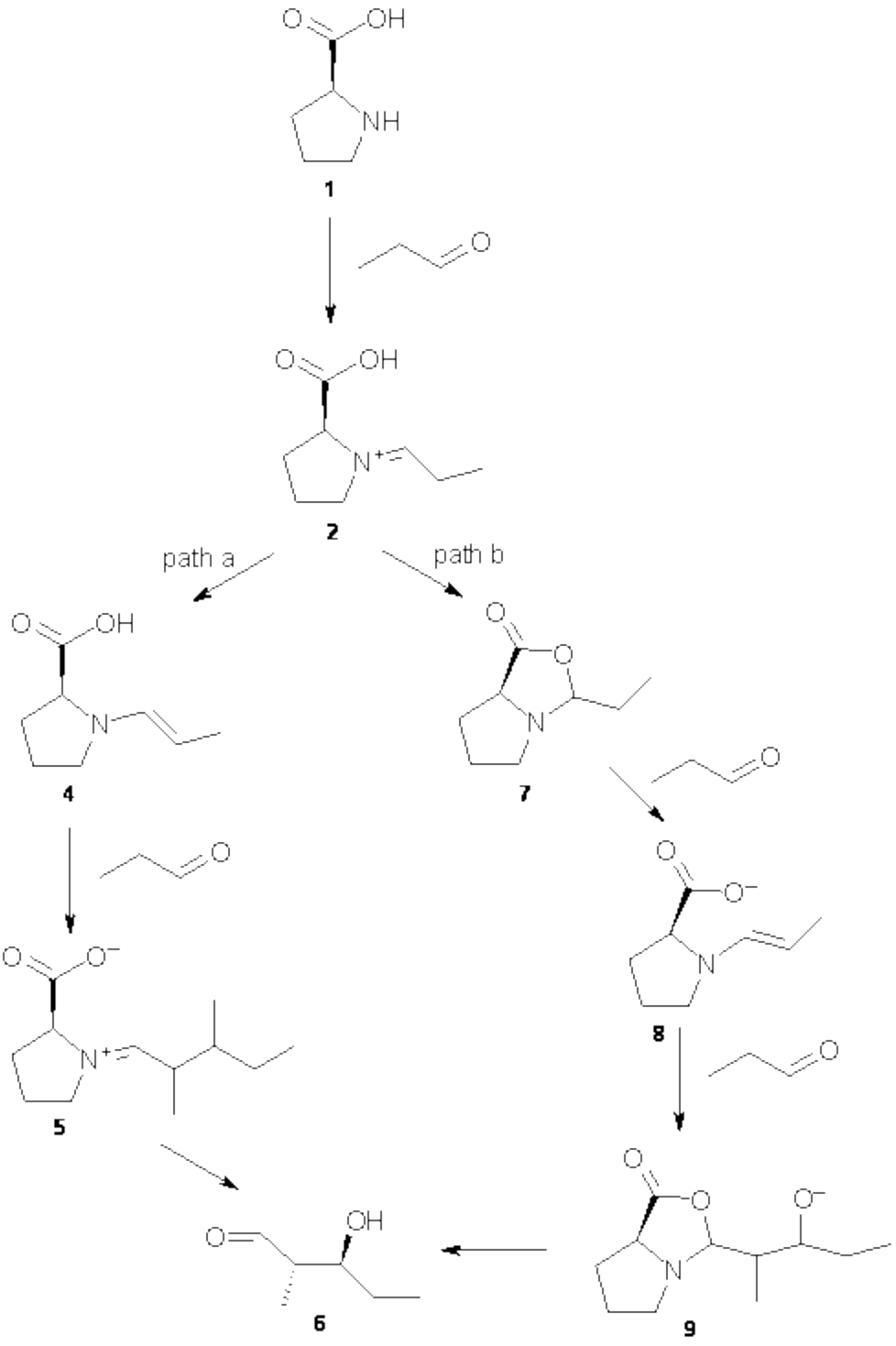
OXAZOLIDINONE INTERMEDIATES IN PROLINE-CATALYZED ALDOL REACTIONS?

The proline-catalyzed aldol reaction is discussed in Chapter 5.3 of my book. This is an area of continued research and the recent paper of Sharma and Sunoj addresses an alternative mechanism involving oxazolidinone.[1] They examine the proline-catalyzed aldol self-condensation of propanal with B3LYP/6-31+G** and MP2/6-31+G** computations. This reaction is found to proceed[2] with 4:1*anti*:*syn* diastereoselectivity.

An oxazolidinone intermediate has been observed in proline-catalyzed aldol condensations. This intermediate is proposed to come about via Path b, whereas the generally accepted mechanism put forth by Houk and List, discussed in my book, follows Path a. Sharma and Sunoj find that the oxazolidinone **7** is lower in energy than the enamine **4**, and its barrier for ring opening back to **3** is large. Thus, it is not unreasonable that it is the observed intermediate.


O
OH
NH
1
O
O
OH
N+
2
path a
path b
O
OH
N
4
O
O
N
7
O
O
O−
N
8
O
O
O−
N+
5
O
O
O−
N
9
O
OH
6

Gas phase computations of the reaction of **4** to **5** predict a 99% ee and an *anti*:*syn* ratio of about 5:1, in nice agreement with experiment. However, incorporation of solvent reduces the ration to 2:1, and the MP2 computations give a ratio of 1.2:1, in even worse agreement with experiment. However, the major predicted product has the same absolute configuration as the observed product.

The other mechanism is examined in the key step **8** to **9**. Here all computations predict that *syn*addition is favored over *anti* addition and the enantiomer of the experimentally observed product is predicted to be formed. In addition, intermediate **9** and the TSs leading to it are much higher in energy than intermediate **5** and the TSs associated with its formation. Thus, the oxazolidinone addition mechanism is discounted.

Source: http://comporgchem.com/blog/?p=1126