

## 1

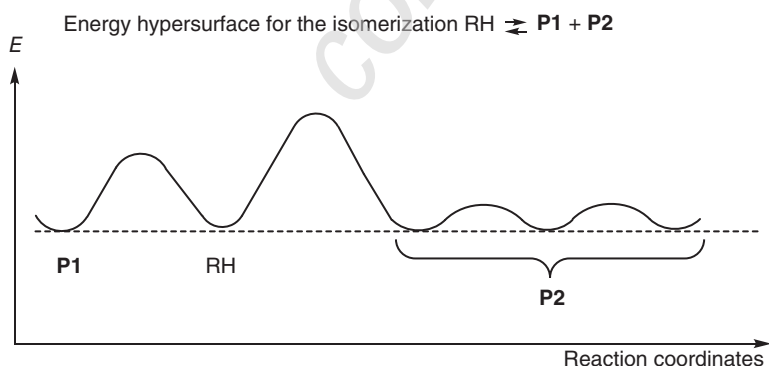
## Equilibria and Thermochemistry

## Answers to Problems

**Problem 1.1** A hydrocarbon, RH, can be isomerized in reversible reactions into two isomeric compounds **P1** and **P2** with the same heat of reaction. Both have  $C_1$  symmetry. **P1** is a rigid molecule, and **P2** is a flexible one adopting several conformations of similar stability. Which product will be preferred at equilibrium?

## Answer

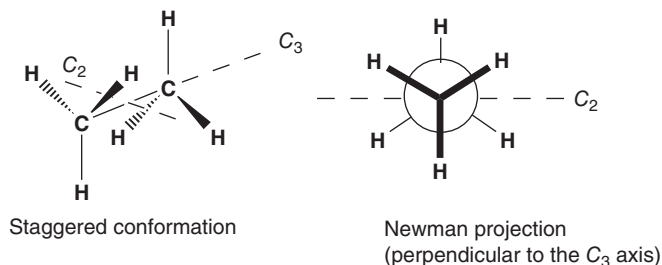
Products **P1** and **P2** equilibrate with RH in reversible reactions at temperature  $T$ . The preferred product will be that for which the free energy of reaction  $\Delta_r G^T(\text{reactants} \rightleftharpoons \text{product } \mathbf{P1} \text{ or } \mathbf{P2}) = \Delta_r H^T - T\Delta_r S^T$  is the smallest. If  $\Delta_r H^T(\text{RH} \rightleftharpoons \mathbf{P1}) = \Delta_r H^T(\text{RH} \rightleftharpoons \mathbf{P2})$ , the product with the largest entropy ( $S^T(\mathbf{P1})$ ,  $S^T(\mathbf{P2})$ ), will be favored at equilibrium at temperature  $T$ . Entropy expresses the degree of freedom available to an ensemble of molecules of a given compound. It depends upon the number of different microscopic states available to these molecules, and this depends on the size of the molecules themselves (**P1** and **P2** have the same molecular weight as they are isomers of the starting material RH), and the energy separation between the microscopic states available to them. The microscopic states that contribute most to the entropy are translational and rotational states for which the energy separation between quantum levels are the smallest. A rigid molecule is a molecule that does not equilibrate with several conformers of similar stabilities. It has only one energy minimum along all the coordinates that describe its geometrical deformations, including torsion about its  $\sigma$ - and  $\pi$ -bonds and bond elongation. A flexible molecule evolves at temperature  $T$  among several energy minima. In other words, several energy minima are populated significantly at the given temperature  $T$ . This is the case for **P2**, not for **P1**. If those energy minima correspond to different geometries (no rotation symmetry axis,  $\sigma = 1$ ) the flexible molecule has a larger entropy than the rigid molecule; thus  $S^T(\mathbf{P2}) > S^T(\mathbf{P1})$ , and  $\Delta_r G^T(\text{RH} \rightleftharpoons \mathbf{P2}) < \Delta_r G^T(\text{RH} \rightleftharpoons \mathbf{P1})$ . Product **P2** that is composed of flexible molecules will be formed to a larger extent than product **P1** composed of rigid molecules at temperature  $T$ .



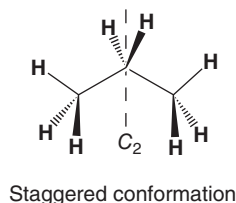
**Problem 1.2** Define the symmetry numbers,  $\sigma$ , of ethane, propane, cyclopropane, cyclobutane, cyclohexanone, ferrocene, bicyclo[2.2.1]hepta-2,5-diene (norbornadiene), 1,4-difluorobenzene, *meso*-tartaric acid, and (*R,R*)-tartaric acid (see Figure 1.24 for the structure of the two latter compounds).

**Answer**

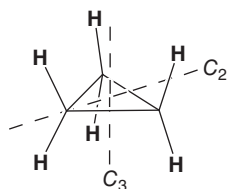
Ethane is a flexible molecule that adopts a preferred staggered conformation (c.  $3 \text{ kcal mol}^{-1}$  more stable than the eclipsed conformation (Section 2.5.1), transition state of the rotation about its  $\sigma(\text{C}-\text{C})$  bond). Ethane has a  $C_3$ - and three  $C_2$ -axes that are interconverted by rotation about the  $C_3$ -axis. Thus, the symmetry number  $\sigma = 3 \times 2 = 6$ .



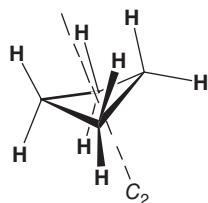
Propane is a flexible molecule for which the doubly staggered conformation is the most stable one ( $C_{2v}$  symmetry: one mirror plane of symmetry containing a  $C_2$ -axis of rotation) has one  $C_2$ -axis of rotation. Thus, the symmetry number  $\sigma = 2$ .



Cyclopropane is a rigid molecule ( $D_{3h}$  symmetry) with a  $C_3$ - and three  $C_2$ -axes of rotation. Rotation about the  $C_3$  axis interconverts the  $C_2$ -axis. Thus, the symmetry number  $\sigma = 3 \times 2 = 6$ .



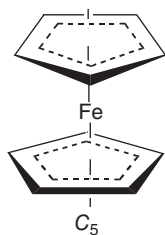
Cyclobutane adopts a puckered conformation (envelope,  $C_{2v}$  symmetry) with one  $C_2$ -axis of rotation. Thus, its symmetry number  $\sigma = 2$ . The planar conformation ( $D_{4h}$  symmetry) is much less stable (Section 2.6.1).



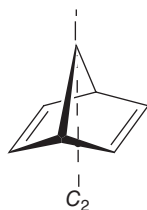
Cyclohexanone adopts a chair conformation (Section 2.6.4) of  $C_s$  symmetry (one mirror plane of symmetry), no rotation axis. Thus, the symmetry number  $\sigma = 1$ .



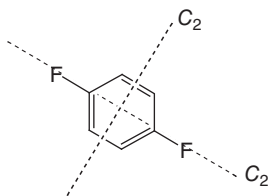
Ferrocene has a  $C_5$ - and five  $C_2$ -axes of rotation. The  $C_2$ -axes are interconverted by rotation about the  $C_5$ -axis. Thus, the symmetry number  $\sigma = 5 \times 2 = 10$ .



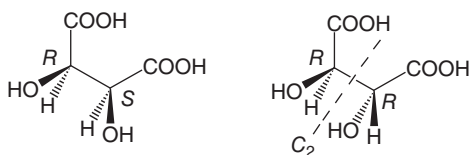
Bicyclo[2.2.1]hepta-2,5-diene (norbornadiene) is  $C_{2v}$  symmetrical (one mirror plane containing a  $C_2$ -axis of rotation). Thus, the symmetry number  $\sigma = 2$ .



1,4-Difluorobenzene has two non-interconvertible  $C_2$ -axis of rotation. Thus, the symmetry number  $\sigma = 2 \times 2 = 4$ .



*Meso*-tartaric acid is (*R,S*)-tartaric acid with a mirror plane of symmetry. It does not have any axis of rotation, and thus  $\sigma = 1.0$ . (*R,R*)-Tartaric acid has a  $C_2$ -axis, and thus  $\sigma = 2$ .



**Problem 1.3** Enantiomerically pure  $\alpha$ -amino acids such as alanine (with one stereogenic center) are isomerized into their racemic mixtures. What is the Gibbs energy of this reaction at 25 °C?

### Answer

Enantiomers are stereoisomers that have the same stability and the same properties except for their optical rotation (opposite  $[\alpha]$  values at any wavelength) and chiroptical properties (opposite Cotton effect in their circular dichroism spectra). Enantiomers cannot have a mirror plane of symmetry. They might have  $C_1$ -symmetry (no element of symmetry) like alanine, or have a rotation axis of symmetry like (*R,R*)-tartaric acid. The two enantiomers have the same enthalpy of formation and the same entropy. Thus,

$\Delta_r G^T((R)\text{-enantiomer}) \rightleftharpoons (S)\text{-enantiomer} = \Delta_r H^T((S)\text{-enantiomer}) - \Delta_r H^T((R)\text{-enantiomer}) - T\Delta_r S^T((S)\text{-enantiomer}) + T\Delta_r S^T((R)\text{-enantiomer}) = 0$ . Thus,  $RT \ln K = 0$ . At equilibrium,  $K = [(S)\text{-enantiomer}]/[(R)\text{-enantiomer}] = 1$ .

**Problem 1.4** What products do you expect to be formed combining HO<sup>•</sup> with organic compounds? What happens to NO in the air, to SO<sub>2</sub> in the air?

