Answer: A tetracycle is unraveled to a monocyte; in other words, the three cyclobutane rings are opened, leaving a cyclooctadiene. Fifth, what are the qualitative bond changes? Answer: Three single bonds are lost, three double bonds are gained.

Armed with the results of this analysis, we can now write a mechanism: We need to break the three C–C bonds by pyrolysis (Section 3-3). The result is seemingly a very exotic hexahedral; however, closer inspection shows that the six radical centers divide into three respective pairs of electrons on adjacent carbons: the three double bonds. Thus, a possible mechanism of this process requires only one step.

b. Regardless of the mechanism, is the isomerization thermodynamically feasible? Estimate the approximate ΔH°, using 65 kcal mol⁻¹ for the strength of the π bond (Section 11-2).

SOLUTION

First, let us be clear about the question. It does not ask us whether it is kinetically feasible to break the three cyclobutane bonds, either as shown in part (a) or by some other sequence. Instead, the issue is where the equilibrium A ⇌ B lies: Is it in the forward direction (Section 2-1)? We have learned how to get an estimate of the answer: by calculating ΔH° = (sum of strengths of bonds broken) − (sum of strengths of bonds made) (Sections 2-1 and 3-4). The second term in this equation is easy: We are making three π bonds, worth 195 kcal mol⁻¹. How do we deal with the three σ bonds that are broken? Table 3-2 provides an estimate for the strength of a C₃–C₃ bond: 83.5 kcal mol⁻¹. In our case, this bond is weakened by ring strain (Section 4-2, Table 4-2): 83.5 − 26.3 = 57.2 kcal mol⁻¹. Multiplied by 3, this provides the first term of our ΔH° equation, 171.6 kcal mol⁻¹. Thus, the ΔH° (A ⇌ B) = −17.4 kcal mol⁻¹. Conclusion: Indeed, this reaction should go! Note how the strain inherent in structure A affects its function in the thermolysis. Without strain, the reaction would be endothermic.

Important Concepts

1. Cycloalkane nomenclature is derived from that of the straight-chain alkanes.

2. All but the 1,1-disubstituted cycloalkanes exist as two isomers: If both substituents are on the same face of the molecule, they are cis; if they are on opposite faces, they are trans. Cis and trans isomers are stereoisomers—compounds that have identical connectivities but differ in the arrangement of their atoms in space.

3. Some cycloalkanes are strained. Distortion of the bonds about tetrahedral carbon introduces bond-angle strain. Eclipsing (torsional) strain results from the inability of a structure to adopt staggered conformations about C–C bonds. Steric repulsion between atoms across a ring leads to transannular strain.

4. Bond-angle strain in the small cycloalkanes is largely accommodated by the formation of bent bonds.

5. Bond-angle, eclipsing, and other strain in the cycloalkanes larger than cyclopropane (which is by necessity flat) can be accommodated by deviations from planarity.

6. Ring strain in the small cycloalkanes gives rise to reactions that result in opening of the ring.

7. Deviations from planarity lead to conformationally mobile structures, such as chair, boat, and twist-boat cyclohexane. Chair cyclohexane is almost strain free.

8. Chair cyclohexane contains two types of hydrogens: axial and equatorial. These interconvert rapidly at room temperature by a conformational chair–chair ("flip") interconversion, with an activation energy of 10.8 kcal mol⁻¹ (45.2 kJ mol⁻¹).
9. In monosubstituted cyclohexanes, the ΔG° of equilibration between the two chair conformations is substituent dependent. Axial substituents are exposed to 1,3-diaxial interactions.

10. In more highly substituted cyclohexanes, substituent effects are often additive, the bulkiest substituents being the most likely to be equatorial.

11. Completely strain-free cycloalkanes are those that can readily adopt an all-anti conformation and lack transannular interactions.

