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Unprecedented selectivity in molecular recognition of carbohydrates by a metal-organic framework

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Metal-organic framework (MOF) material NU-1000 adsorbs dimers cellobiose and lactose from aqueous solution, in amounts exceeding 1250 mg g_{NU-1000}⁻¹ while completely excluding the adsorption of the monomer glucose, even in a competitive mode with cellobiose. The MOF also discriminates between dimers consisting of α and β linkages, showing no adsorption of maltose. Electronic structure calculations demonstrate that key to this selective molecular recognition is the number of favorable CH– π interactions made by the sugar with pyrene units of the MOF.

Molecular recognition processes involving sugars are common to nearly all living systems, and may be crucial for the selective synthesis of glucose from biomass-based feedstocks via cellulose depolymerization, as currently accomplished by enzymes (*i.e.* cellulases). Yet our molecular-level understanding of the interactions responsible for selective carbohydrate molecular recognition has in general been limited; until now, only enzymes have demonstrated the ability to selectively bond the β -linked dimer of glucose, cellobiose, while completely rejecting the bonding of glucose itself. This feature has been thought to be crucial for avoiding both product inhibition and glucose product degradation due to rebinding and reaction at the active site, during enzyme-catalyzed depolymerization of β -glucan oligomers.¹ Some crucial molecular-level features that facilitate carbohydrate bonding to a host site have been demonstrated, and consist of axial CH groups on the sugar interacting with extended π conjugated domains on the host, such as tryptophan residues

in proteins as well as extended aromaticity in high-surface area carbon-based materials.^{2–7} On the other hand, the factors that control the ability to selectively discriminate between closely related carbohydrates in an on-off manner have remained elusive. So far, though larger oligomers are preferentially adsorbed; all sugars demonstrate significant adsorption affinity to synthetic hosts such as carbon-based materials.^{4,5} Here, in this manuscript, building on the observation of long-chain β -glucan bonding within the confined three-dimensional environments of microporous carbon materials,⁶ we investigate the possibility of simple carbohydrate adsorption from aqueous solution to a water-stable mesoporous metal-organic framework (MOF) material – NU-1000 (Fig. S1, ESI†),⁸ which possesses hydrophobic organic framework pyrene units as framework linked by inorganic metal-oxide clusters. Our results uniquely demonstrate on-off discrimination between adsorption of cellobiose and lactose, which are both on, while glucose and maltose are off. Such selective recognition in what are closely related carbohydrates is to the best of our knowledge unique in synthetic host systems. The results highlight the importance of MOF environment and uniformity when adsorbing sugars, and motivate future work along this new frontier.

Fig. 1 shows isotherms of simple carbohydrates adsorbing on NU-1000 from aqueous solution at 297 K. For cellobiose, a continual increase in adsorption uptake is observed upon increasing concentration (as represented by the normalized concentration relative to saturation for each carbohydrate, c/c_{sat}), up to 1260 mg of cellobiose per gram of NU-1000. We observed a cellobiose uptake as high as 2050 mg g_{NU-1000}⁻¹ under slightly supersaturated conditions of $c/c_{\text{sat}} = 1.04$ in Fig. 1. These data represent the highest adsorption weight uptake of a sugar by synthetic adsorbent materials reported to date.^{4,5,9–13} The cellobiose isotherm shape exhibits no plateau and instead is characteristic of Type II behavior that is typically associated with multilayer adsorption, signifying a similarity between the energetics for monolayer coverage and multilayer adsorption regimes.^{14,15}

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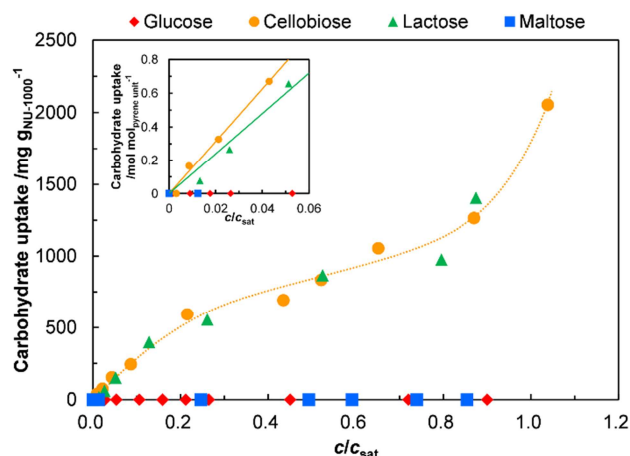