**Answer**

- Water is the most stable oxide of hydrogen. Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and the radicals hydroxyl (HO<sup>•</sup>) and hydroperoxyl (HOO<sup>•</sup>) are expected to be reactive compounds that tend to form water on combining them with organic and inorganic compounds containing hydrogen atoms.
- The most stable oxidized form of nitrogen is NO<sub>2</sub>, and this is the brown gas of air pollution. Nitric oxide (NO) is an important diatomic molecule that regulates many biological functions, such as blood pressure and erectility. It is produced from arginine by NO synthase in mammals. The drug Viagra inhibits an enzyme that normally reverses the action produced by NO. Within seconds of its formation in air, colorless NO undergoes oxidation to brown NO<sub>2</sub>, and then to nitrite and nitrate (2NO<sub>2</sub> + H<sub>2</sub>O ⇌ HNO<sub>2</sub> + HNO<sub>3</sub>).
- Sulfur trioxide (SO<sub>3</sub>) is the most stable oxidized form of sulfur. Burning sulfur does not produce SO<sub>3</sub> but SO<sub>2</sub>, a major air pollutant. The oxidation of SO<sub>2</sub> by air into SO<sub>3</sub> requires special catalysts used in industrial sulfuric acid production. Sulfate from hydrolysis of SO<sub>3</sub> (SO<sub>3</sub> + H<sub>2</sub>O ⇌ H<sub>2</sub>SO<sub>4</sub>) is involved in air pollution and acid rain, as sulfuric acid.

**Problem 1.5** Propose a reaction for diimide (HN=NH) + cyclohexene and calculate its heat of reaction.

**Answer**

(Z)- and (E)-Diimide (HN=NH) are metastable combinations of nitrogen and hydrogen. They are sources of dihydrogen (Garbisch alkene hydrogenation, dyotropic transfer of dihydrogen, Section 5.6.2) liberating N<sub>2</sub>.  $\Delta_f H^\circ = \Delta_f H^\circ(\text{N}_2) + \Delta_f H^\circ(\text{cyclohexane}) - \Delta_f H^\circ((Z)\text{-diimide}) - \Delta_f H^\circ(\text{cyclohexene}) = 0 - 29.5 - 50.9 + 1.03 = -79.4 \text{ kcal mol}^{-1}$ .

**Problem 1.6** Among the amino acids serine and cysteine, which of these gives stable adducts with cyclohex-2-enone at 37 °C when they are part of a protein?

**Answer**

Serine (HOCH<sub>2</sub>CH(NH<sub>2</sub>)COOH) incorporated in a protein has a primary alcohol function. Its addition to an alkene is not exothermic enough to lead to a stable adduct with cyclohexenone at 37 °C as indicated with the model equilibrium:

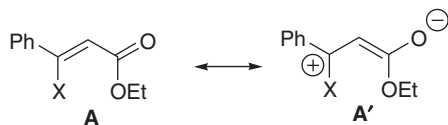
$\Delta_r H^\circ(\text{EtOH} + \text{CH}_2=\text{CH}_2 \rightleftharpoons \text{EtOEt}) = -51.7 - (-56.0) - 12.5 = -8.2 \text{ kcal mol}^{-1}$ . The heat of reaction cannot compensate for the entropy of condensation  $-T\Delta_r S^{310\text{K}} > 10 \text{ kcal mol}^{-1}$ .

Cysteine is like serine but with a thiol function instead of a primary alcohol function for which a much higher heat of reaction is estimated for its addition to an alkene as shown with  $\Delta_r H^\circ(\text{EtSH} + \text{CH}_2=\text{CH}_2 \rightleftharpoons \text{EtSEt}) = -19.9 - (-11.0) - 12.5 = -21.4 \text{ kcal mol}^{-1}$ . Thus cysteine, not serine, incorporated in a protein will equilibrate with an adduct resulting from the conjugate addition of its thiol unit to cyclohex-2-enone.

**Problem 1.7** Explain the difference in C=O bond stretching frequencies ( $\nu_{\text{C=O}}$ ) between ethyl (Z)-3-fluorocinnamate (1736 cm<sup>-1</sup>) and ethyl cinnamate ((E)-PhCH=CHCOOEt: 1715 cm<sup>-1</sup>) [1].

**Answer**

The stretching frequency  $\nu_{\text{C=O}}$  is proportional to the C=O bond strength. The latter depends on conjugation. Compared with saturated esters ( $\nu_{\text{C=O}}$ : 1750–1735 cm<sup>-1</sup>),  $\alpha,\beta$ -unsaturated esters have smaller  $\nu_{\text{C=O}}$  (1730–1715 cm<sup>-1</sup>) due to C=O bond elongation and weakening resulting from the  $\pi$ -conjugation.



On substituting a  $\alpha,\beta$ -unsaturated ester by a  $\beta$ -fluoro group, one destabilizes the zwitterionic limiting structure A' because of the strong dipole realized by the C—F bond. Retrodonation  $n(\text{F})/\pi^*(\text{C}=\text{C})$  is inexistent since

the amount of positive charge appearing at the  $\beta$ -center remains relatively weak (see electrostatic model of substituent effects on the stability of charged species). Thus the C=O bond in ethyl (*Z*)-3-fluorocinnamate (**A**, X = F,  $\nu_{\text{C=O}}$ : 1726  $\text{cm}^{-1}$ ) is stronger than the C=O bond in (*E*)-cinnamate (**A**, X = H,  $\nu_{\text{C=O}}$ : 1715  $\text{cm}^{-1}$ ) [1].

**Problem 1.8** Estimate the standard heat of the esterification of ethanol with acetic acid. Estimate the variation of entropy of this reaction at 298.15 K and calculate the equilibrium constant at the same temperature and under one atmosphere, in tetrahydrofuran (THF) solution. Is the equilibrium constant the same under the same conditions for the esterification of anthracene-2-carboxylic acid with 2-hydroxyanthracene?

### Answer

$\Delta_r H^\circ(\text{EtOH} + \text{MeCOOH} \rightleftharpoons \text{MeCOOEt} + \text{H}_2\text{O}) = -106.5(\pm 0.2) - 57.8(\pm 0.01) - (-56.0)(\pm 0.5) - (-103.5)(\pm 0.6) = -4.8 \pm 1.3 \text{ kcal mol}^{-1}$  (Table 1.A.4).

$\Delta_r S^\circ(\text{EtOH} + \text{MeCOOH} \rightleftharpoons \text{MeCOOEt} + \text{H}_2\text{O}) = 86.7 + 45.1 - 67.6 - 66.7 = -2.5 \text{ eu}$ . One thus obtains  $\Delta_r G^\circ(\text{EtOH} + \text{MeCOOH} \rightleftharpoons \text{MeCOOEt} + \text{H}_2\text{O}) = -4.8 - 298(0.0025) \approx -4.0 \text{ kcal mol}^{-1}$ , giving  $K = \exp(-\Delta_r G^\circ/RT) = \exp.(4000/1.987 \times 298) = 858$  at 25 °C for an ideal solution.

If one considers only the entropy of translation and Eq. (1.31) for the calculation of the entropy of monoatomic molecules,

$$S_{\text{trans}} = 6.86 \log M_r(\text{g}) + 11.44 \log T - 2.31 \text{ eu}$$

$\Delta_r S_{\text{trans}}^\circ(\text{EtOH} + \text{MeCOOH} \rightleftharpoons \text{MeCOOEt} + \text{H}_2\text{O}) = 6.86 \log[M_r(\text{MeCOOEt}) \cdot M_r(\text{H}_2\text{O})/M_r(\text{EtOH}) \cdot M_r(\text{AcOH})] = 6.86 \log[88.1 \times 18/46.07 \times 60.05] = 6.86 \log(0.5732145) = -1.65 \text{ eu}$  is not nil because two molecules of similar size are equilibrated with a larger molecule and a smaller one ( $\text{H}_2\text{O}$ ). Water molecule has a  $C_2$ -axis of symmetry, its symmetry number  $\sigma = 2$ . The other molecules intervening in this equilibrium have  $\sigma = 1$ . The same molecular groups and freely rotating bonds are present in reactants and products. If one consider the loss of rotational entropy by forming  $\text{H}_2\text{O}$ , a correction of  $-R \ln 2 = -1.987(0.693) = -1.37 \text{ eu}$  has to be considered. On this basis, the calculated  $\Delta_r S_{\text{trans+rot}}^\circ(\text{EtOH} + \text{MeCOOH} \rightleftharpoons \text{MeCOOEt} + \text{H}_2\text{O}) = -1.65 - 1.37 \approx -3 \text{ eu}$ , a value very close to the value of  $-2.5 \text{ eu}$  estimated from the experimental entropies given for these compounds.