12. Bicyclic ring systems may be fused or bridged. Fusion can be cis or trans.

13. Natural products are generally classified according to structure, physiological activity, taxonomy, and biochemical origin. Examples of the last class are the terpenes, of the first the steroids.

14. Terpenes are made up of isoprene units of five carbons.

15. Steroids contain three angularly fused cyclohexanes (A, B, C rings) attached to the cyclopentane D ring. Beta substituents are above the molecular plane, alpha substituents below.

16. An important class of steroids are the sex hormones, which have a number of physiological functions, including the control of fertility.

Problems

21. Write as many structures as you can that have the formula C₆H₁₀ and contain one ring. Name them.

22. Write as many structures as you can that have the formula C₆H₁₂ and contain one ring. Name them.

23. Name the following molecules according to the IUPAC nomenclature system.

24. Draw structural representations of each of the following molecules. Give a systematic name for any compound whose name is not in accord with IUPAC nomenclature: (a) isobutylcyclopentane; (b) cyclopropylcyclobutane; (c) cyclohexylethane; (d) (1-ethylethyl)cyclohexane; (e) (2-chloropropyl)cyclopentane; (f) tert-butylecycloheptane.

25. Draw structural representations of each of the following molecules: (a) trans-1-chloro-2-ethylcyclopropane; (b) cis-1-bromo-2-chlorocyclopentane; (c) 2-chloro-1,1-diethylylcyclopropane; (d) trans-2-bromo-3-chloro-1,1-diethylylcyclopropane; (e) cis-1,3-dichloro-2,2-dimethylecyclobutane; (f) cis-2-chloro-1,1-difluoro-3-methylecyclopentane.

26. The kinetic data for the radical chain chlorination of several cycloalkanes (see the adjoining table) illustrate that the C-H bonds of cyclopropane and, to a lesser extent, cyclobutane are somewhat abnormal. (a) What do these data tell you about the strength of the cyclopropane C-H bond and the stability of the cyclopropyl radical? (b) Suggest a reason for the stability characteristics of the cyclopropyl radical. (Hint: Consider bond-angle strain in the radical relative to cyclopropane itself.)

27. Write out a mechanism for the radical monobromination of cyclohexane, showing initiation, propagation, and termination steps. Draw the product in its most stable conformation.

28. Use the data in Tables 3-2 and 4-2 to estimate the ΔΗ° value for a C-C bond in (a) cyclopropane; (b) cyclobutane; (c) cyclopentane; and (d) cyclohexane.
28. Draw each of the following substituted cyclobutanes in its two interconverting “puckered” conformations (Figure 4-3). When the two conformations differ in energy, identify the more stable shape and indicate the form(s) of strain that raise the relative energy of the less stable one. (Hint: Puckered cyclobutane has axial and equatorial positions similar to those in chair cyclohexane.)

(a) Methycyclobutane  
(b) cis-1,2-Dimethycyclobutane  
(c) trans-1,2-Dimethycyclobutane  
(d) cis-1,3-Dimethycyclobutane  
(e) trans-1,3-Dimethycyclobutane

Which is more stable: cis- or trans-1,2-dimethycyclobutane; cis- or trans-1,3-dimethycyclobutane?

30. For each of the following cyclohexane derivatives, indicate (i) whether the molecule is a cis or trans isomer and (ii) whether it is in its most stable conformation. If your answer to (ii) is no, flip the ring and draw its most stable conformation.

(a)  
(b)  
(c)  
(d)  
(e)  
(f)  
(g)  
(h)  
(i)  
(j)  

31. Using the data in Table 4-3, calculate the $\Delta G^\circ$ for ring flip to the other conformation of the molecules depicted in Problem 30. Make sure that the sign (i.e., positive or negative) of your values is correct.

