# ENHANCING THE ACIDITY OF PROLINE – APPLICATION TO ORGANOCATALYSIS

Organocatalysis affected by proline is an extremely active research area, and computational chemists have made considerable contributions (see Chapter 5.3 of my book – and this is expanded on in the 2nd edition which should be out in just a few months). Most importantly, the Houk-List model[1] for the catalysis was largely developed on the basis of computations.

Recent experiments have indicated cocatalysts that can hydrogen bond to proline may increase the catalytic effect, including the enantioselectivity. Xue and co-workers have examined a series of potential cocatalysts for their ability to enhance the acidity of proline.[2] This is important in that a proton transfer is a component to the key step of the Houk-List model.

The cocatalysts examined included such compounds as **1**-**6**. The deprotonation energy of proline with the associated cocatalysts was compared with that of proline itself. The energies were computed at M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) with the SMD treatment of five solvents. The structure of **5** with proline is shown in Figure 1.

5 with proline conjugate base
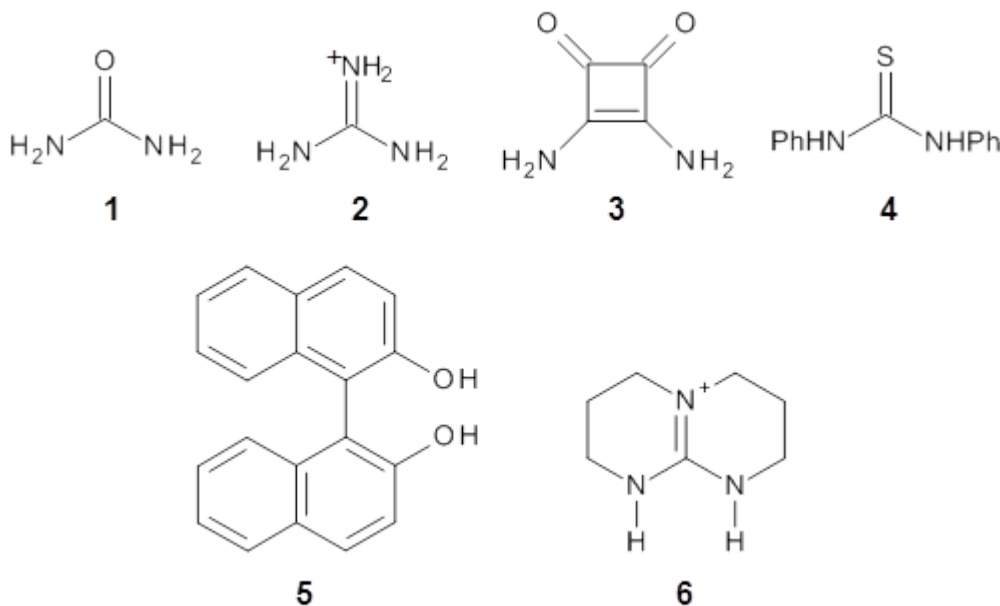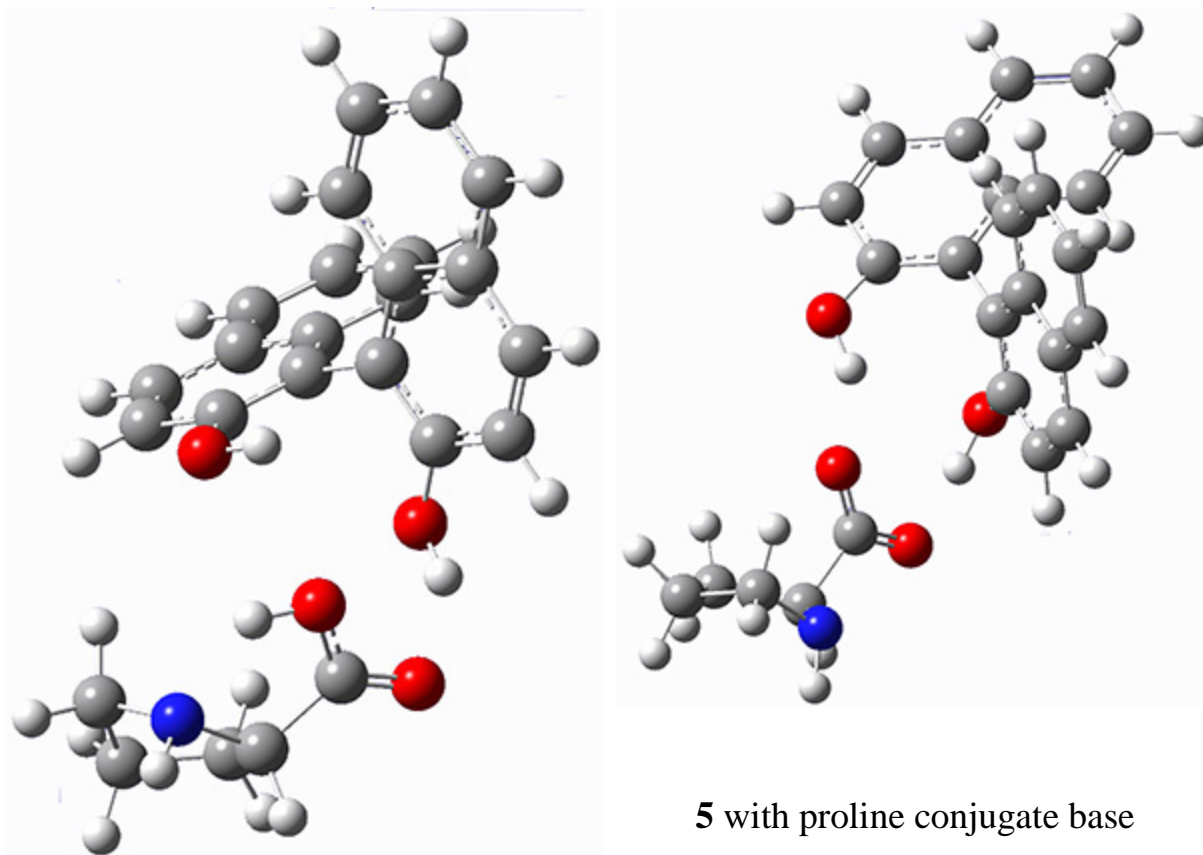
5 with proline

Figure 1. M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) optimized structure of **5** with proline and its conjugate base.

The effect of the cocatalysts is striking. In the gas phase, these additives decrease the pK_a of proline by 15 – 70 pK_a units, with **2** showing the largest effect. In solvent, the effect of the cocatalyst is attenuated, especially in more polar solvents, but still a considerable decrease in the pK_a is seen (as much as a 12 pK_a unit increase in acidity). Further exploration of potential cocatalysts seems fully warranted.

Source : http://comporgchem.com/blog/?p=3018