Experimental standard heats of formation and entropies of anthracene-2-yl anthracene-2-carboxylate ( $M_r = 398.463$ ), of anthracene-2 carboxylic acid ( $M_r = 222.245$ ), and of 2-hydroxyanthracene ( $M_r = 194.234$ ) are not available. If one considers the model reaction  $\text{PhCOOH} + \text{MeOH} \rightleftharpoons \text{PhCOOMe} + \text{H}_2\text{O}$  for which  $\Delta_r H^\circ(\text{PhCOOH} + \text{MeOH} \rightleftharpoons \text{PhCOOMe} + \text{H}_2\text{O}) = -64.4 - 57.8 - (-70.3) - (-49) = -2.9 \text{ kcal mol}^{-1}$  is estimated (Table 1.A.4), one can predict that the exothermicity of the esterification of the anthracene derivatives should be less than of the formation of ethyl acetate because of steric effect. For the contribution of the entropy of translation to the equilibrium that converts anthracene-2 carboxylic acid and 2-hydroxyanthracene into the corresponding ester + water one estimates it to be more negative than in the case of the formation of ethyl acetate as given by

$\Delta_r S_{\text{trans}}^\circ(2\text{-anthracenol} + 2\text{-anthracenecarboxylic acid} \rightleftharpoons \text{anthracen-2-yl anthracene-2-carboxylate} + \text{H}_2\text{O}) = 6.86 \log[M_r(\text{C}_{14}\text{H}_9\text{COOC}_{14}\text{H}_9) \cdot M_r(\text{H}_2\text{O})/M_r(\text{C}_{14}\text{H}_9\text{OH}) \cdot M_r(\text{C}_{14}\text{H}_9\text{COOH})] = 6.86 \log[398.5 \times 18.02/194.2 \times 222.2] = 6.86 \log(0.166414) = -5.34 \text{ eu}$ . If one now considers the loss of rotational entropy due to the formation of water, one estimates

$\Delta_r S_{\text{trans+rot}}^\circ(2\text{-anthracenol} + 2\text{-anthracenecarboxylic acid} \rightleftharpoons \text{anthracen-2-yl anthracene-2-carboxylate} + \text{H}_2\text{O}) = -5.34 - 1.37 = -6.7 \text{ eu}$ .

The free enthalpy for this equilibrium at 25 °C is estimated to be  $\Delta_r G^\circ(2\text{-anthracenol} + 2\text{-anthracenecarboxylic acid} \rightleftharpoons \text{anthracen-2-yl anthracene-2-carboxylate} + \text{H}_2\text{O}) = -2.9 - 298(-0.0067) = -2.9 + 1.99 \approx -0.9 \text{ kcal mol}^{-1}$

From what precedes we can predict that  $K(2\text{-anthracenol} + 2\text{-anthracenecarboxylic acid} \rightleftharpoons \text{anthracen-2-yl anthracene-2-carboxylate} + \text{H}_2\text{O}) < K(\text{EtOH} + \text{AcOH} \rightleftharpoons \text{AcOEt} + \text{H}_2\text{O})$ .

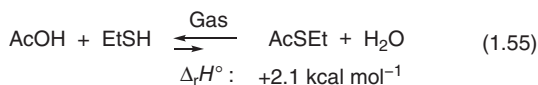
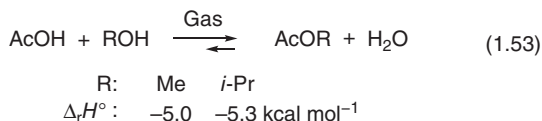
At 298 K and under one atmosphere for ideal solution in THF  $K(2\text{-anthracenol} + 2\text{-anthracenecarboxylic acid} \rightleftharpoons \text{anthracen-2-yl anthracene-2-carboxylate} + \text{H}_2\text{O}) = \exp.(900/1.987 \times 298) = 4.6$ .

**Problem 1.9** The Newman–Kwart rearrangement is a valuable synthetic technique for converting phenols to thiophenols via their *O*- and *S*-thiocarbamates [2–4].

Explain why the *S*-thiocarbamates are more stable than their isomeric *O*-thionocarbamates.

**Answer**

In the equilibrium  $\text{Ar}-\text{O}-(\text{C}=\text{S})-\text{X} \rightleftharpoons \text{Ar}-\text{S}-(\text{C}=\text{O})-\text{X}$ , one exchanges a thionoester moiety into a thioester function. Since carbon and sulfur have similar electronegativities (Table 1.A.5) the  $\text{C}=\text{S}$  double bond is not as polar as the  $\text{C}=\text{O}$  double bond. According to the Pauling theory, the  $\text{C}=\text{S}$  bond is weaker than the  $\text{C}=\text{O}$  bond. The  $\text{C}=\text{S}$  bond is longer than the  $\text{C}=\text{O}$  bond, which contributes also to make it weaker. For that reason  $\text{Ar}-\text{S}-(\text{C}=\text{O})-\text{X}$  must be more stable than  $\text{Ar}-\text{O}-(\text{C}=\text{S})-\text{X}$ . Furthermore, part of the stability of an ester arises from the  $n(\text{O})/\pi(\text{C}=\text{O})$  conjugation ( $\text{ArO}-\text{C}=\text{O} \leftrightarrow \text{ArO}^{(+)}=\text{C}-\text{O}^{(-)}$ ) and  $n(\text{C}=\text{O})/\sigma(\text{O})$  hyperconjugation ( $\text{Ar}-\text{O}-\text{C}=\text{O} \leftrightarrow \text{Ar}-\text{O}^{(-)} + \text{C}^{(+)}=\text{O} \leftrightarrow \text{Ar}-\text{O}^{(-)} + \text{C} \equiv \text{O}^{(+)}$ ). In thioester the  $n(\text{S})/\pi(\text{C}=\text{O})$  conjugation and  $n(\text{C}=\text{O})/\sigma(\text{S})$  hyperconjugation intervene also but to a smaller extent than in ester as shown by the heat of the following reactions:



**Problem 1.10** A mixture of 1 mmol cyclohex-2-enone, 1 mmol of thiophenol, and 5 mg of  $\text{Et}_3\text{N}$  is kept at 25 °C in 1 ml of  $\text{CH}_2\text{Cl}_2$ . After 30 minutes at 25 °C, the  $^1\text{H}$ -NMR spectra of the reaction mixture shows that the corresponding 1,4-adduct is formed almost completely. Attempted purification of the adduct by column chromatography on silica gel gives, however, only a low yield of adduct (10–20%) and recovered cyclohex-2-enone (80%) and thiophenol (80%). Why?

**Answer**

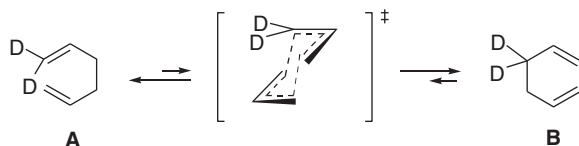
Thiol conjugate additions to conjugated enones are reversible in the presence of a base catalyst such as  $\text{Et}_3\text{N}$  at 25 °C. For a reaction using molar concentrations of thiophenol and cyclohex-2-enone the corresponding adduct (2-phenylthiocyclohexanone) forms to a large extent since the reaction has an exothermicity (c. -20 kcal mol<sup>-1</sup>, see Problem 1.6) able to compensate for the cost of the entropy (c. 10 kcal mol<sup>-1</sup>) of condensation at 25 °C. During the column chromatography on silica gel ( $\text{SiO}_2$ ), the thiol, enone, 1,4-adduct, and catalyst interact with the solid support, more or less strongly. The most polar compound makes the strongest bonding with silicagel and thus is retained the longest on the column. The least polar compound is the least retained on the column and elutes the fastest. If the rate of elimination from the adduct giving thiophenol + cyclohex-2-enone is as fast as or faster than the rate of elution, the enone, thiol, and adduct will elute separately. Silica gel is acidic and catalyzes also the conjugate addition and elimination. The basic catalyst ( $\text{Et}_3\text{N}$ ) remains on the column.

In order to avoid this type of problem due to the reversibility of the conjugate addition, one should extract the basic catalyst ( $\text{Et}_3\text{N}$ ) from the final reaction mixture, for instance, by adding to it and at low temperature (<0 °C) a minimum amount of acidic alumina or silica gel to absorb it and then run a quick filtration at low temperature. Purification by chromatography should then be carried out on a cooled (circulating cooled [ $<-40$  °C] ethanol in a double-walled column) column of silica gel. The extraction of  $\text{Et}_3\text{N}$  could also be done by extraction with a cooled (0 °C) diluted aqueous solution of  $\text{HCl}$ , and then washing with an aqueous solution of  $\text{NaHCO}_3$  (to remove traces of  $\text{HCl}$  from the  $\text{CH}_2\text{Cl}_2$  solution).  $\text{HCl}$  would catalyze the elimination from the adduct once the mixture is poured onto the chromatography column.

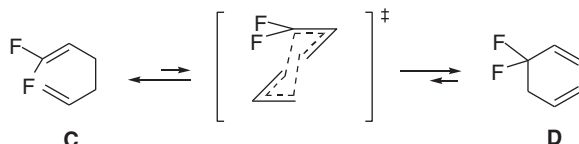
**Problem 1.11** On heating 1,1-dideuteriohexa-1,5-diene equilibrates with 3,3-dideuteriohexa-1,5-diene (reversible Cope rearrangement: Section 5.5.9.1). Similarly 1,1-difluorohexa-1,5-diene equilibrates with 3,3-difluorohexa-1,5-diene. Which of these two last isomeric compounds is most stable? [5]

**Answer**

At equilibrium, there is a slight preference for D at the  $sp^3$  center  $K = [B]/[A] \approx 1.1$ :

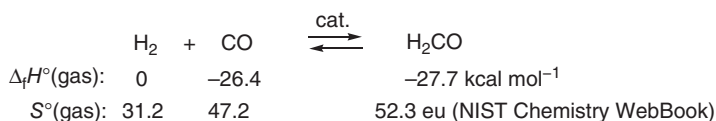


At equilibrium  $K = [D]/[C] \gg 1/1$ :

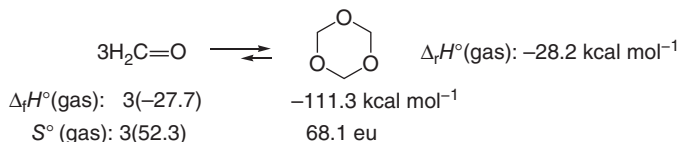


Compound **D** is more stable than **C** since geminal difluoro substitution prefers  $sp^3$ -hybridized carbon centers rather than  $sp^2$ -carbon centers.

