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Metal-organic polyhedra containing 36 and 24 folds of amide groups for selective luminescent recognition of natural disaccharides[†]

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An octa-nuclear bicoronal Ce-based triangular prism and tetranuclear molecular tetrahedron containing 36 and 24 folds amides within their main backbones were achieved and structurally characterized for the selective luminescent recognition of lactose and sucrose, respectively, over other related natural mono- and disaccharides.

Molecular recognition of carbohydrates has been recognized as a subject of paramount importance in chemistry and biology,^{1,2} on which a number of biological processes rely, such as cell adhesion, cell infection and immune response.³ While these synthetic carbohydrate receptors operating through noncovalent interactions have provided valuable model systems to study the underlying principles of carbohydrate-based molecular recognition process,⁴ few of them can span or encapsulate oligosaccharides, selecting for and among these larger substrates,⁵ despite the fact that most carbohydrate recognition in biology involves oligosaccharides.⁶ The design of highly selective and effective receptors for these ubiquitous and important biomolecules represents a significant challenge,⁷ due to the fact that saccharides exhibit high hydrophilicity and non-charged three-dimensional structures with subtle variations.

Metal–organic polyhedra represent a unique class of functional molecular containers that display interesting molecular recognition properties mimicking natural enzymes.^{8,9} Inspired by the binding motifs within the biotic carbohydrate recognition and the hydrogen-patterns within the artificial macrocyclic and acyclic receptors operating through noncovalent interactions,^{10,11} we have developed metal–organic polyhedra for luminescent discrimination of natural mono- and disaccharides in solution through spatial restriction by incorporating amide groups as both the multiple hydrogen bonding triggers.¹² As in natural complexes, the participation of different types of hydrogen bonding groups in the recognition process was expected to be favorable for achieving a high binding affinity and selectivity towards the target carbohydrate.¹¹ Herein, we modified our synthetic approach to the new face-driven Ce-based octanuclear bicoronal triangular prism and molecular tetrahedron by incorporating two kinds of amide groups inside the cavities of the cage. We envisioned that the functionalization with amide groups would provide appropriate matches for polar groups to address the structural diversity of oligosaccharides and that the difficulty of predicting the favored conformations of the saccharides could be overcome.

Ligand H₄**TRBS**, N,N'-bis(3,5-bis(2-(2-hydroxybenzylidene) hydrazinecarbonyl)phenyl) terephthalamde was synthesized by reacting N, N'-bis(3,5-bis(2-(hydrazinecarbonyl) phenyl) terephthalamide with salicylaldehyde in a methanol solution. The ligand contains two "free" amide groups and four amide moieties, which were the constituent parts of the tridentate chelating units. Ce-TRBS was obtained as a M₈L₆ complex by diffusing methanol into a DMF solution containing H₄TRBS and Ce(NO₃)₃·6H₂O in the presence of NaOAc. The ESI-MS spectrum of Ce-TRBS in DMF/CH₃CN solution in the presence of KOH exhibited two intense peaks at m/z = 2293.55 and 2339.92, with the isotopic distribution patterns separated by 0.33 Da. These peaks were assignable to the species of $[Ce_6^{III}Ce_2^{IV}(TRBS)_6-5H]^{3-}$, through the exact comparison of these peaks with the simulation on the basis of natural isotopic abundances. It is thus suggested that the M8L6 species is formed in solution and that it is stable.

X-ray crystal analysis (ESI⁺) revealed the formation of an octa-nuclear bicoronal triangular prism, M₈L₆ (see Fig. 1). Each cerium center in a M_8L_6 fragment is coordinated by three tridentate chelating groups to complete a nine coordination geometry. Each ligand connects four cerium centers in two different types. Six cerium(III) centers are linked by three of the six ligands, forming a tricycle prism (see Fig. 2). The long and short edges of each Ce₄ tetragon are about 17.9 and 9.8 Å, respectively, on an average. The two phenyl B rings in these ligands just slightly bend with an angle of 18° and almost do not twist. The left two Ce centers formed a helical pillar inside the tricycle though coordinated with the other three ligands, with the Ce-Ce separations in the helix being about 18.9 A. Two tridentate chelating moieties in one ligand, but in a different phenyl ring spanned around the helical axis, the other two chelating sites coordinate with the two Ce centers on a tricycle column. From the top view, the structure just looked like the famous "Mercedes Benz" star. The 24 metal-coordinated amide groups and 12 "free" amide groups amide groups were located inside these spaces and the central phenyl ring could

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Fig. 1 The molecular structure of the octa-nuclear bicoronal triangular prism of Ce-**TRBS**. Hydrogen atoms, and solvent molecules are omitted for clarity. The metal, oxygen and nitrogen atoms are represented by green, red, blue. The carbon atoms represented by grey, cyan and organe, respectively. Selective bond distance in average (Å): Ce–N 2.66, Ce–O(amide) 2.46, Ce–O(hydroxyl) 2.18, C–N(coordinated amide) 1.31, C–O(coordinated amide) 1.24, C–N(free amide) 1.36, C–O(free amide), 1.22.

rotate freely to fit with the structural diversity of oligosaccharides, Ce-**TRBS** thus was a suitable candidate in carbohydrate recognition.¹³

