

Workshop 3 Solutions

$$\begin{aligned}
 1. \text{ a) } \Delta\Delta G_{\text{dim}} &= \{\Delta G_{\text{dim}}(\mathbf{2}) - \Delta G_{\text{dim}}(\mathbf{1})\} = RT\{\ln K_{\text{dim}}(\mathbf{2})\} - RT\{\ln K_{\text{dim}}(\mathbf{1})\} \\
 &= RT\ln\{K_{\text{dim}}(\mathbf{2})/K_{\text{dim}}(\mathbf{1})\} \\
 &= 3.2 \text{ kcal/mol}
 \end{aligned}$$

If you wanted to, you could also estimate $\Delta\Delta G_{\text{dim}}$ from the fact that each order of magnitude in K is worth 1.4 kcal/mol of ΔG ; that would mean that the difference of a little more than 2 orders of magnitude in K_{dim} would equal a difference of a little more than 2.8 kcal/mol in ΔG . That's less than one H-bond is worth in CHCl_3 (5-9 kcal/mol), but not much less.

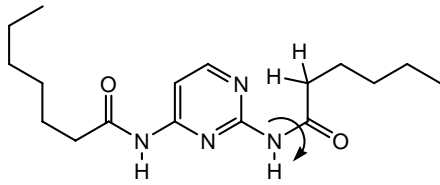
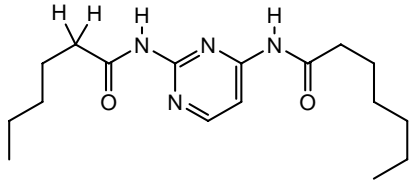
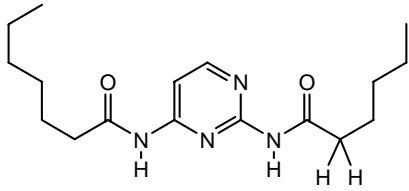
- b) (See scheme on next page.) The only difference between the structures of **1** and **2** is an N-H substitution. As it turns out, this N-H is perfectly situated to interact with a pyrimidine ring nitrogen, which locks things into place for molecule **2**. In molecule **1**, on the other hand, the amide carboxyl group is free to rotate in a way that avoids steric interactions between CH_2 hydrogens and the ring.

As a result, as the scheme shows, although $K_{\text{dim}}(\mathbf{2})$ should have contributions from $K_{\text{H-bond}}(\mathbf{2})$ alone, $K_{\text{dim}}(\mathbf{1}) = K_{\text{H-bond}}(\mathbf{1})K_{\text{rotate}}(\mathbf{1})$.

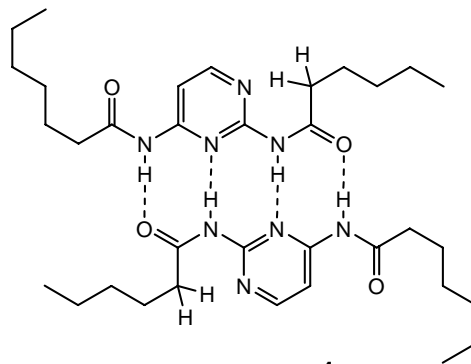
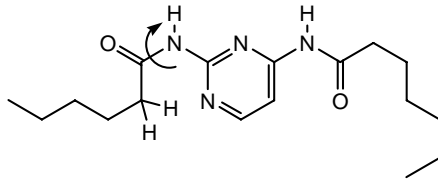
Or, put another way,

$$\begin{aligned}
 \Delta G_{\text{dim}}(\mathbf{2}) &= \Delta G_{\text{H-bond}}(\mathbf{2}); \\
 \Delta G_{\text{dim}}(\mathbf{1}) &= \Delta G_{\text{H-bond}}(\mathbf{1}) + \Delta G_{\text{rotate}}(\mathbf{1}).
 \end{aligned}$$

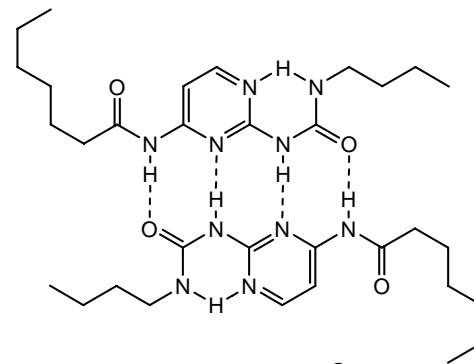
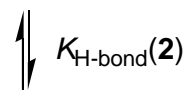
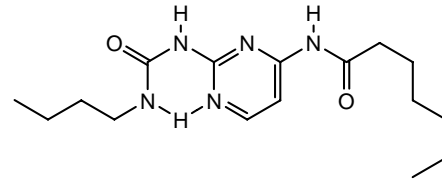
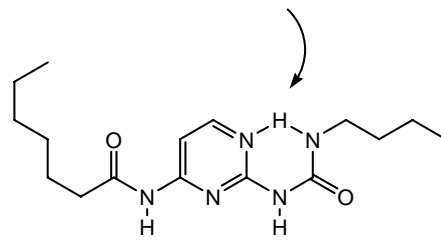
This $\Delta G_{\text{rotate}}(\mathbf{1})$ is probably responsible for the difference $K_{\text{dim}}(\mathbf{2}) > K_{\text{dim}}(\mathbf{1})$.