**Problem 1.12** Is the hydrogenation of carbon monoxide into formaldehyde a feasible reaction provided that a suitable catalyst is available to catalyze this reaction?

**Answer**

This reaction is endergonic ( $\Delta_r G^\circ = \Delta_r H^\circ - T\Delta_r S^\circ$ ) since it has an exothermicity ( $\Delta_r H^\circ$ ) of only  $-1.3$  kcal mol<sup>-1</sup>, which is not enough to compensate for the cost of entropy of condensation ( $-T\Delta_r S^\circ = -298(-26.1) = 6.5$  kcal mol<sup>-1</sup>) at room temperature ( $T = 298$  K). Nevertheless, formaldehyde (methanal) may form in small amounts at equilibrium and then be trimerized into 1,3,5-trioxane (metaformaldehyde), a reaction that brings an exothermicity of  $-28.2$  kcal mol<sup>-1</sup> at  $25^\circ\text{C}$  and under one atmosphere. This is not enough to pay for the entropy cost of the hydrogenation of carbon monoxide (three times  $6.5$  kcal mol<sup>-1</sup>) and that of the trimerization of formaldehyde ( $298(88.8) = 26.4$  kcal mol<sup>-1</sup>). If one considers the overall process  $\Delta_r G^\circ(3CO + 3H_2 \rightleftharpoons 1,3,5\text{-trioxane}) = \Delta_r H^\circ(3CO + 3H_2 \rightleftharpoons 1,3,5\text{-trioxane}) - T\Delta_r S^\circ(3CO + 3H_2 \rightleftharpoons 1,3,5\text{-trioxane}) = -111.3 - 3(-26.4) - 298(52.3 - 3(31.2) - 3(47.2)) = -32.1 - 298(-157.6) = -32.1 + 46.9 = 14.8$  kcal mol<sup>-1</sup>, a highly endergonic process at  $25^\circ\text{C}$  and under one atmosphere. On lowering the temperature of the reaction, it becomes less endergonic. Increasing pressure will help shift the equilibrium in favor of 1,3,5-trioxane. In theory, and for an ideal solution, the equilibrium constant  $K(3CO + 3H_2 \rightleftharpoons 1,3,5\text{-trioxane})$  approaches unity ( $\Delta_r G^\circ = 0$ ) when  $T\Delta_r S^\circ = \Delta_r H^\circ$ . In this case, one estimates  $T = -32\,100/(-157.6) = 203.7$  K  $\approx -94^\circ\text{C}$ . As 1,3,5-trioxane is a solid, it could be eliminated from the reaction mixture by precipitation or crystallization (shifting of the equilibrium, Section 1.14.1). For such a process to be possible, one would have to find a suitable catalyst allowing one to run the condensation at low temperature and high pressure.



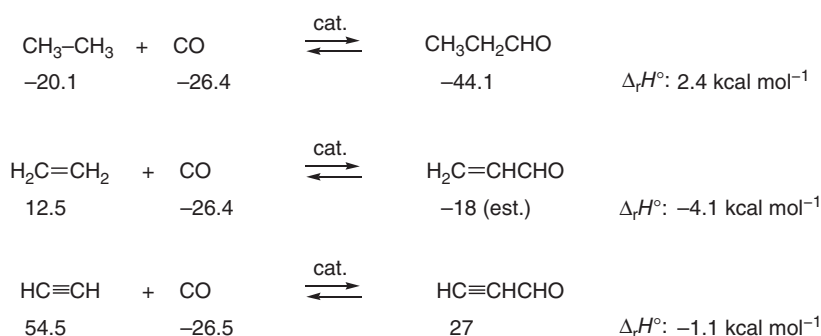
Formaldehyde is produced in the industry by catalyzed oxidation of methanol ( $2\text{MeOH} + \text{O}_2 \rightleftharpoons 2\text{H}_2\text{CO} + 2\text{H}_2\text{O}$ ). In the “former process” the reaction occurs between  $250$  and  $400^\circ\text{C}$  and uses a solid catalyst made of iron oxide combined with molybdenum or/and vanadium oxides.



Hydrogenation of carbon monoxide is used to produce methanol in the industry. Under one atmosphere the overall reaction  $\text{CO} + 2\text{H}_2 \rightleftharpoons \text{MeOH}$  has an exothermicity of  $-22.6 \text{ kcal mol}^{-1}$ . Several catalysts have been developed for this reaction, which is run under high pressure and temperatures above  $200^\circ\text{C}$  [6]. Under one atmosphere and at  $200^\circ\text{C}$  the entropy cost ( $-T\Delta_r S^\circ(\text{CO} + 2\text{H}_2 \rightleftharpoons \text{MeOH}) = -473(54 - 47.2 - 2(31.2)) = 26.3 \text{ kcal mol}^{-1}$ ; it is not compensated by the exothermicity of the reaction. Nevertheless, pressure insures the formation of methanol. For instance, under 100 bars the reaction occurs between  $275$  and  $325^\circ\text{C}$  in the presence of Pt/Co/SiO<sub>2</sub> catalysts [7].

**Problem 1.13** Are the hydrocarbations of carbon monoxide by alkanes, alkenes, or alkynes (or carbonylations of alkanes, alkenes, and alkynes) possible reactions provided suitable catalysts are available?

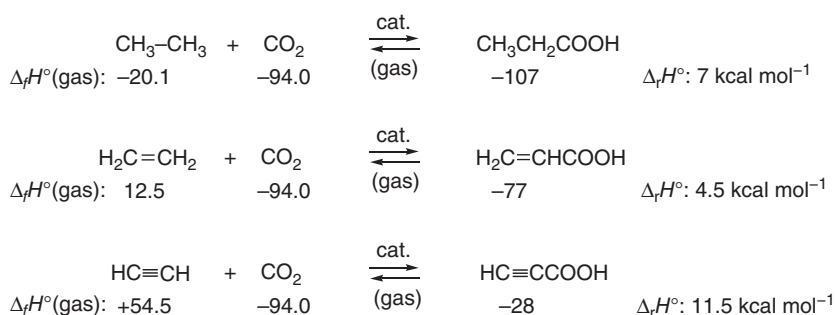
**Answer**



None of these reactions would be exergonic at room temperature (condensations with an entropy cost  $-T\Delta_r S$  of  $7\text{--}10 \text{ kcal mol}^{-1}$ ). However, in the case of the formation of unsaturated compounds their polymerizations are exothermic enough ( $< -20 \text{ kcal mol}^{-1}$ ; see Problem 1.14) to pay for the entropy cost and thus displace the reaction in the sense of polycondensations.

**Problem 1.14** Are the hydrocarbations of carbon dioxide possible for alkanes, alkenes, and alkynes provided suitable catalysts are available to catalyze them?

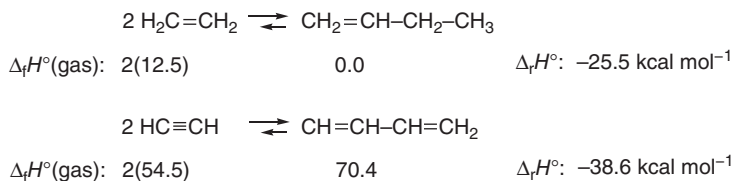
**Answer**



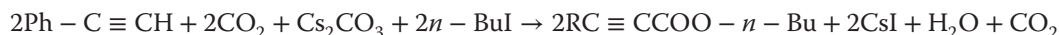
The three reactions are endothermic and they all have negative entropies, being condensations. Based on their heat of reaction they are more difficult than the corresponding carbonylation (Problem 1.13). They are impossible at room temperature and under 1 atm. Under low temperature and high pressure the second reaction (formation



of acrylic acid) might become feasible if a suitable catalyst is available. If the unsaturated carboxylic acids that form in the second and third reaction would undergo polymerization the polycondensation might occur since each new C—C bond generated is accompanied by a substantial exothermicity (better than  $20 \text{ kcal mol}^{-1}$ ) that can compensate for the endothermicity of the hydrocarbations of  $\text{CO}_2$  and the entropy cost ( $-T\Delta_r S$ ) of the latter reactions and of the polymerization reactions.



One way to make the C—H carboxylation working is to quench the initial carboxylic product ( $\text{RCOOH}$ ) in an exothermic reaction such as neutralization with a base to form the corresponding carboxylate salt ( $\text{RCOOH} + \text{B} \rightleftharpoons \text{RCOO}^- \text{BH}^+$ ). An example is given below with the  $\text{CuI}/\text{Ph}_3\text{P}$ -catalyzed carboxylation of phenylacetylene at  $80^\circ\text{C}$  under one atmosphere (solvent: ethylene carbonate) and which converts the carboxylate salt into its *n*-butyl ester (overall yield: 99%). The base used is  $\text{Cs}_2\text{CO}_3$  [8].