Ce-TRBS exhibited two absorption bands centered at 290 and 375 nm. The addition of several monosaccharides or disaccharides did not cause any obvious spectral changes on the absorption spectrum (see Fig. 3). Emission spectrum of Ce-TRBS (20 µM) exhibited an intense band at about 424 nm, when the solution was excited at 315 nm. Upon the addition of lactose (0.6 mM), the luminescence of Ce-TRBS enhanced gradually with the increasing concentration of the guest. The Hill-plot profile of the fluorescence titration curves at 424 nm demonstrated the 1:1 host-guest complexation behavior with the association constants (log K_{ass}) being 3.06 \pm 0.24.¹⁴ The addition of other disaccharides and several monosaccharides did not cause any obvious spectroscopic change. The selectivity of the fluorescence spectrum should be contributed to by the spatial selectivity for lactose and the weak interaction of hydrogen bonds between the Ce-TRBS and lactose. Ce-TRBS was described as the first artificial receptor that can specifically discriminate lactose over other disaccharides in a luminescent enhancement manner. The ESI-MS spectrum of Ce-TRBS upon the addition of lactose exhibited a new peak at m/z = 2408.58. The exact comparison of the peak with the simulation on the basis of natural isotopic abundances suggested the presence of $[(Ce_6^{III}Ce_2^{IV}(TRBS)_6 \supset (lactose)-5H]^{3-}]$. This result supported the 1:1 complexation of host-guest species in the solution.



Fig. 2 The molecular structure of the octa-nuclear bicoronal triangular prism of Ce-**TRBS** showing the trisprand helical fashion of the inside pillar and the tricycle prism, respectively. The metal, oxygen, nitrogen and carbon atoms are represented by green, red, blue, and grey, respectively. Selective bond distance in average (Å): Ce–N 2.66, Ce–O(amide) 2.46, Ce–O(hydroxyl) 2.18, C–N(coordinated amide) 1.31, C–O(coordinated amide) 1.24, C–N(free amide) 1.36, C–O(free amide), 1.22.



Fig. 3 Left Picture: Fluorescence responses of Ce-**TRBS** (red bars) and Ce-**TBAS** (blue bars) for saccharides mentioned. Emission intensity was recorded at 424 nm for Ce-**TRBS** or 435 nm for Ce-**TBAS** ($20 \ \mu$ M in DMF/acetonitrile 1:9 (v/v), excited at 315 and 340 nm, respectively). Right: Fluorescence responses of Ce-**TRBS** upon addition of Lactose (excitation at 315 nm).

The excellent selectivity of Ce-**TRBS** toward special oligosacchrides encourage us to further investigate the interaction detail of the host–guest complexation. A ligand H₃**TBAS** N,N',N''tris(4-(2-hydroxybenzylidene)hydrazinecarbonyl)phenyl) benzene 1,3,5-tricarboxamide, that has molecular C_3 symmetry was synthesized. Diffusing of methanol into a DMF solution containing H₃TBAS and Ce(NO₃)₃·6H₂O in the presence of



Fig. 4 Molecular structure of the Ce-**TBAS** tetrahedral cage. Hydrogen atoms and solvent molecules are omitted for clarity. The metal, oxygen, nitrogen and carbon atoms are represented by green, red, blue, and grey, respectively. Selective bond distance in average (Å): Ce–N 2.66, Ce–O(amide) 2.41, Ce–O(hydroxyl) 2.20, C–N(coordinated amide) 1.32, C–O(coordinated amide) 1.25, C–N(free amide) 1.33, C–O(free amide), 1.25.

NaOAc gave the compound Ce-**TBAS** (65%). Single crystal X-ray structure analysis (ESI[†]) revealed the formation of Ce₄(H₂**TBAS**)₄ tetrahedron in the solid state (see Fig. 4). The tetrahedron is comprised of four vertical metal centers and four deprotonated ligands. Each cerium ion is chelated by three tridentate chelating groups from three different ligands to form a ternary coronary trigonal prism coordination geometry with a *pseudo-C*₃ symmetry. The ligands are positioned individually on the four triangle faces of the tetrahedron defined by four metal ions. The Ce···Ce separation is *ca*. 21.0 Å and the inner volume of the tetrahedron is about 1000 Å³.

The ESI-MS spectrum of Ce-**TBAS** exhibited an intense peak at m/z = 1451.50, which was assigned to $[(Ce_4^{IV}(TBRS)_4-(CH_3CN)_3-7H]^{3-}$ species, revealing the formation of M_4L_4 specie in the solution. For the experimental spectra of Ce-**TBAS** in the presence of sucrose, the exact comparison of the peak at m/z = 1565.84 with the simulation on the basis of natural isotopic abundance revealed the presence of complexation species [(Ce-**TBRS** $)-3H \supset (sucrose)\cdot(CH_3CN)_3]^{3-}$.

When Ce-**TBAS** (20μ M) was excited at 340 nm, it exhibited a broad emission band at 435 nm in a DMF/acetonitrile solution. The addition of sucrose (5 mM) caused a significant luminescence enhancement (1.3 fold). The addition of other mono- and disaccharides did not cause any obvious spectroscopic changes, indicating the selectivity of Ce-**TBAS** towards sucrose over other disaccharides.

In summary, with the tunability of the topology and size of these polyhedrons, as well as the position of the weak interaction environment within the cages, the Ce-based coordination polyhedra worked as efficient selective chemosensors for special natural saccharides. Accordingly, changing the topology and the arrangement of hydrogen binding sites in the confined space of host, the selectivity toward other target guests could be expected.

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