

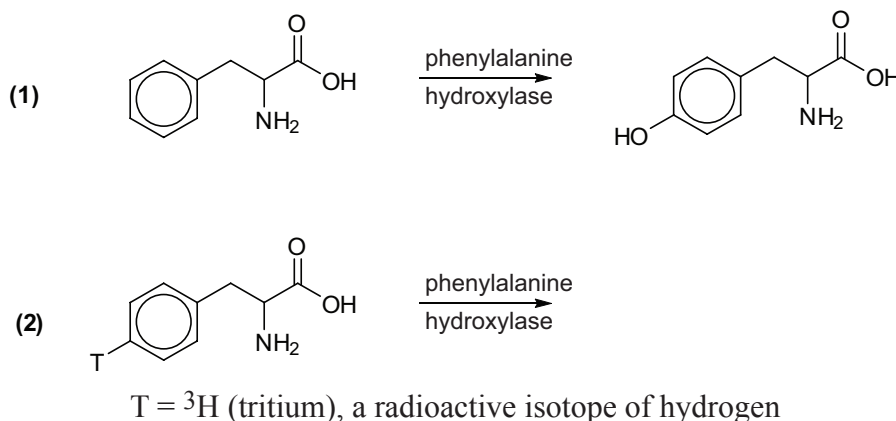
FOCUS QUESTION

How can isotopic substitution be used to elucidate mechanisms?

MODEL 1

Isotopic Labeling¹

Isotopes are atoms that have the same number of protons but different numbers of neutrons, and therefore different masses, but almost identical chemical reactivity. E.g. ^1H , ^2H (deuterium, abbreviated D), ^3H (tritium, abbreviated T); ^{12}C , ^{13}C , ^{14}C ; ^{16}O , ^{18}O .



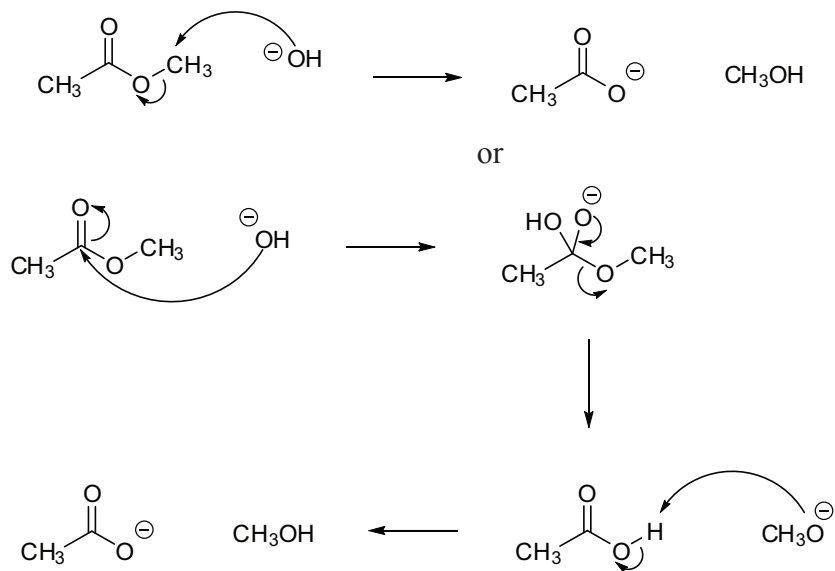
- Reaction 1 is clearly a net substitution reaction. Circle the atom on the reactant that appears to be lost during this reaction.
- Draw the product from reaction 2 that you would expect based on the product from reaction 1.
- The second reaction's product is radioactive. What does this tell you about the structure of this product?
- Does the information given in question 3 support your prediction of the product of reaction 2?
- What does using tritium in reaction 2 tell you about the mechanism that cannot be seen in the unlabeled reaction 1?

MODEL 2

Basic Hydrolysis of an Ester



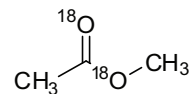
There are a number of possible mechanisms for this reaction, two of which are shown below.



6. In the first mechanism, from where do the oxygens in the carboxylate anion come, the starting ester or the starting alcohol?

In the second mechanism?

7. What products would be formed in each mechanism if the starting ester has both oxygens labeled with ^{18}O as shown below?

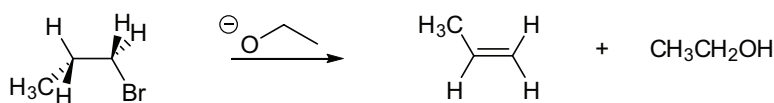


8. If you knew the structure of the products of the reaction in question 7, could you determine which of the mechanisms is correct? If so, explain how you could do this. If not, explain why.