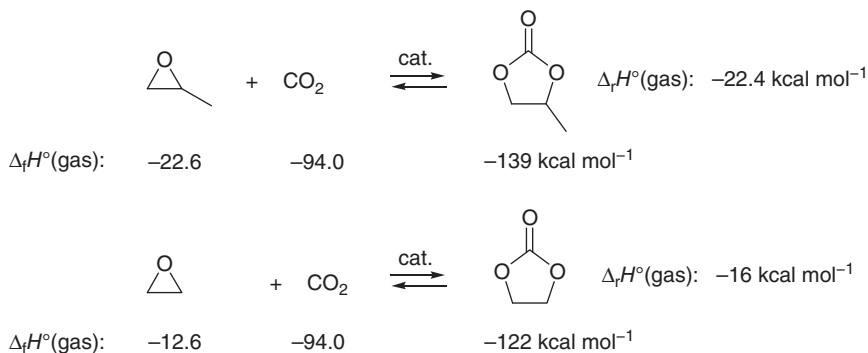


Another way to have the carboxylation of alkenes and acetylenes working is to couple them with the hydrogenation of the  $\alpha,\beta$ -unsaturated carboxylic that forms initially [9].

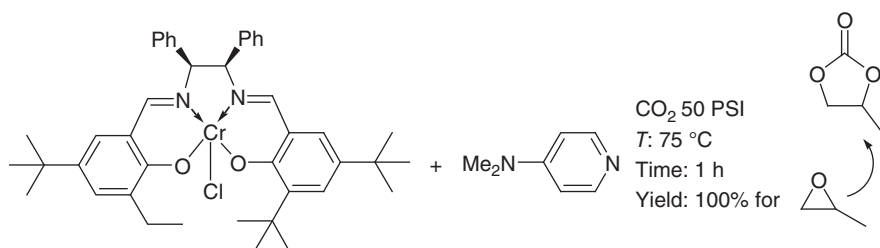
**Problem 1.15** Can one fix  $\text{CO}_2$  with epoxides? What products are expected (catalysts: mixed Mg/Al oxides, dimethylformamide [DMF] as solvent) to be formed at  $100^\circ\text{C}$ ?

### Answer

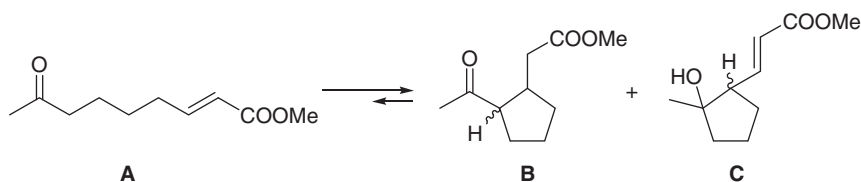
The thermochemical data shows that the condensations of  $\text{CO}_2$  with methyl oxirane and oxirane can occur at  $100^\circ\text{C}$ . Assuming an entropy of condensation of  $-40 \text{ eu}$ , the entropy cost of these reactions at  $100^\circ\text{C}$  amounts to  $-T\Delta^\ddagger S = 373(-40 \text{ eu}) \approx 15 \text{ kcal mol}^{-1}$ . Depending on the reaction conditions the vinylidene carbonates obtained can be polymerized into polycarbonates [10].



An example of catalyst for the carboxylation of methyloxirane is the  $\text{Cr(III)salen}$  complex represented below associated with 4-dimethylaminopyridine [11].

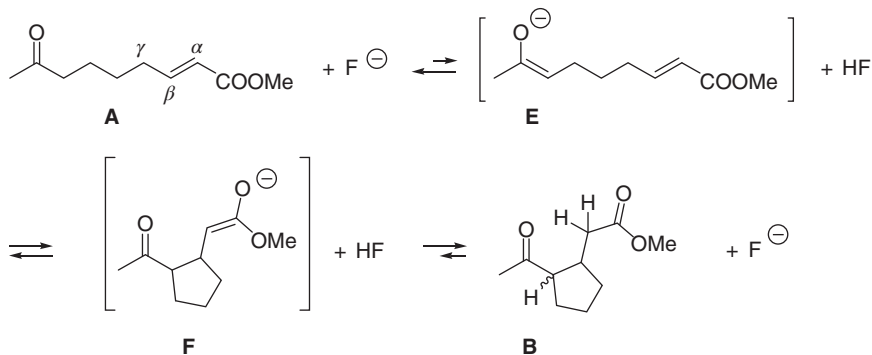


**Problem 1.16** Which of the two products **B** and **C** is the favored product of cyclization of **A** catalyzed by  $\text{Bu}_4\text{N}^+\text{F}^-$  (base catalyst) in DMF.

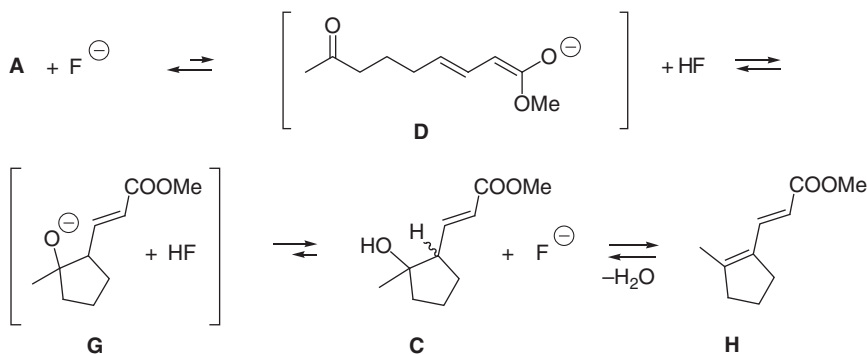


### Answer

Under the action of the base (fluoride anion) ketone **A** equilibrates with two enolates (see Table 1.A.24 for  $\text{p}K_a$  values in dimethylsulfoxide [DMSO]). The ketone enolate **E** undergoes an intramolecular Michael addition onto the acrylic moiety of **E** generating the ester enolate **F**, which equilibrates with **B**, the main product of the reaction.



Alternatively, the acrylic ester **A** could also be deprotonated and be equilibrated with the dienolate intermediate **D**. An intramolecular 1,2-addition of **D** onto its methyl ketone moiety would generate alcoholate **G** that could equilibrate with the tertiary alcohol **C**. Since the hydrocarbation of a ketone is much less exothermic than the hydrocarbation of an alkene, this latter reaction might not be seen at room temperature. Product **C** could form under kinetic control (would form faster than **B**). On heating in the presence of the base it would equilibrate into the more stable product **B**. Both the intramolecular hydrocarbations are reversible reactions at high temperature because of their entropies of cyclization (Section 2.10) that make their exergonicity to diminish on raising temperature.



**Problem 1.17** Are the Diels–Alder reactions ((4+2)-cycloadditions) of benzene with ethylene, acetylene, and allene thermodynamically possible at room temperature? Are the intramolecular versions possible? [12–15]

**Answer**

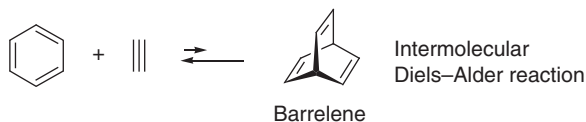
Using the standard heats of formation given in Tables 1.A.2 and 1.A.3 one can estimate the following standard heats of reaction:



$\Delta_r H^\circ(\text{benzene} + \text{ethylene} \rightleftharpoons \text{bicyclo[2.2.2]octa-2,5-diene}) = \Delta_f H^\circ(\text{bicyclo[2.2.2]octa-2,5-diene}) - \Delta_f H^\circ(\text{benzene}) - \Delta_f H^\circ(\text{ethylene}) = 34 - 19.8 - 12.5 = 1.7 \text{ kcal mol}^{-1}$ . This condensation has a negative entropy of reaction similar to the Diels–Alder reaction of butadiene + ethylene giving cyclohexene ( $-44.8 \text{ eu}$ , Section 1.4.4). Thus  $\Delta_r G^\circ(\text{benzene} + \text{ethylene} \rightleftharpoons \text{bicyclo[2.2.2]octa-2,5-diene}) = 1.7 - 298(-0.045) = 1.7 + 13.4 = 15.1 \text{ kcal mol}^{-1}$ , a very endergonic reaction. This intermolecular cycloaddition will not occur at room temperature under standard conditions. If benzene and ethylene would be attached through a tether as in **A**, and assuming the negative entropy of cyclization (blocking rotation about  $\sigma$  bonds of the tether) would be small, the intramolecular process will remain endergonic as it is highly endothermic.



For the intermolecular cycloaddition of benzene with acetylene that would equilibrate with bicyclo[2.2.2]octa-2,5,7-triene one estimates

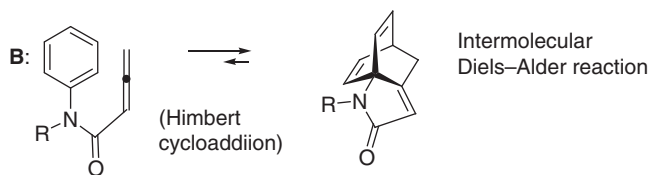


$\Delta_r H^\circ(\text{benzene} + \text{acetylene} \rightleftharpoons \text{bicyclo[2.2.2]octa-2,5,7-triene}) = \Delta_f H^\circ(\text{barrelene}) - \Delta_f H^\circ(\text{benzene}) - \Delta_f H^\circ(\text{acetylene}) = 73 - 19.8 - 54.2 = -1 \text{ kcal mol}^{-1}$ . The situation is slightly better than for the cycloaddition of benzene to ethylene, but this exothermicity is not enough to compensate for the entropy cost ( $10\text{--}13 \text{ kcal mol}^{-1}$ ) of condensation. As for the hydrocarbations and the dihydrogenation, the cycloadditions of alkynes are at least  $10\text{--}15 \text{ kcal mol}^{-1}$  more exothermic than the cycloadditions of alkenes. For instance, for butadiene + acetylene  $\rightarrow$  cyclohexa-1,4-diene one estimates the exothermicity  $-55.8 \text{ kcal mol}^{-1}$  to be compared with  $-39.9 \text{ kcal mol}^{-1}$  for the cycloaddition of butadiene + ethylene  $\rightarrow$  cyclohexene. It is because of the electronic strain present in barrelene (the barrelene effect, Sections 2.9 and 4.7.6) that the intermolecular Diels–Alder reaction of benzene with acetylene (or an alkyne) is not possible. For an intramolecular version, the formation of tricyclic cycloadducts (strain increase) and the cost of entropy for blocking rotation about the  $\sigma$  bonds of the tether make the equilibrium favor the reactants (cycloaddends), not the product (cycloadduct).