Fig. 1 Adsorption isotherms of carbohydrates on NU-1000 at 297 K. In the figure, c/c_{sat} represents equilibrium concentration relative to saturation concentration. The dashed line is shown for visual clarity. The inset shows isotherms in a low concentration range, in which the straight lines are drawn according to eqn (S1), and the results are thermodynamically discussed in Experimental (Adsorption of carbohydrates on NU-1000, ESI†).

To investigate the interior versus exterior nature of cellobiose adsorption on NU-1000, we performed N_2 physisorption at 77 K on materials before and after cellobiose uptake at $c/c_{\text{sat}} = 0.52$ and 1.04 (Fig. S2, ESI†). The qualitatively increasing pore-volume decrease after cellobiose uptake at higher c/c_{sat} (*i.e.* comparing decrease at $c/c_{\text{sat}} = 0.52$ and 1.04) is consistent with adsorption occurring within micro- and mesopores rather than external surface sites of NU-1000. The consumption of internal pores during cellobiose adsorption can be elucidated based on pore-size distribution data (Fig. S3, ESI†). This data set demonstrates cellobiose adsorption at lower c/c_{sat} of 0.52 to occur mainly in micropores (Fig. S1, ESI†) while leaving mesopores largely unoccupied; whereas at c/c_{sat} of 1.04, it occurs in both types of pores. This observed preference for micropore rather than mesopore filling is consistent with previous observations of β -glucan adsorption on carbon materials.⁶ The pore-volume decrease after cellobiose uptake at $c/c_{\text{sat}} = 1.04$ ($1.13 \text{ cm}^3 \text{ g}_{\text{NU-1000}}^{-1}$) corresponds closely with the amount expected if the adsorbed cellobiose possesses a density equal to its solid crystalline state. Such a high density for an adsorbed sugar is highly unusual, as typical densities have been closer to half of the crystalline state, even in enzyme systems.^{4,16}

Control experiments using powder X-ray diffraction (PXRD, Fig. S4, ESI†) and scanning electron microscopy (SEM, Fig. S5, ESI†) demonstrate a lack of difference in the structure as well as morphology of the MOF material following cellobiose adsorption at both of these c/c_{sat} values: the NU-1000 MOF behaves as a rigid adsorbent that does not change structure, even when adsorbing more than twice its weight in cellobiose. This result is in contrast to organic molecules adsorption in other MOF systems such as MOROF-1 and MIL-53, which demonstrate breathing phenomena and changes to the PXRD accompanying MOF adsorption.^{17–19} We hypothesize that part

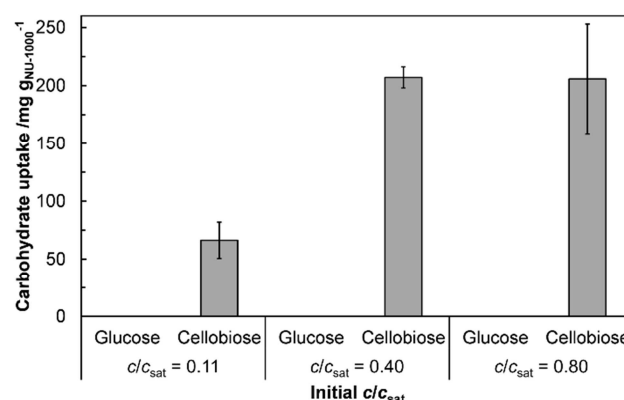


Fig. 2 Competitive adsorption of glucose and cellobiose on NU-1000 at 297 K. The values of c/c_{sat} are for each compound.

of the reason for the enhanced stability of NU-1000 is its triangular geometry of pores, in addition to its high chemical and thermal stability.²⁰ Unlike the hexagonal geometry of MOROF-1 or square one of MIL-53, the geometry of the triangle has no distorted shape that would otherwise preserve the same edge length (*e.g.* rhombus for a square – see Fig. S6, ESI†).^{21,22}