32. Draw the most stable conformation for each of the following substituted cyclohexanes; then, in each case, flip the ring and redraw the molecule in the higher energy chair conformation:

(a) cyclohexanol; (b) trans-3-methylcyclohexanol (see structures in the margin); (c) cis-1-methyl-3-(1-methylethyl)cyclohexane; (d) trans-1-ethyl-3-methoxycyclohexane (see structure in the margin); (e) trans-1-chloro-4-(1,1-dimethylethyl) cyclohexane.

33. For each molecule in Problem 32, estimate the energy difference between the most stable and next best conformation. Calculate the approximate ratio of the two at 300 K.

34. Sketch a potential-energy diagram (similar to that in Figure 4-9) for methylcyclohexane showing the two possible chair conformations at the left and right ends of the reaction coordinate for conformational interconversion.

35. Draw all the possible all-chair conformers of cyclohexylcyclohexane.

36. What is the most stable of the four boat conformations of methylcyclohexane, and why?

37. The most stable conformation of trans-1,3-bis(1,1-dimethylethyl)cyclohexane is not a chair. What conformation would you predict for this molecule? Explain.

38. The bicyclic hydrocarbon formed by the fusion of a cyclohexane ring with a cyclopentane ring is known as hexahydroindane (in margin). Using the drawings of trans- and cis-decalin for reference (Figure 4-13), draw the structures of trans- and cis-hexahydroindane, showing each ring in its most stable conformation.

39. On viewing the drawings of cis- and trans-decalin in Figure 4-13, which do you think is the more stable isomer? Estimate the energy difference between the two isomers.

40. Several tricyclic compounds exist in nature with a cyclopropane ring fused to a cis-decalin structure, as shown in the molecule tricyclo[5.4.0$^{12-0}$]jundecane (margin). In various countries, some of these substances have a history of use as folk medicines for purposes such as contraception. Make a model of this compound. How does the cyclopropane ring affect the conformations of the two cyclohexane rings? The cyclohexane rings in cis-decalin itself are
Cycloalkanes

capable of (simultaneous) chair–chair interconversion (recall Exercise 4-13). Is the same true in tricyclo[5.4.0.0^1,3.0^1,7]undecane?

41. The naturally occurring sugar glucose (Chapter 24) exists in the two isomeric cyclic forms shown below. These are called α and β, respectively, and they are in equilibrium by means of chemical processes that are introduced in Chapter 17.

(a) Which of the two forms is more stable?
(b) At equilibrium the two forms are present in a ratio of approximately 64:36. Calculate the free energy difference that corresponds to this equilibrium ratio. How closely does the value you obtained correlate with the data in Table 4-3?

42. Identify each of the following molecules as a monoterpane, a sesquiterpene, or a diterpene (all names are common).

(a) H₃C
   H₂C
   CH₃ CH₂OH Geraniol

(b) \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{CH₂CH₂} \)
    \( \text{O} \)
    \( \text{CO} \)
    \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{Eremothin} \)

(c) \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{CH₂H₃} \)
    \( \text{OH} \)
    \( \text{Eudesmol} \)

(d) \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{Ipomeamarone} \)

(e) \( \text{CH₃} \)
    \( \text{O} \)
    \( \text{COCH₃} \)
    \( \text{HOCH₂} \)
    \( \text{Genipin} \)

(f) \( \text{HOCH₂} \)
    \( \text{Castoramine} \)

(g) \( \text{CH₃} \)
    \( \text{C} \)
    \( \text{C} \)
    \( \text{C} \)
    \( \text{C} \)
    \( \text{C} \)
    \( \text{C} \)
    \( \text{Cantharidin} \)

(h) \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{CH₃} \)
    \( \text{Vitamin A} \)

43. Circle and identify by name each functional group in the structures pictured in Problem 42.

44. Find the 2-methyl-1,3-butadiene (isoprene) units in each of the naturally occurring organic molecules pictured in Problem 42.

45. Circle and identify by name all the functional groups in any three of the steroids illustrated in Section 4-7. Label any polarized bonds with partial positive and negative charges (δ⁺ and δ⁻).
46. Several additional examples of naturally occurring molecules with strained ring structures are shown here.