For the cycloaddition of benzene to allene one estimates

$\Delta_r H^\circ(\text{benzene} + \text{allene} \rightleftharpoons \text{7-methylidenebicyclo[2.2.2]octa-2,5-diene}) = \Delta_f H^\circ(\text{7-methylidenebicyclo[2.2.2]octa-2,5-diene}) - \Delta_f H^\circ(\text{benzene}) - \Delta_f H^\circ(\text{allene}) = 55 - 19.8 - 45.5 = -10.3 \text{ kcal mol}^{-1}$ , just enough exothermicity to compensate the entropy cost of condensation at  $25^\circ\text{C}$  under one atmosphere or an ideal solution under one atm. Alternatively, if the benzene and allene moiety are tethered as in **B**, the intramolecular version of this Diels–Alder addition is feasible at room temperature and above. It is called the Himbert cycloaddition [16, 17].



As the standard heat of formation of 7-methylidenebicyclo[2.2.2]octa-2,5-diene is not available, we can estimate it in the following way:  $\Delta_f H^\circ(7\text{-methylidenebicyclo[2.2.2]octa-2,5-diene}) = \Delta_f H^\circ(\text{bicyclo[2.2.2]octa-2,5-diene}) + \Delta_f H^\circ(2\text{-methylidenebicyclo[2.2.2]octane}) - \Delta_f H^\circ(\text{bicyclo[2.2.2]octane}) = 34 - 2 + 23 = 55 \text{ kcal mol}^{-1}$ .

Contrary to barrelene, 7-methylidenebicyclo[2.2.2]octa-2,5-diene is not destabilized electronically. Since allenes have the same relative stability as isomeric alkynes ( $\Delta_f H^\circ(\text{allene}) = 45.5 \text{ kcal mol}^{-1}$ ,  $\Delta_f H^\circ(\text{propyne}) = 44.2 \text{ kcal mol}^{-1}$ ) the heat of their cycloadditions is similar to those of alkynes.

**Problem 1.18** Interpret the relative electron affinities of  $\text{HO}^\cdot$ ,  $\text{HS}^\cdot$ , and  $\text{HSe}^\cdot$ . Interpret the relative electron affinities of halide radicals. What makes the trends observed?

### Answer

Table 1.A.13 gives  $-\text{EA}(\text{X}^\cdot) = -78.4, -83.4, -77.6$ , and  $-70.5 \text{ kcal mol}^{-1}$  for  $\text{F}^\cdot$ ,  $\text{Cl}^\cdot$ ,  $\text{Br}^\cdot$ , and  $\text{I}^\cdot$ , respectively.  $-\text{EA}(\text{X}^\cdot) = \Delta_f H^\circ(\text{X}^-) - \Delta_f H^\circ(\text{X}^\cdot)$ . The trend observed for  $\text{Cl}^\cdot$ ,  $\text{Br}^\cdot$ , and  $\text{I}^\cdot$  is consistent with the fact that Cl is more electronegative than Br, and Br is more electronegative than I. One thus would have expected for fluorine atom  $-\text{EA}(\text{F}^\cdot) < -\text{EA}(\text{Cl}^\cdot)$ , which is not the case. In the gas phase anions are stabilized by the electronegativity of the atom that bears the negative charge and by the polarizability of this atom. Polarizability is the property that chemical species and atoms have to delocalize the charge, and thus stabilize the anion or cation. This is done by the formation of induced dipole,  $\pi$ -conjugation and hyperconjugation ( $\sigma/\pi$ -interactions) for polyatomic species. The larger the atoms that constitute the charged species under examination, the larger their number, and the larger the number of bonds, the more the anion or cation is stabilized (electrostatic theory of substituent effects on charge species: dipole/charge stabilization or destabilization:  $V_C = \pm q\mu|\cos \theta|/\epsilon r^2$ ; stabilization due to the induced dipole  $V_I = -q^2\alpha/2\epsilon r^4$ ;  $q$ , the charge;  $\epsilon$ , the dielectric constant of the medium;  $\theta$ , the angle that the dipole  $\mu$  makes with the electrostatic field line;  $\alpha$ , the polarizability;  $r$ , the distance between the substituent and the charged center). For monoatomic anions and cations, their polarizability is the ability of all electrons circulating about the nucleus to follow deformed trajectories and thus to generate induced dipoles that stabilize the charge by charge/dipole interactions. Since fluoride anion is smaller (has fewer electrons) than chloride anion, its negative charge cannot be stabilized by polarizability as well as in chloride anion. There is a competition between stabilization of the charge by electronegativity (attractive interaction between the charge and the nucleus) and formation of induced dipoles due to electron trajectory deformations that stabilize the charge.

Table 1.A.13 gives  $-\text{EA}(\text{X}^\cdot) = -42, -52.7$ , and  $-51 \text{ kcal mol}^{-1}$  for  $\text{HO}^\cdot$ ,  $\text{HS}^\cdot$ , and  $\text{HSe}^\cdot$ , respectively. Based on the greater electronegativity for oxygen than for sulfur one would have expected  $-\text{EA}(\text{HO}^\cdot) < -\text{EA}(\text{HS}^\cdot)$ , which is not the case. Stabilization by electronegativity (attraction of the negative charge of the anion by the nucleus) competes with the stabilization of the anion by its polarizability. Thus the larger the atom ( $\text{Se} > \text{S} > \text{O}$ ), the more the anion is stabilized by polarizability. The data for  $\text{HS}^\cdot$  and  $\text{HSe}^\cdot$  are consistent with the greater electronegativity of S compared with that of Se.

**Problem 1.19** Why is the hydride anion more stable than hydrogen radical in the gas phase?

### Answer

Table 1.A.13 gives  $\text{IE}(\text{H}^\cdot) = 313.6 \text{ kcal mol}^{-1}$ ,  $\Delta_f H^\circ(\text{H}^+) = 365.2 \text{ kcal mol}^{-1}$ ,  $\Delta_f H^\circ(\text{H}^\cdot) = \frac{1}{2}DH^\circ(\text{H}^\cdot/\text{H}^\cdot) = 52.1 \text{ kcal mol}^{-1}$ , and  $\Delta_f H^\circ(\text{H}^-) = 34.7 \text{ kcal mol}^{-1}$ .

Hydride anion enjoys stabilization with respect to hydrogen radical due to the filling of its valence shell (doublet of electrons instead a single valence electron).

**Problem 1.20** Interpret the differences in electron affinities between alkyl, alkenyl, and alkynyl radicals.

**Answer**

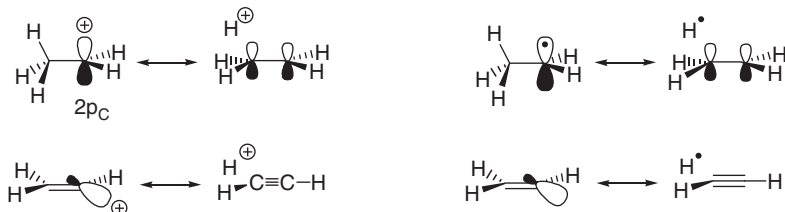
Tables 1.A.8 and 1.A.13 give  $DH^\circ(\text{Et}^\cdot/\text{H}^\cdot) = 100.7$ ,  $DH^\circ(\text{CH}_2=\text{CH}^\cdot/\text{H}^\cdot) = 110.6$ , and  $DH^\circ(\text{CH}\equiv\text{C}^\cdot/\text{H}^\cdot) = 111.9$  kcal mol<sup>-1</sup>.

Table 1.A.13 gives  $DH^\circ(\text{Et}^-/\text{H}^+) = 420.1$ ,  $DH^\circ(\text{CH}_2=\text{CH}^-/\text{H}^+) = 406$ , and  $DH^\circ(\text{CH}\equiv\text{C}^-/\text{H}^+) = 377$  kcal mol<sup>-1</sup>.

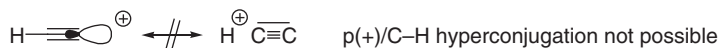
Table 1.A.14 gives  $DH^\circ(\text{Et}^+/\text{H}^-) = 270$ ,  $DH^\circ(\text{CH}_2=\text{CH}^+/\text{H}^-) = 291$  kcal mol<sup>-1</sup>.