In stark contrast to cellobiose, no adsorption (up to $c/c_{\text{sat}} = 0.90$) is observed with aqueous solutions of glucose in NU-1000 in Fig. 1. This is highly unusual for a synthetic host. When comparing the relative affinities (as measured by the equilibrium constant for adsorption) of glucose and cellobiose on mesoporous carbon nanoparticle adsorbent, cellobiose is favored over glucose by a factor of only 2.6 when accounting for aqueous solubility differences on a c/c_{sat} scale (see Fig. S7, ESI†).⁴ We have also performed competitive adsorption experiments in which glucose and cellobiose are treated with NU-1000 simultaneously in the same aqueous solution at a glucose and cellobiose concentration corresponding to either c/c_{sat} of 0.11, 0.40 or 0.80 (where c_{sat} is referenced to the single-component aqueous solution). These data are shown in Fig. 2. Under all three concentrations of glucose and cellobiose investigated in competitive-mode adsorption experiments, we observe the complete lack of glucose adsorption, while significant cellobiose adsorption still occurs. The absence of any observed glucose uptake requires that glucose is not a competitive adsorbent to cellobiose. These data underlie the same trend observed when treating NU-1000 with a single-component sugar in Fig. 1. The type of on-off specificity in adsorption of cellobiose and glucose, both when the sugars are treated with NU-1000 individually as well as in a competitive adsorption mode, is reminiscent of enzymes, which have been reported to adsorb cellobiose while completely excluding glucose (*i.e.* no adsorption).¹⁶

Based on known $\text{CH}-\pi$ interactions driving carbohydrate adsorption in synthetic host materials, we modeled the interactions between adsorbing sugars and the MOF pyrene unit (see Fig. S8, ESI†) with density functional theory (DFT) calculations, using the supersystems shown in Fig. S9 (ESI†). The highest occupied molecular orbital (HOMO) of the pyrene unit involves a highly delocalized aromatic system (Fig. S10, ESI†), facilitating $\text{CH}-\pi$ interactions with carbohydrates. The

Table 1 Binding energies between β -glucose and cellobiose with pyrene unit in water^a

Supersystem ^b	Single point at PBE-D3/SMD		Optimized at PBE-D3/SMD	
	ΔH	ΔG	ΔH	ΔG
Glucose-pyrene (configuration 1)	−14.7	−0.5	−15.5	−1.4
Glucose-pyrene (configuration 2)	−14.1	−0.4	−14.4	−1.1
Cellobiose-pyrene (configuration 1)	−21.2	−5.1	−21.6	−4.7
Cellobiose-pyrene (configuration 2)	−20.4	−5.2	−20.8	−4.7

^a The unit of ΔH and ΔG is kcal mol^{−1}. ^b The optimized structures are shown in Fig. 3 and Fig. S11 (ESI[†]).

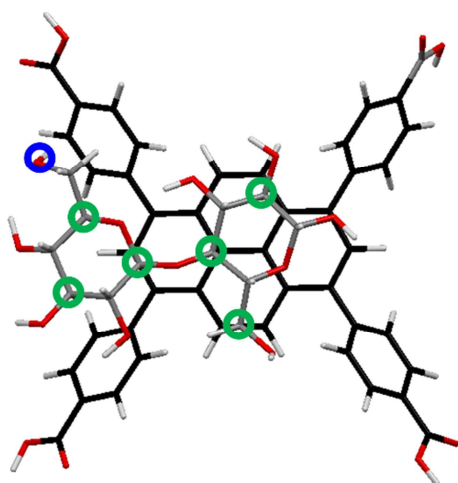


Fig. 3 Optimized geometry of cellobiose-pyrene (configuration 1). The geometries of other supersystem models are shown in Fig. S11 (ESI[†]). The green circles represent CH groups facing pyrene unit, and the blue circles highlight OH groups interacting with the unit. Legends: black = carbon atoms of pyrene unit; grey = carbon atoms of cellobiose; red = oxygen atoms; and white = hydrogen atoms.