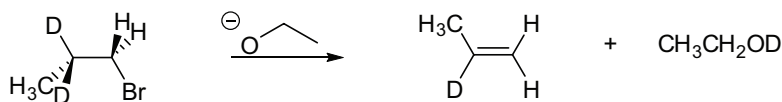
9. What would be the best method to experimentally determine which product is formed from the labeled starting material...IR spectroscopy, mass spectrometry, or NMR? Explain your reasoning.

MODEL 3

Other Reactions with Isotopes²



$$\text{rate} = k_{\text{H}}[\text{bromopropane}][\text{ethoxide}]$$

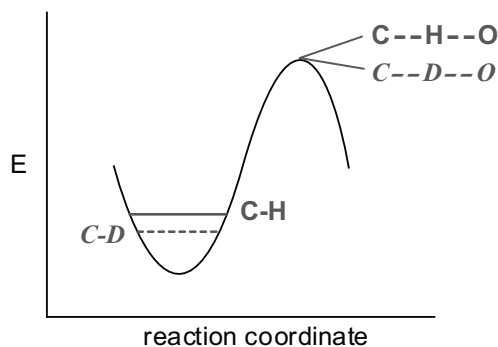


$$\text{rate} = k_{\text{D}}[\text{deuterated bromopropane}][\text{ethoxide}]$$

10. The reactions in Model 3 occur in one step. Draw curved arrows to show electron flow.
11. In the second reaction, is deuterium involved in the reaction? If so, how?
12. If a carbon-deuterium bond requires more energy to break than a carbon-hydrogen bond, which reaction would be faster?
13. When an isotopic substitution causes the rate of a reaction to change, we call that a kinetic isotope effect. This effect can be measured by the ratio of the rate constant of the reaction without isotopic substitution to the rate constant of the reaction with isotopic substitution. When both reactions in Model 3 are run with the same concentrations of reactants, $k_{\text{H}}/k_{\text{D}} = 6.7$, which reaction is faster?
14. Based on the information given in question 13, which bond is easier to break, a C-H bond or a C-D bond?

MODEL 4**Zero-point Energy**

Zero-point energy is the energy from the vibrations of a molecule in its normal state. Since the vibrational energy is dependent upon the mass of the atoms, isotopic substitution changes the zero-point energy. However, the electronic energy is not affected because it is not mass dependent.



A vibrational energy diagram for the reaction in Model 3

15. According to Model 4, which has a lower zero-point energy, a C-H bond or a C-D bond?

16. One model we can use to rationalize this difference in zero-point energies is in terms of the vibration of a spring attached to a ball in classical physics (the spring is the bond and the ball is the hydrogen or deuterium). Explain.

17. How does the C-H bond strength in the transition state compare to that of the reactant?

18. How does the C-D bond strength in the transition state compare to that of the reactant?

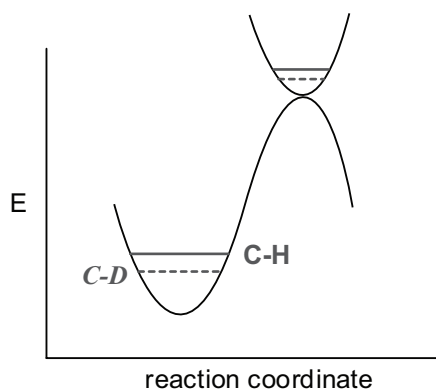
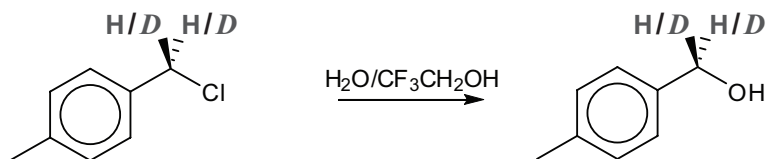
19. Propose an explanation for why the vibrational energies of the C-H and C-D bonds are the same in the transition state.

20. On the energy diagram in Model 4, draw arrows to show the activation energy for both reactions.
21. Which reaction do you expect to be faster, the one with the hydrogen or the one with the deuterium?
22. Does your answer to question 21 agree with the information in question 13? If not, go back and rethink your answers.

