

ENZYMATIC CATALYSIS OF LADDER ETHER FORMATION

Biosynthesis of ladder polyethers is the topic of a very nice experimental/computational study by Chen and Houk.¹ The x-ray structure of the enzyme that catalyzes the nucleophilic attack on epoxides to create the 6-member ring ether was determined, but the geometry did not completely indicate the mechanism.

Gas phase computations of the 5-*exo*-tet and 6-*endo*-tet ring openings of **1** were examined for both the acid and base catalyzed routes at B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d).

The results are summarized in Figure 1. Basically, as expected by Baldwin's rules, the closure to the tetrahydrofuran (5-*exo*-tet) is favored under both catalyzed conditions. However, the preference is small under base conditions, with the difference in the free energy of activation of only 1.2 kcal mol⁻¹.

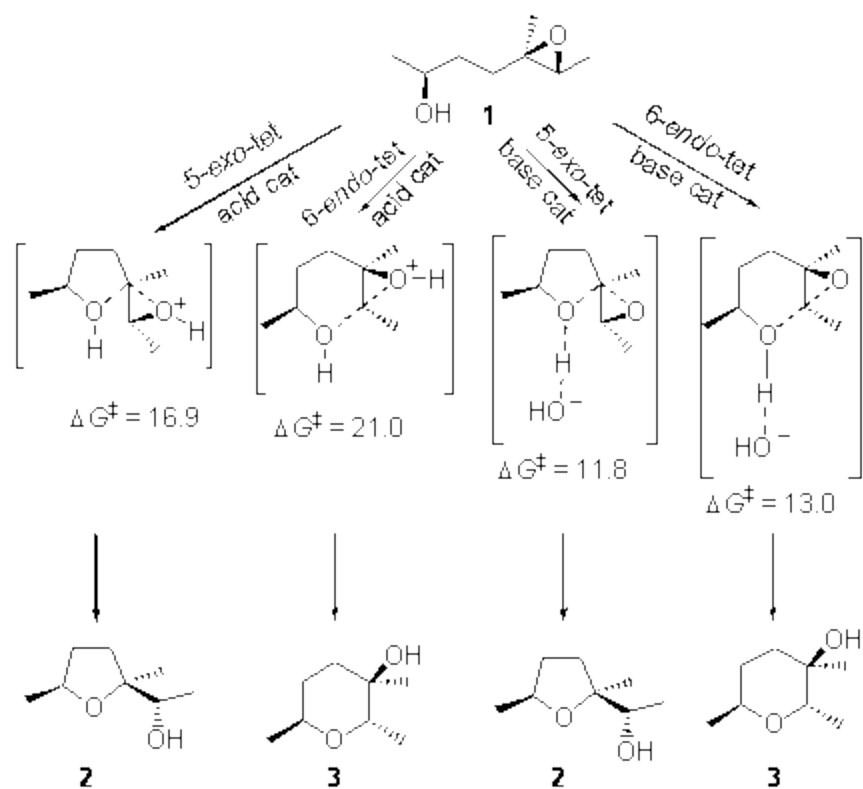
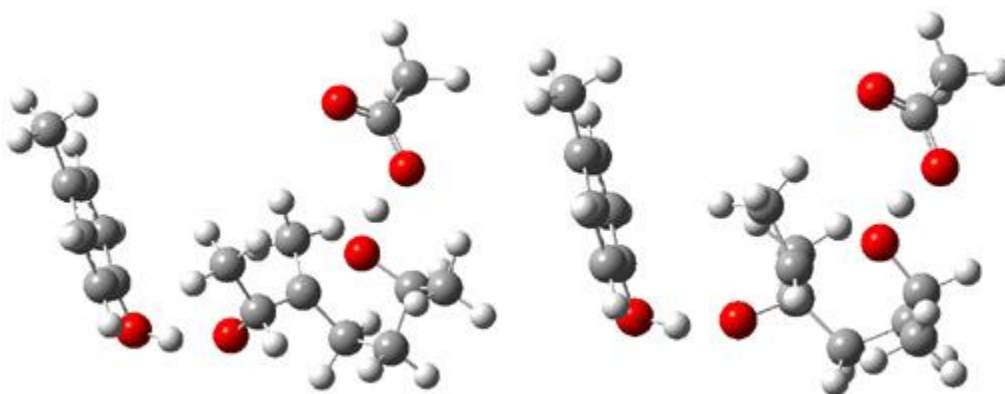


Figure 1. Gas phase energies (kcal mol⁻¹) for the acid and base catalyzed reactions of 1 to 2 or 3.

The enzyme Lsd19B produces just the analogue of 3. So, the two regioisomeric TSs were reoptimized with an aspartic acid group and a tyrosine group in the positions they occupy in the active site of the enzyme Lsd19b. The two resulting transition states, evaluated at B2LYP/6-311++G(d,p)//MO6-2x/6-31G(d), are shown in Figure 2. The activation energy for the 6-*endo*-tet reaction is 18.0 kcal mol⁻¹, 2.5 kcal mol⁻¹ lower than for the 5-*exo*-tet route. This energy difference would give rise to a 100:1 selectivity for the tetrahydropyran product, in accord

with experiment. The enzyme preorganizes for and favors the base catalyzed path that leads to **3**.



5-exo-tet TS model

$$\Delta G^\ddagger = 20.5$$

6-endo-tet TS model

$$\Delta G^\ddagger = 18.0$$

Figure 2. Transition state models of the active site. Activation energies in kcal mol⁻¹.

Source: <http://comporgchem.com/blog/?p=2192>