

**Problem 1** (20 points)

a) Propose a synthesis of **1** starting, amongst others, from **2** and **3** (indicate reaction conditions).

(6 points)

b) Also, propose a synthesis of **4** starting from catechol (**5**). (3 points)

c) When the backbone of **1** is assembled in the presence of **4**, an interlocked structure **1·4** forms.

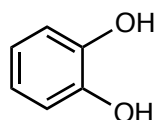
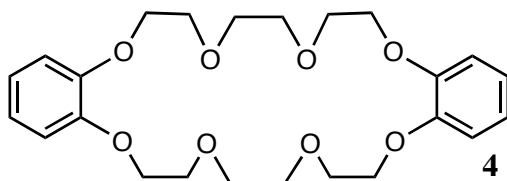
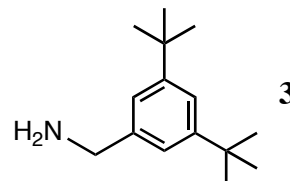
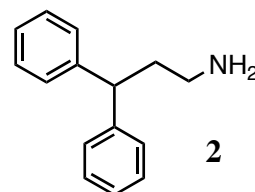
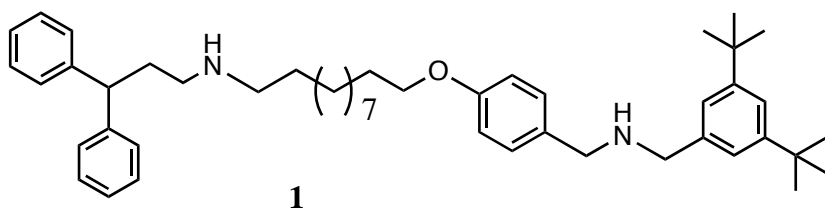
Propose a structure for this assembly (can be done schematically). (3 points)

d) When **1** is doubly protonated (**1·2H<sup>+</sup>**), **4** prefers two positions in the resulting supramolecular structure **1·2H<sup>+</sup>·4**. Suggest which ones are preferred (again, schematical structures are acceptable).

(3 points)

e) Exchange between the two positions in **1·2H<sup>+</sup>·4** is slow on the NMR time scale, so the ratio of the two isomers can be determined by <sup>1</sup>H NMR. Suggest how. (3 points)

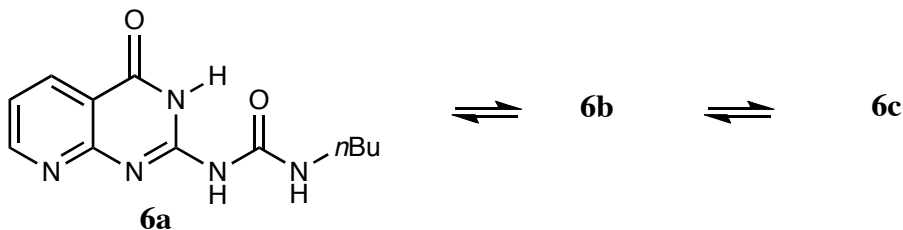
f) What type of isomerism is present? (2 points)



**Problem 2** (20 points)

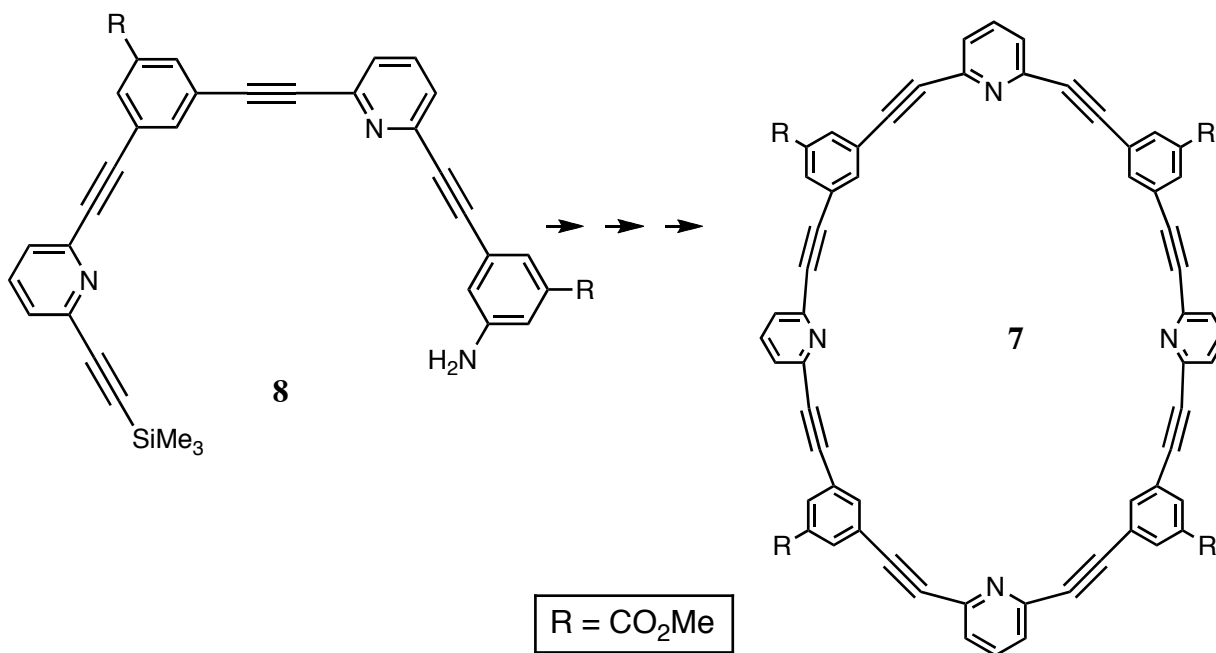
The following ureido-substituted heterocycle **6a** can form several tautomers which present an H-bonding edge with 4 donor or acceptor centers.

- Ignoring tautomerism of the urea moiety (i.e. it stays  $\text{-NH-CO-NH}n\text{Bu}$  at all times), propose two additional tautomers **6b** and **6c** with favorable conformations. Show how these conformations are stabilized intramolecularly. (6 points)
- Propose the structures of homo-dimers of **6a**, **6b**, and **6c**, that are observed in  $\text{CHCl}_3$  solution. (6 points)
- Indicate the order of stability for these homo-dimers. (4 points)
- The situation in solution is further complicated by the fact that hetero-dimers can also form. Propose the structure for a hetero-dimer that rivals the best homo-dimers in stability. (4 points)



**Problem 3** (10 points)

Propose the stepwise synthesis of macrocycle **7** starting from **8**. Suggest detailed reaction conditions, reagents, and solvents. (10 points)



**Problem 4** (10 points)

The following natural product **9** is prepared in two steps starting from the three components **10-12**, using reactions that have been explicitly discussed in class. Suggest these reactions and their conditions and propose their mechanisms.