![Chemical structures]

Identify the terpenes (if any) in the preceding group of structures. Find the 2-methyl-1,3-butadiene units in each structure and classify the latter as a mono-, sesqui-, or diterpene.

47. **Challange** If cyclobutane were flat, it would have exactly 90° C–C–C bond angles and could conceivably use pure $p$ orbitals in its C–C bonds. What would be a possible hybridization for the carbon atoms of the molecule that would allow all the C–H bonds to be equivalent? Exactly where would the hydrogens on each carbon be located? What are the real structural features of the cyclobutane molecule that contradict this hypothesis?

48. Compare the structure of cyclodecane in an all-chair conformation with that of trans-decalin. Explain why all-chair cyclodecane is highly strained, and yet trans-decalin is nearly strain free. Make models.

![Chemical structures]

49. Fusidic acid is a steroidalike microbial product that is an extremely potent antibiotic with a broad spectrum of biological activity. Its molecular shape is most unusual and has supplied important clues to researchers investigating the methods by which steroids are synthesized in nature.

![Chemical structure]

(a) Locate all the rings in fusidic acid and describe their conformations.
(b) Identify all ring fusions in the molecule as having either cis or trans geometry.
(c) Identify all groups attached to the rings as being either $a$- or $b$-substituents.
(d) Describe in detail how this molecule differs from the typical steroid in structure and stereochemistry. (As an aid to answering these questions, the carbon atoms of the framework of the molecule have been numbered.)

50. The enzymatic oxidation of alkanes to produce alcohols is a simplified version of the reactions that produce the adrenocortical steroid hormones. In the biosynthesis of corticosterone from progesterone (Section 4-7), two such oxidations take place successively ($a$, $b$). It is thought that the monooxygenase enzymes act as complex oxygen-atom donors in these reactions.
A suggested mechanism, as applied to cyclohexane, consists of the two steps shown below the biosynthesis.

\[
\begin{align*}
\text{Progesterone} & \xrightarrow{\text{Steroid monoxygenases, } \text{O}} \text{Corticosterone} \\
\text{Iodobenzene dichloride} & \rightarrow \\
\end{align*}
\]

Calculate $\Delta H^\circ$ for each step and for the overall oxidation reaction of cyclohexane. Use the following $DH^\circ$ values: cyclohexane C–H bond, 98.5 kcal mol$^{-1}$; bond in O–H radical, 102.5 kcal mol$^{-1}$; cyclohexanol C–O bond, 96 kcal mol$^{-1}$.

51. **Challenge** Iodobenzene dichloride, formed by the reaction of iodobenzene and chlorine, is a reagent for the chlorination of alkane C–H bonds. Chlorinations in which iodobenzene dichloride is used are initiated by light.

(a) Propose a radical chain mechanism for the chlorination of a typical alkane RH by iodobenzene dichloride. To get you started, the overall equation for the reaction is given below, as is the initiation step.

\[
\text{RH} + \text{I} + \text{Cl}_2 \rightarrow \text{RCl} + \text{HCl} + \text{I}
\]

Initiation:

\[
\text{I} + \text{Cl}_2 \xrightarrow{hv} \text{I}\cdot + \text{Cl}\cdot
\]

(b) Radical chlorination of typical steroids by iodobenzene dichloride gives, predominantly, three isomeric monochlorination products. On the basis of both reactivity (tertiary, secondary, primary) considerations and steric effects (which might hinder the approach of a reagent toward a C–H bond that might otherwise be reactive), predict the three major sites of chlorination in the steroid molecule. Either make a model or carefully analyze the drawings of the steroid nucleus in Section 4-7.

52. **Challenge** As Problem 50 indicates, the enzymatic reactions that introduce functional groups into the steroid nucleus in nature are highly selective, unlike the laboratory chlorination described in Problem 51. However, by means of a clever adaptation of this reaction, it is