The latter data demonstrate that the positive charge is better supported by an sp<sup>3</sup>-hybridized carbon center than by an sp<sup>2</sup>-hybridized carbon center. The greater the s-character the more the positive charge that approaches the protons of the nucleus, and the less stable is the carbocation. The situation is reversed for carbanions. The greater the s-character of the doubly occupied orbital of the anion, the more these two electrons are stabilized by attraction by the protons of the nucleus. Carbon-centered radicals are electron-deficient species since they lack one electron to fulfill the octet rule. One thus expects a parallelism between the relative stabilities of sextet carbocations (carbenium ions) and their radical analogs. Carbenium ions such as alkyl cations are stabilized by hyperconjugation. In the case of ethyl cation the positive charge is delocalized by three C—H bonds (Mulliken hyperconjugation, see Section 4.8.1). In vinyl cation, only one C—H bond can hyperconjugate with the cationic center, whereas in ethynyl cation hyperconjugation is not possible. Hyperconjugation is evidenced in radicals by the fine structure of their electron spin resonance (ESR) spectra that shows spin/spin coupling between the electron and the nearby C—H protons.

For simple alkyl cations their relative stabilities (as given by  $DH^\circ(\text{R}^+/\text{H}^-)$ ) follow the sequence: methyl cation < primary < secondary < tertiary cations. The more  $\beta$   $\sigma(\text{C—H})$  bonds are available to interact (hyperconjugate) with the empty 2p<sup>(+)</sup> orbital localized at the electro-deficient carbon center, the more stable is the carbocation. A similar, but very much attenuated trend is observed for the corresponding alkyl radicals as given by  $DH^\circ(\text{R}^\cdot/\text{H}^\cdot)$ . This has been attributed also to hyperconjugation (interaction between 2p and  $\beta$   $\sigma(\text{C—H})$  bonds) as suggested by the ESR spectra of the radicals that demonstrate delocalization of the spin onto their  $\beta$  H atoms. However, steric destabilizing interactions in the precursor (R—H) that are reduced in the radical R<sup>·</sup> might be the origin of this stability trend (see Section 4.8.5).



sp<sup>2</sup>: s-character, brings the positive charge closer to the C nucleus. This destabilizes the vinyl cation but stabilizes the vinyl anion relatively to ethyl anion.



sp<sup>1</sup>: more s-character, brings the positive charge closer to the C nucleus



sp<sup>1</sup>: more s-character, brings the negative charge closer to the C nucleus: terminal alkynes are more acidic than terminal alkenes, and alkenes are more acidic than alkanes.

**Problem 1.21** Why is there no linear relationship for the homolytic bond dissociation enthalpies  $DH^\circ(\text{Me}^\cdot/\text{Me}^\cdot) = 89$  kcal mol<sup>-1</sup>,  $DH^\circ(t\text{-Bu}^\cdot/\text{Me}^\cdot) = 81.8$  kcal mol<sup>-1</sup> and  $DH^\circ(t\text{-Bu}^\cdot/t\text{-Bu}^\cdot) = 68.8$  kcal mol<sup>-1</sup>?

**Answer**

Alkane  $t\text{-Bu}-t\text{-Bu}$  is destabilized by front strain (F-strain) and back strain (B-strain) (steric repulsion between the methyl groups, see Section 2.5.1), thus rendering its homolysis less endothermic than expected ( $DH^\circ(t\text{-Bu}^\cdot/t\text{-Bu}^\cdot) = 89 - 2(7.2) = 74.6$  kcal mol<sup>-1</sup> instead of the observed  $DH^\circ(t\text{-Bu}^\cdot/t\text{-Bu}^\cdot) = 68.8$  kcal mol<sup>-1</sup>) on the basis of the relative stability of the radical fragments formed in the homolysis. Both F- and B-strains are relieved in the two  $t$ -butyl radicals.

**Problem 1.22** Why is the homolytic dissociation enthalpy of HF higher than that of HCl?

**Answer**

H—F bond is stronger than H—Cl bond because of the greater electronegativity difference between H/F pair of atoms than between H/Cl pair of atoms and shorter H—F bond than H—Cl bond.

**Problem 1.23** Why are oxygen-centered radicals more reactive than analogous carbon-centered radicals?

**Answer**

Oxygen-centered radicals such as R—O· and Ph—O· are more reactive than alkyl radicals such as R—CH<sub>2</sub>· and Ph—CH<sub>2</sub>· because they form alcohols (R—O—H) and phenols (Ph—O—H) in which the O—H bonds are significantly stronger than the corresponding C—H bonds in the corresponding hydrocarbons (R—CH<sub>2</sub>—H, Ph—CH<sub>2</sub>—H). This is a manifestation of the electronegativity difference, which is larger between atom pair H/O than between atomic pair H/C.

**Problem 1.24** Give an interpretation for the better stabilizing effect of 4-amino group than of 4-CN and 4-nitro group in 4-substituted phenoxyl radicals.

**Answer**

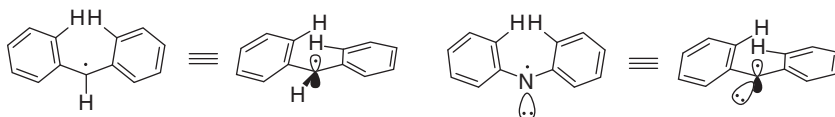
Table 1.A.11 gives  $DH^\circ(\text{PhO}\cdot/\text{H}\cdot) = 90.4$ ,  $DH^\circ(4\text{-H}_2\text{N-C}_6\text{H}_4\text{O}\cdot/\text{H}\cdot) = 77.3$ ,  $DH^\circ(4\text{-O}_2\text{N-C}_6\text{H}_4\text{O}\cdot/\text{H}\cdot) = 94.7$  and  $DH^\circ(4\text{-NC-C}_6\text{H}_4\text{O}\cdot/\text{H}\cdot) = 94.2$  kcal mol<sup>-1</sup> (in DMSO). Phenoxy radical is electrophilic (electron-poor) because of its tendency to take an electron from its neighborhood, a manifestation of the electronegativity of oxygen that is greater than that of carbon. Thus, the oxy radical pulls on the  $\pi$ -electrons of the phenyl ring, making it electron poor at position C(4). As a consequence, a 4-amino substituent, which is a strong electron-releasing group, better stabilizes the phenoxy radical than any electron-withdrawing 4-substituents such as CN and NO<sub>2</sub>.

**Problem 1.25** Compare the N—H homolytic bond dissociation enthalpies of amines (Table 1.A.11) and explain the non-additivity of phenyl substitution on the stability of nitrogen-centered radical.

**Answer**

Table 1.A.11 gives  $DH^\circ(\text{H}_2\text{N}\cdot/\text{H}\cdot) = 108$  kcal mol<sup>-1</sup> (gas phase) and  $DH^\circ(\text{PhNH}\cdot/\text{H}\cdot) = 88$  kcal mol<sup>-1</sup> (gas phase), indicating stabilizing effect of 20 kcal mol<sup>-1</sup> by a phenyl substituent on the nitrogen-centered radical. This is significantly higher than for the phenyl substituent effect (14.5 kcal mol<sup>-1</sup>) measured for the corresponding carbon-centered radical (methyl radical) as given (Table 1.A.7) by comparing  $DH^\circ(\text{H}_3\text{C}\cdot/\text{H}\cdot) = 104.2$  kcal mol<sup>-1</sup> (gas phase) and  $DH^\circ(\text{PhCH}_2\cdot/\text{H}\cdot) = 89.7$  kcal mol<sup>-1</sup> (gas phase).

Table 1.A.11 gives also  $DH^\circ(\text{PhNH}\cdot/\text{H}\cdot) = 92$  kcal mol<sup>-1</sup> and  $DH^\circ(\text{Ph}_2\text{N}\cdot/\text{H}\cdot) = 87.5$  kcal mol<sup>-1</sup> in DMSO solution. A comparison of the two latter values shows a much weaker phenyl substituent effect of 4.5 kcal mol<sup>-1</sup> on the stabilization of the phenylaminyl radical. In the case of related carbon-centered radicals,  $DH^\circ(\text{PhCH}_2\cdot/\text{H}\cdot) = 89.7$  kcal mol<sup>-1</sup> (gas phase) and  $DH^\circ(\text{Ph}_2\text{CH}\cdot/\text{H}\cdot) = 81.4$  kcal mol<sup>-1</sup> (gas phase) are measured. This gives a phenyl substituent stabilizing effect of 8.3 kcal mol<sup>-1</sup> on the benzyl radical, almost twice as much as the phenyl substituent effect on the stabilization of PhNH·. The difference between the nitrogen and carbon-centered radical arises from the fact that nitrogen is more electronegative than carbon. The electron demand of radical H<sub>2</sub>N· is higher than that of H<sub>3</sub>C·. As a consequence, the electron-rich and highly polarizable phenyl substituent responds more when substituting H<sub>2</sub>N· instead of H<sub>3</sub>C·. The spin is more delocalized in PhNH· than in PhCH<sub>2</sub>·. This represents a first hypothesis to explain the smaller phenyl stabilizing effect on PhNH· than on PhCH<sub>2</sub>·. Once the spin is delocalized by the phenyl substituent a second phenyl substituent cannot stabilize as much as the first one. A second hypothesis is to invoke the non-planarity of the two phenyl rings in Ph<sub>2</sub>CH· and Ph<sub>2</sub>N·. Because of gauche interactions between the two geminal phenyl rings in these radicals, conjugation between the radicals and the  $\pi$ -systems is reduced compared with PhCH<sub>2</sub>· and PhNH·, respectively. Because of the shorter C—N bond (between Ph and N) compared with the C—C bond (between Ph and CH<sub>2</sub>·) the two phenyl rings in Ph<sub>2</sub>N· are closer to each other than in Ph<sub>2</sub>CH·. Consequently, deviation from planarity might be larger in Ph<sub>2</sub>N· than in Ph<sub>2</sub>CH·. The above discussion ignores the error on the phenyl substituent effect considered. If it should be  $\pm 2\text{--}3$  kcal mol<sup>-1</sup>, more hypotheses should be examined!





