PRF #: 58671-ND7

Project Title: Highly Efficient Macrocycle Formation from Petrochemicals Isocyanates and Hindered Amines

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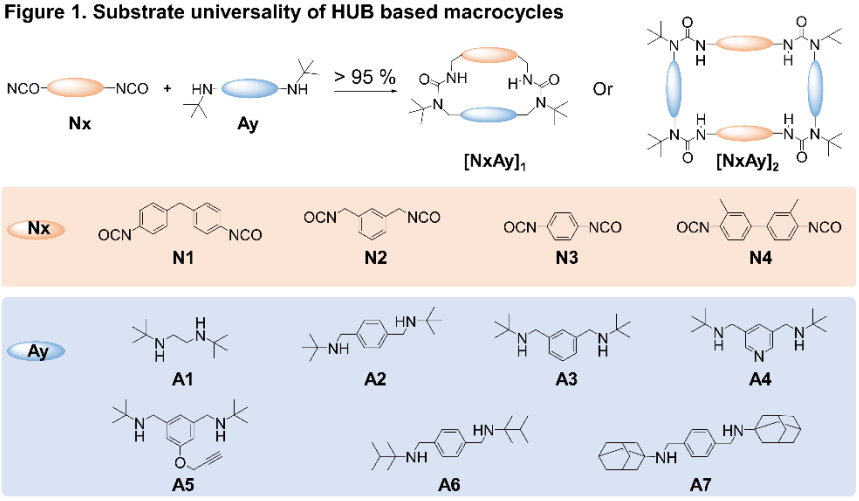
During the reporting period, significant progress was achieved toward the aims in our initial proposal. We also have a paper entitled 'Quantitative synthesis of urea macrocycles enabled by bulky *N*-substituent' in submission. Below is a brief summary of our progress:

1. We demonstrated the feasibility of this strategy and proved hindered urea bond (HUB) as a versatile macrocycle enabling structural motif for the synthesis of hindered urea macrocycles (HUMs).

A large library of HUMs was constructed from the combination of various diisocyanates and hindered diamines, all in high to quantitative yields. We also discovered that by choosing specific building blocks, [1+1] type of monomeric macrocycles or [2+2] dimeric macrocycles can be selectively formed. The strategy was versatile enough to demonstrate a self-sorting phenomenon where macrocycles were formed independently in a multi-component system. More interestingly, the presence of other functional groups (such as pyridine and the pendant alkyne groups in monomers A4 and A5 in Figure 1) did not interfere with the macrocycle formation process, implying the potential for further functionalization and structural diversity extension in future designs. When the *t*-Bu group in A2 was replaced with even bulkier ones (A6 and A7), similar macrocycles formation behaviors were shown, further demonstrating the versatility of this strategy.

Figure 1. Substrate universality of HUB based macrocycles



2. We illustrated the underlying mechanism behind the highly efficient HUM formation: the combined effect of the 'self-correction' property enabled by the dynamic bond as well as the '*cis*-urea preference' and template effect mediated by the bulky group.

We demonstrated that bulky groups are playing multiple roles to achieve high-efficient macrocycle synthesis in our system: first of all, it activates the covalent urea bond to provide reversible feature and enable systems to find their minimum energy state, which is the characteristic feature of dynamic covalent bond. Secondly, it promotes the formation speed of the macrocycles by conformation lock, which increases the effective molarity of local reactants and the probability of the ring closing steps. We used 2D NMR to demonstrate the '*cis*-urea preference' of HUB and proved that the conformation preference was induced by the bulky group, which was further supported by DFT calculations performed by Prof. Yang Zhang's group. They also helped to establish a correlation between structural conformation and total free energy, which supported the argument that the bulky group induced '*cis*-urea preference' can facilitate macrocyclization (Figure 2a). Thirdly, it reduces the energy and promote the dominance of the macrocycle system through 'host-guest interaction' with the ring pocket. Concentration dependent NMR and 2D NMR showed an interaction between macrocycles and the bulky *t*-Bu group. XRD crystal structure clearly demonstrated the interaction pattern, with the *t*-Bu from one macrocycle sitting right inside the cavity of another one, forming a host-guest pair (Figure 2b). Atomistic level MD calculations further added support to the argument of the template effect and its influence on the highly efficient macrocycle formation.

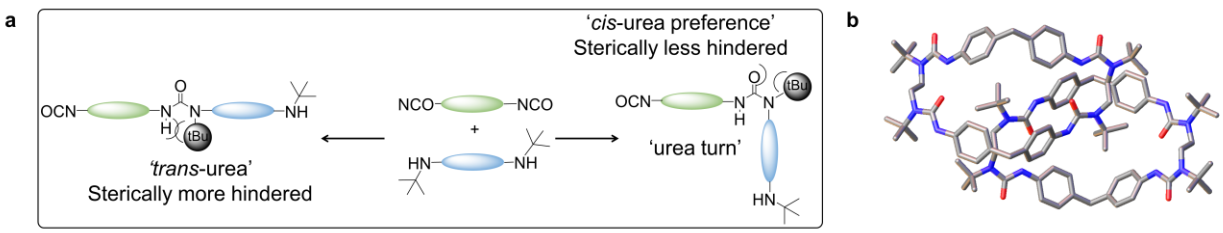


Figure 2. (a) Schematic illustration for the *t*-Bu induced '*cis*-urea preference'. (b) A representative XRD structure showing the host-guest interaction between *t*-Bu and the macrocycle

3. We successfully expanded the strategy to more sophisticated structures beyond macrocycles.

By using triisocyanates or triamines, a number of cage compounds with micro-porosity were obtained in quantitative yields (Figure 3a, 3b, 3c). When multi-functional building blocks were used, such as tetraamines or octaamines, some more elaborate structures such as

dumbbell, bridged bicyclic structures, four-leaf clover (Figure 3d) or hourglass-shaped structures (Figure 3e) were formed. The final architectures were determined by the number of functional groups as well as rigidity and length of the building blocks. Similar to macrocycles, these compounds can also be facilely stabilized with acid treatment.

