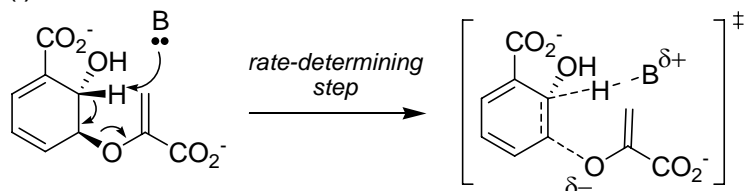
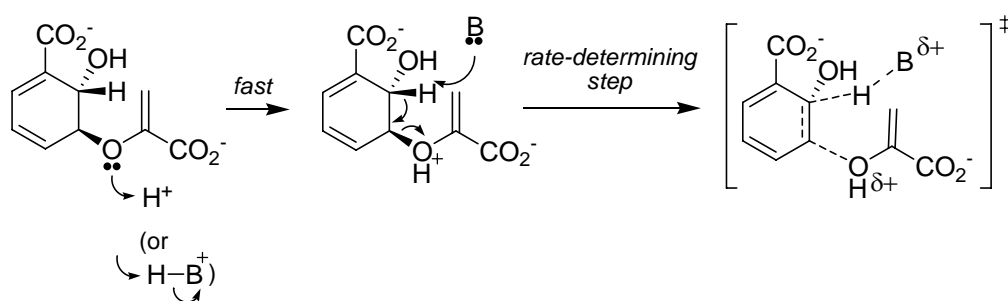


Problem Set 8 Answer Key

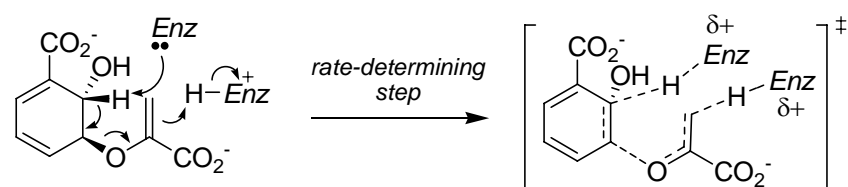
1. a) (i)



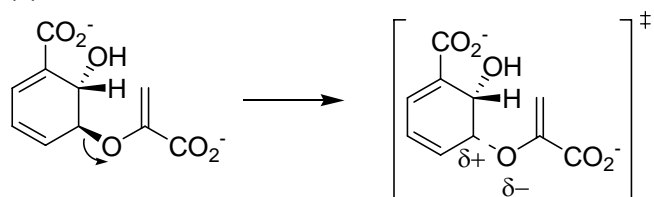
OR



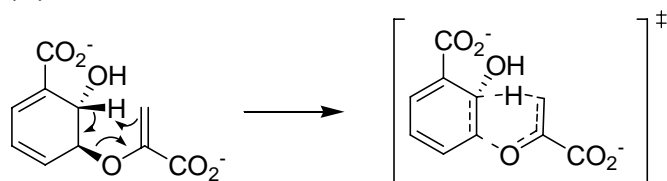
OR, in enzyme active site only
(where acids and bases can be all lined up),



(ii)



(iii)



- b) Mechanisms (i) and (iii) exhibit C-H/D bond breaking in the rate-determining step, and are the only mechanisms that are consistent with a large, 1° KIE around two. Mechanism (ii) would have a 2° KIE near one (we calculated maximum effects near 1.4 in class) and is therefore not a possible mechanism.
- c) The enzyme catalyzed reaction has 100% D incorporated at C*. The mechanism that describes this result best is mechanism (iii). The uncatalyzed reaction has only 5% D incorporated at C*, which is consistent with the carbon collecting a proton from a different source than the molecule itself. Mechanisms (i) and (ii) would be consistent with this observation. Together with (b) above, it seems likely that mechanism (i) is the correct one for the uncatalyzed reaction.
- d) (i) The enzyme could act as the base and deprotonate isochorismate.
- (ii) Noncovalent interactions (maybe ionic ones) between the enzyme and transition state could stabilize developing charge.
- (iii) The enzyme could promote the orientation of isochorismate such that the orbitals are aligned and can easily undergo the concerted mechanism.
2. a) (i) The observation of a heavy atom isotope effect is inconsistent with mechanism I because the rate determining step does not involve C-N₂ bond scission. Such scission is rate controlling in mechanisms II and III, however, so the KIE is consistent with both of these.
- (ii) The observation of a small amount of rearranged product is consistent with mechanism III, which involves reversible cleavage of the C-N₂ bond. This bond breaking is not reversible in I and II, so rearranged product would not be observed if these mechanisms were operative.
- (iii) In mechanism I, rehybridization of the ortho C atom occurs in the rate determining step, so a secondary isotope effect would be expected, but the rehybridization is from sp² to sp³, which would give an inverse KIE, inconsistent with the observed KIE of 1.22. A secondary KIE would not be expected for mechanism II, where no change in the ortho C-H/D modes are perturbed in the slow step. In mechanism III, the slow step involves formation of a carbocation that features an empty orbital orthogonal to the arene pi system and aligned in the same plane as the ortho C-H/D bond. The result would be a hyperconjugative interaction that would weaken the C-H/D bond in the transition state,

thus leading to a secondary KIE consistent with the observed value of 1.22.

- (iv) Both mechanisms I and II involve associative rate determining steps, which are not supported by a positive entropy of activation. This positive entropy of activation is consistent with mechanism III, however, because the rate determining step is dissociative in character (with loss of N_2).
- b) The only mechanism that is consistent with all of the data is III. Since this path involves rate determining formation of a carbocation (positive charge development in the transition state), one would expect the rate to increase as para substituents became electron donating. Thus, a plot of $\log(k)$ vs. σ would have a negative slope.