fixed geometry with limited flexibility by C=C bond(s) or a ring structure. Furthermore, these three acids with the highest catalytic acclivities show similar glycosidic oxygen to dicarboxylic acid closest acidic H distances in the range of 3.5-3.6 Å in the preferred α-D-cellobiose - dicarboxylic acid Down configuration. In conclusion, the stronger binding between D-cellobiose - dicarboxylic acid is an important factor in determining the catalytic activity for the 1,2-dicarboxylic acids studied. Apparently, the 0,0 and 1,1-dicarboxylic acids, oxalic and malonic, do not fit into the interaction patterns of 1,2-dicarboxylic acids. Furthermore, the glycosidic oxygen to dicarboxylic acid closest acidic H distances does not directly correlate with the catalytic activity of the D-cellobiose hydrolysis reaction; on the other hand, the 1,2-dicarboxylic acid functional groups on a rigid structure is more important for the higher catalytic activity.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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