amide bond can rotate...



intramolecular H-bond locks this conformation

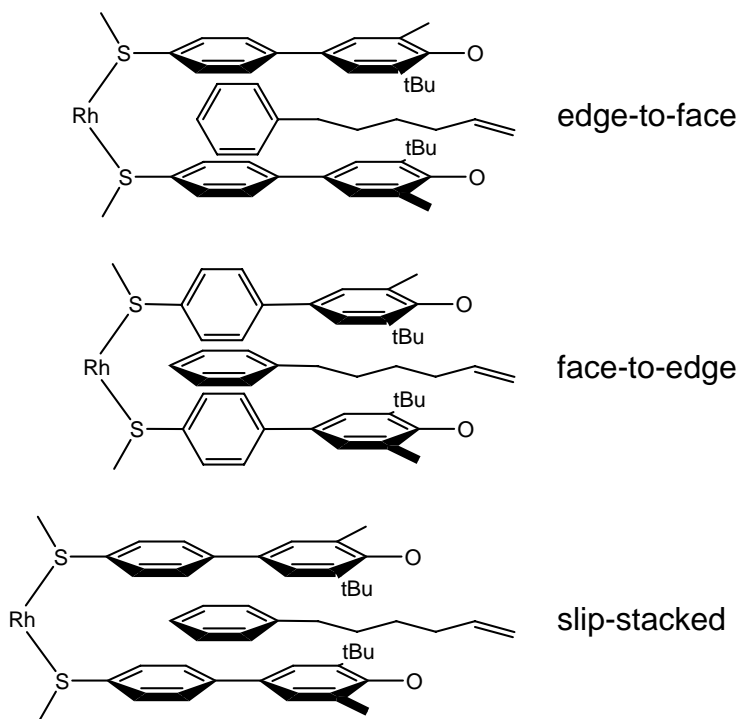


- c) Clearly, hydrogen bonding is one important driving force for forming these “polymeric” stacks, but it isn’t the only one. Arene-arene slip-stacking is also contributing (illustrated by the “twist” in the column of half-disks). In the case of **3b**, the hydrophobic effect is also probably driving the hydrophobic aromatic groups away from the water, while the oligo(ethyleneoxide) sidechains segregate towards the water.

As the solvent is switched from non-H-bonding to H-bonding, the solvent competes for the intermolecular hydrogen bonds that hold the half-disks together, and the structure comes apart. However, in H₂O, **3b** does something interesting—as noted above, it self-segregates into a hydrophobic center and a hydrophilic shell, keeps H₂O out of the center, and once again strengthens the H-bonds that hold the structure together.

This is, in principle, much like what happens to proteins, DNA, and other structured biomolecules in solvent. In aqueous buffer, biomolecules are well-folded, but add a less polar cosolvent like DMF, DMSO or formamide, and these structures are easily denatured. (Sometimes even pure water isn’t enough to maintain structure—DNA, for example, needs salty water to stay assembled in its double-helix.) This isn’t because DMF is a better H-bonding solvent than H₂O, but rather because it prevents hydrophobic segregation from reinforcing that H-bonding.

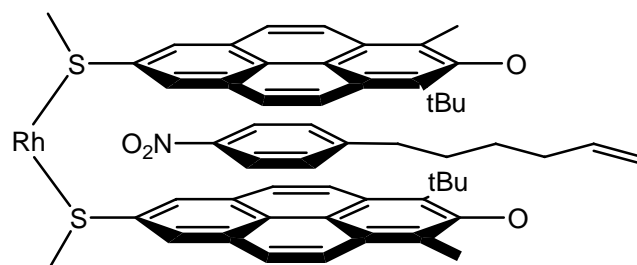
2. a) Well, the wording of the problem made it pretty clear that arene interactions play an important role here.
- b) But what do these interactions mean for the way that the rings of the reagent cleft might interact with the ring of the substrate? Arene rings that don't interact with electron-transfer character can assemble edge-to-face, or can slip stack. So you might imagine things could look like:



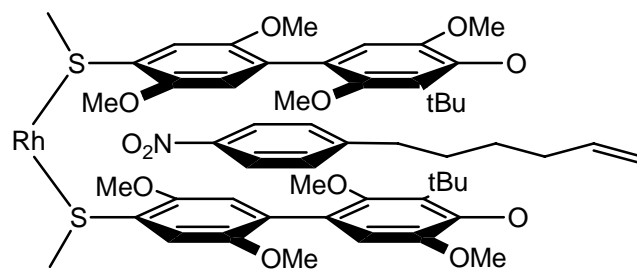
It's not clear from the cartoon whether there is enough space to fit edge-to-face-oriented structures inside the cleft—presumably, some molecular modeling might answer this question.

- c) In class, we discussed how electron-poor arenes can interact selectively with electron-rich arenes in a face-to-face manner, and this may already be occurring for the nitro-substituted substrate in the original Mirkin catalyst. But two different ways to reinforce this sort of interaction might be to: (i) prevent the catalyst arenes from twisting out of plane, forcing them to present faces to the cleft; or (ii) attaching more electron-donating groups to the receptor phenyl rings.

i)



ii)



Lots of possible answers here though.