MODEL 5

Primary vs. Secondary Kinetic Isotope Effect³

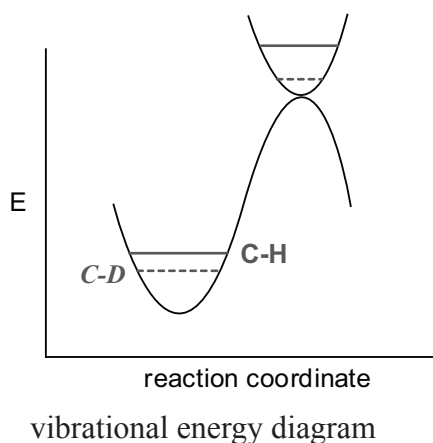
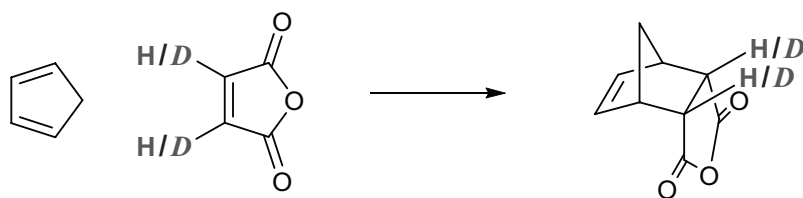
A kinetic isotope effect that comes from isotopic substitution at a bond being broken is called a primary kinetic isotope effect, and the k_H/k_D values are usually greater than 2. However, isotopic substitution can affect the rate of a reaction even when it is not involved in the bond being broken. This is called a secondary isotope effect.



A vibrational energy diagram of the slow step

23. The reaction in Model 5 is an S_N1 reaction. Draw out the mechanism.
24. Which step is the rate determining step? Explain your reasoning.

25. In contrast to Model 4, the C-D and C-H bonds have some vibrational energy in the transition state in Model 5. Explain the reason for this difference.
26. On the energy diagram, draw arrows to show the activation energy for the slow step in each reaction.
27. For the reaction in Model 5, $k_{\text{H}}/k_{\text{D}}$ will be
- greater than 1
 - less than 1
 - equal to 1
28. For the reaction in Model 5, $k_{\text{H}}/k_{\text{D}}$ will be
- greater than the ratio for the reaction in Model 3
 - less than the ratio for the reaction in Model 3
 - equal to the ratio for the reaction in Model 3
29. Do your answers to questions 27 and 28 agree with the experimentally determined value of 1.30 for $k_{\text{H}}/k_{\text{D}}$ in the reaction in Model 5? If not, explain where you went wrong.
30. Explain, in grammatically correct sentences, why a primary isotope effect is larger in magnitude than a secondary isotope effect.

MODEL 6**More Isotope Effects⁴**

31. What type of reaction is shown in Model 6?
32. How many steps are involved in this reaction?
33. On the energy diagram, draw arrows to show the activation energy for each reaction.
34. For the reaction in Model 6, the k_H/k_D will be
 - a. greater than 1
 - b. less than 1
 - c. equal to 1
35. For the reaction in Model 6, the k_H/k_D will be
 - a. greater than the ratio for the reaction in Model 3.
 - b. less than the ratio for the reaction in Model 3.
 - c. equal to the ratio for the reaction in Model 3.
36. Do your answers to questions 34 and 35 agree with the experimentally determined value of 0.95 for k_H/k_D ? If not, explain where you went wrong.

37. Secondary kinetic isotope effects arise from the change in vibrational energy that usually comes from a change in bond hybridization. This change can either raise or lower the vibrational energy present in the transition state. In Model 5, does the difference in vibrational energy of the C-H bond and the C-D bond increase, decrease, or stay the same?

In Model 6?

38. What is the change in hybridization at the carbon attached to the H/D in Model 5?

In Model 6?

39. A k_H/k_D that is greater than one is called a normal isotope effect and indicates a decrease in coordination (which loosens the C-H bond) in the transition state (e.g. sp^3 to sp^2). Which reaction, the one in Model 5 or the one in Model 6, has a normal secondary isotope effect?

40. A k_H/k_D that is less than one is called an inverse isotope effect and indicates an increase in coordination (which tightens the C-H bond) in the transition state (e.g. sp^2 to sp^3). Which reaction, the one in Model 5 or the one in Model 6, has an inverse secondary isotope effect?

41. Do your answers to questions 37 and 38 agree with your answers to questions 39 and 40? If not, explain where you went wrong.

42. Are there normal and inverse primary isotope effects? Explain your reasoning.

Summary of Kinetic Isotope Effects

43. Describe the primary kinetic isotope effect. When and why does it occur? How is it measured? What are the typical values? If it is present, what does that indicate about the mechanism of a reaction?

44. Describe the secondary kinetic isotope effect. When and why does it occur? How is it measured? What are the typical values? If it is present, what does that indicate about the mechanism of a reaction?

REVISITING THE FOCUS QUESTION

How can isotopic substitution be used to elucidate mechanisms?

(Endnotes)

- 1 Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms*; Springer: New York, 2004; p. 225.
- 2 www.chem.umn.edu/groups/taton/chem4011/Lecture%20Notes/11_17.pdf (accessed April 2007).
- 3 Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms*; Springer: New York, 2004; p. 224.
- 4 www.chem.umn.edu/groups/taton/chem4011/Lecture%20Notes/11_17.pdf (accessed April 2007).