calculated binding energies between β -glucose and cellobiose with the pyrene unit are shown in Table 1, and the optimized structures are reported in Fig. 3 and Fig. S11 (ESI[†]). In water, configurations 1 and 2 of cellobiose-pyrene are energetically similar and both show significantly stronger binding (−21.2 and −20.4 kcal mol^{−1}) than the two glucose-pyrene configurations (−14.7 and −14.1 kcal mol^{−1}). Table 1 also shows single-point calculations with a continuum solvent model SMD and the results give similar binding energies; thus, single-point SMD results are reported hereafter. One of the reasons why cellobiose interacts more strongly with the pyrene unit compared with β -glucose is the larger number of CH and OH hydrogen atoms interacting with the aromatic electron cloud. In Table S1 (ESI[†]), we present the energy differences for

structures optimized with three density functionals, PBE-D3, M06-L, and M06-2X, which are recommended for weak interactions and systems where dispersion effects are important.²³ The PBE-D3 functional predicts an interaction enthalpy for cellobiose that is 3.3 kcal mol^{−1} more favorable than β -glucose, whereas the M06-L and M06-2X functional predict an enthalpy difference of 5.2 and 5.9 kcal mol^{−1}, respectively, favoring cellobiose over β -glucose adsorption. When using M06-L, a positive interaction free energy is obtained for glucose, but the overall difference is comparable to PBE-D3 and M06-2X. The further investigation of sensitivity of the binding energies to the choice of functional is summarized in Table S2 (ESI[†]); in brief, we have observed similar relative energy differences between the binding energies of cellobiose and glucose independently of the functional choice.

We also investigated the adsorption of lactose and maltose from aqueous solution onto NU-1000 under similar conditions, in order to ascertain the importance of stereochemistry (lactose versus cellobiose) and an α rather than β linkage within the glucan (maltose). While results in Fig. 1 show a similar adsorption for dimers consisting of lactose and cellobiose, maltose exhibits no adsorption. We interpret these results to indicate that the MOF is able to make the same number of CH– π interactions with axial CH groups on the sugar for cellobiose and lactose, as shown schematically in Fig. 4. This is intuitively satisfying as they both have nearly identical chemical structures except for an exchange in the position of one of the axial CH groups with an OH at a non-reducing end. They both have a total of five axial CH groups on a single face of the molecule that can interact with the pyrene unit in Fig. 4. In contrast, it appears that the step resulting from the α -linkage in maltose results in a significantly decreased interaction with NU-1000 – leading to reduced adsorption affinity – similarly to the glucose case.

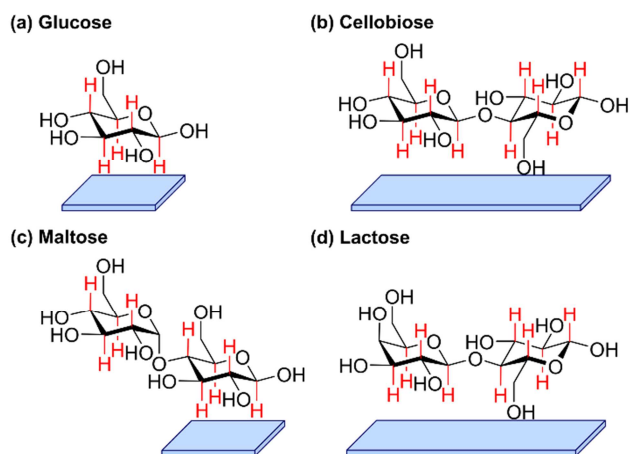


Fig. 4 Structure of carbohydrates used for adsorption on NU-1000. In this figure, we consider β -anomers to simplify the systems. The red protons are on an axial plane of each carbohydrate. The blue plates represent plausible adsorptive area.

Altogether, these results point to a high degree of molecular recognition of sugars by NU-1000, and suggest that the MOF may be useful for the discrimination of other sugars as well. This will be investigated along with the possibility of selective hydrolysis catalysis of the oligomeric glucans, based on the previously reported hydrolysis activity of the NU-1000 MOF.²⁴

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