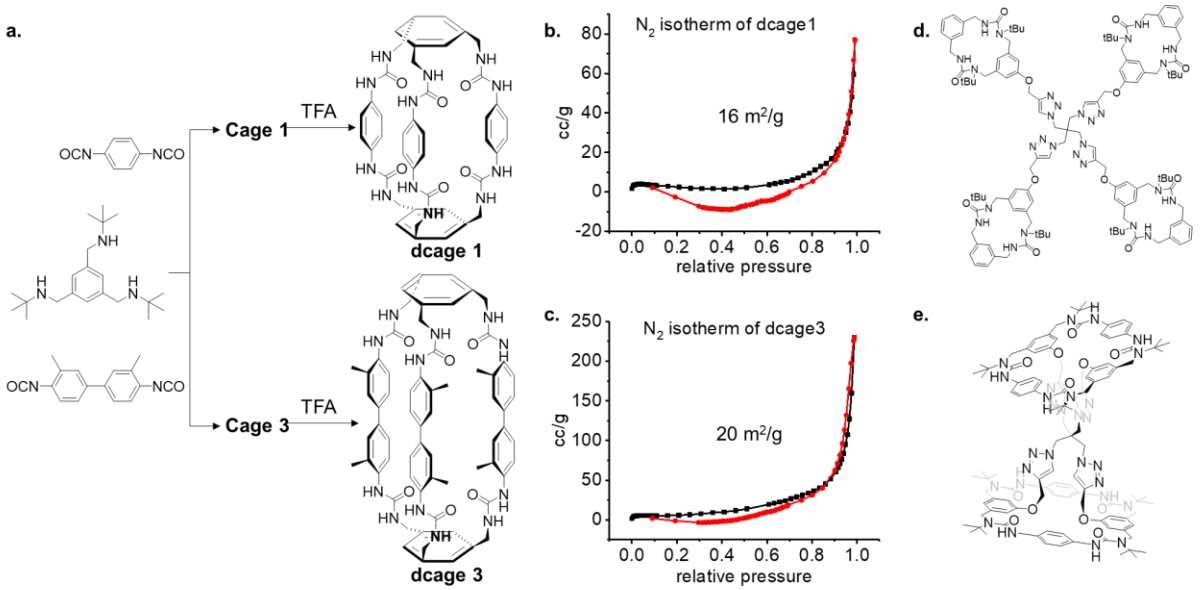
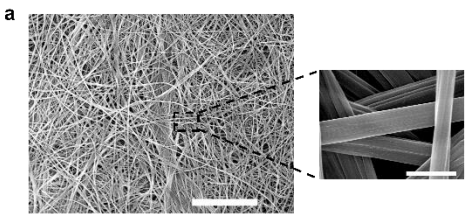


Figure 3. (a) Examples for the synthesis of two cage compounds. (b) BET test of dcage 1. (c) BET test of dcage 3. (d) Example for the structure of the four-leaf clover. (d) Example of the hourglass-shaped structure.

4. We demonstrated some applications of the macrocycles, such as heterogeneous H bond catalyst, self-assembled nanofiber and antimicrobial agent

The urea moiety is capable of forming strong hydrogen bonding and several applications were explored along this direction. We demonstrated that the urea macrocycles can function as heterogeneous hydrogen bonding catalyst for a model Henry reaction. In comparison, the linear model urea compound showed no catalytic activity at all because of self-quenching, which could be alleviated by the structural constraint of the macrocycle. The urea macrocycles also showed high tendency to self-assemble into nanofibers (Figure 4a). More interestingly, after post modification of one class of urea macrocycle, the charged species with C12 alkyl tail showed high antimicrobial activities against three different strains of Methicillin-resistant Staphylococcus aureus (MRSA), with the minimum inhibitory concentration (MIC) comparable to Vancomycin, a clinically widely used antibiotics for MRSA treatment (Figure 4b). More applications are under investigation.



MIC (mg/L)	USA100	USA200	USA300
De-[N2A4]-C12	16	16	8
Vancomycin	4	2	2

Figure 4. (a) SEM image of the self-assembled nanofiber structure of a macrocycle. Scale bar: 20 μm, inset, 50 nm. (b) MIC (minimum inhibitory concentration) of the cationic charged urea macrocycle De-[N2A4]-C12 and the antibiotic vancomycin against three different MRSA strains.

Impact of the research:

For me, my expertise is polymeric biomaterials and polymer chemistry, this project introduced me to a completely new direction of molecular macrocycles and related topics. Nevertheless, it is a great platform for me to combine my expertise in biomaterials/ therapeutics and this new type of material, such as the development of cyclic urea antimicrobial agent. I position this project as a great addition to the research topics in my group and to the whole macrocycle community as well.

For the students participated in this project, they got trained on the basic chemical synthesis and structural characterization. The mechanistic study helped them to develop their ability of deep analysis and critical thinking since they need to formulate different theories and then design experiments or cooperate with a simulation group to prove or disprove them. The identification of various applications helped to broaden their horizons in different areas, which is important in their following studies and future career.