**Problem 1.26** Calculate the standard gas phase heat of reaction of the following additions:

- $R^\cdot + CO \rightleftharpoons RCO^\cdot$  for  $R = \text{Ph, Me, } t\text{-Bu}$
- $\text{Et}^\cdot + \text{MeCOMe} \rightleftharpoons \text{EtC}(\text{Me})_2\text{C}-\text{O}^\cdot$
- $\text{Et}^\cdot + \text{acetone} \rightleftharpoons \text{EtO}-\text{C}^\cdot(\text{Me})_2$
- $\text{Et}^\cdot + \text{cyclopentene} \rightleftharpoons 2\text{-ethylcyclopentyl}^\cdot$

### Answer

Heats of formation of radicals are taken from Table 1.A.7.

- $\Delta_f H^\circ(\text{Ph}^\cdot + CO \rightleftharpoons \text{PhCO}^\cdot) = 26 (\pm?) - 81 (\pm 2.0) - (-26.4 \pm 0.04) = -28.8 \pm 3.$

$$\Delta_f H^\circ(\text{Me}^\cdot + CO \rightleftharpoons \text{MeCO}^\cdot) = -2.9(\pm 0.7) - 34.8(\pm 0.2) - (-26.4 \pm 0.04) = -10.2 \pm 1.$$

$$\Delta_f H^\circ(t\text{-Bu}^\cdot + CO \rightleftharpoons t\text{-BuCO}^\cdot) = \Delta_f H^\circ(t\text{-BuCO}^\cdot) - 11.0(\pm 0.7) - (-26.4 \pm 0.04) = X.$$

Since  $\Delta_f H^\circ(t\text{-BuCO}^\cdot)$  is not given in the table, we can estimate  $\Delta_f H^\circ(t\text{-Bu}^\cdot + CO \rightleftharpoons t\text{-BuCO}^\cdot) = \Delta_f H^\circ(\text{Me}^\cdot + CO \rightleftharpoons \text{MeCO}^\cdot) + \text{correction for the stability difference between } t\text{-Bu}^\cdot \text{ and Me}^\cdot$  that is given by the comparison of  $DH^\circ(\text{Me}^\cdot/\text{H}^\cdot) = 104.7$  with  $DH^\circ(t\text{-Bu}^\cdot/\text{H}^\cdot) = 95.2 \text{ kcal mol}^{-1}$ , i.e.:  $9.5 \pm 2.0 \text{ kcal mol}^{-1}$ , taking  $\pm 1.0 \text{ kcal mol}^{-1}$  for the average standard error on the homolytic bond dissociation enthalpies given in Table 1.A.7. Assuming that the *t*-butyl group of *t*-BuCO $^\cdot$  radical does not stabilize the radical more than the methyl group in MeCO $^\cdot$  (which must be the case since  $DH^\circ(\text{MeCH}_2^\cdot/\text{H}^\cdot) = 100.7$  and  $DH^\circ(\text{PhCH}_2^\cdot/\text{H}^\cdot) = 89.7$ , but  $DH^\circ(\text{MeCO}^\cdot/\text{H}^\cdot) = 86$  and  $DH^\circ(\text{PhCO}^\cdot/\text{H}^\cdot) = 87 \text{ kcal mol}^{-1}$ , Table 1.A.7), one estimates  $\Delta_f H^\circ(t\text{-Bu}^\cdot + CO \rightleftharpoons t\text{-BuCO}^\cdot) = -10.2(\pm 1.0) + 9.5(\pm 2.0) = -0.7 \pm 3.0 \text{ kcal mol}^{-1}$ . This reaction is not exothermic enough to compensate for the entropy cost (condensation). Pivalyl radical (*t*-BuCO $^\cdot$ ) might be formed as an intermediate by addition of *t*-butyl radical to carbon monoxide. This intermediate might give a stable product such as *t*-BuCO-*t*-Bu by reaction with a *t*-butyl radical, or form pivaldehyde (*t*-BuCHO) by hydrogen atom transfer from *t*-Bu $^\cdot$ .

Disproportionation reaction:  $t\text{-BuCO}^\cdot + t\text{-Bu}^\cdot \rightleftharpoons t\text{-BuCHO} + \text{isobutylene}$

But the latter reactions compete with a more frequent reaction that is the disproportionation  $2 t\text{-Bu}^\cdot \rightleftharpoons \text{isobutylene} + \text{isobutane}$ .

At room temperature, the concentration of *t*-BuCO $^\cdot$  remains always much lower than that of *t*-Bu $^\cdot$ .

- Since  $\Delta_f H^\circ(\text{Me}_2(\text{Et})\text{C}-\text{O}^\cdot)$  is not given in the tables, one assumes

$\Delta_f H^\circ(\text{Et}^\cdot + \text{Me}_2\text{CO} \rightleftharpoons \text{Me}_2(\text{Et})\text{CO}^\cdot) = \Delta_f H^\circ(\text{Me}^\cdot + \text{Me}_2\text{CO} \rightleftharpoons \text{Me}_3\text{CO}^\cdot) + \text{correction for the difference in relative stability between methyl and ethyl radicals, which is given on comparing } DH^\circ(\text{Me}^\cdot/\text{H}^\cdot) = 104.7 \text{ with } DH^\circ(\text{Et}^\cdot/\text{H}^\cdot) = 100.7 \text{ kcal mol}^{-1}$ , i.e.  $4.0 \pm 2.0 \text{ kcal mol}^{-1}$ , taking  $\pm 1.0 \text{ kcal mol}^{-1}$  for the average standard error on the homolytic bond dissociation enthalpies given in Table 1.A.7. This implies that the relative stability of the alkoxy radicals is the same irrespective of the size of the alkyl group. This is indeed the case as  $DH^\circ(t\text{-BuO}^\cdot/\text{H}^\cdot) = DH^\circ(\text{MeO}^\cdot/\text{H}^\cdot) = 104\text{--}105 \text{ kcal mol}^{-1}$  (Table 1.A.13).

One finds the following data:

$$\Delta_f H^\circ(\text{Me}^\cdot) = 34.8 \pm 0.2 \text{ (Table 1.A.7)}, \Delta_f H^\circ(\text{Me}_2\text{CO}) = -52.23 \pm 0.14 \text{ kcal mol}^{-1} \text{ (Table 1.A.4)}.$$

$$\Delta_f H^\circ(\text{Me}_3\text{C}-\text{O}^\cdot) \text{ can be calculated from } DH^\circ(t\text{-BuO}^\cdot/\text{H}^\cdot) = 105 \text{ kcal mol}^{-1} \text{ (Table 1.A.11):}$$

$$DH^\circ(t\text{-BuO}^\cdot/\text{H}^\cdot) = 105 \pm 1.0 = \Delta_f H^\circ(t\text{-BuO}^\cdot) + \Delta_f H^\circ(\text{H}^\cdot) - \Delta_f H^\circ(t\text{-BuOH}) = \Delta_f H^\circ(t\text{-BuO}^\cdot) + 52.1(\pm 0.001) - (-74.72 \pm 0.21), \text{ which leads to } \Delta_f H^\circ(t\text{-BuO}^\cdot) = -21.8 \pm 2.0 \text{ (Table 1.A.13 gives } \Delta_f H^\circ(t\text{-BuO}^\cdot) = -21.0) \text{ This gives } \Delta_f H^\circ(\text{Me}^\cdot + \text{Me}_2\text{CO} \rightleftharpoons \text{Me}_3\text{CO}^\cdot) = -21.8(\pm 2) - 34.8(\pm 0.2) - (-52.23 \pm 0.14) = -4.4 \pm 2.4 \text{ kcal mol}^{-1}.$$

$$\text{Thus, } \Delta_f H^\circ(\text{Et}^\cdot + \text{Me}_2\text{CO} \rightleftharpoons \text{Me}_2(\text{Et})\text{CO}^\cdot) = -4.4 \pm (2.4) + 4.0 \pm (2.0) = -0.4 \pm 4.4 \text{ kcal mol}^{-1}.$$

Alternatively, one can estimate  $\Delta_f H^\circ(\text{Me}_2(\text{Et})\text{C}-\text{O}^\cdot)$  from  $\Delta_f H^\circ(\text{Me}_3\text{C}-\text{O}^\cdot)$  by considering the difference  $\Delta_f H^\circ(\text{Me}_2(\text{Et})\text{C}-\text{OH}) = -78.7$  and  $\Delta_f H^\circ(\text{Me}_3\text{C}-\text{OH}) = -74.72 \pm 0.21 \text{ kcal mol}^{-1}$  (Table 1.A.4) of  $-4.0 \pm 0.5 \text{ kcal mol}^{-1}$ . This gives  $\Delta_f H^\circ(\text{Me}_2(\text{Et})\text{C}-\text{O}^\cdot) = \Delta_f H^\circ(\text{Me}_3\text{C}-\text{O}^\cdot) - 4.0 \pm 0.5 \text{ kcal mol}^{-1} = -21.8(\pm 2.0) - 4.0(\pm 0.5) = -25.8 \pm 2.5 \text{ kcal mol}^{-1}$ . Thus,  $\Delta_f H^\circ(\text{Et}^\cdot + \text{Me}_2\text{CO} \rightleftharpoons \text{Me}_2(\text{Et})\text{CO}^\cdot) = -25.8(\pm 2.5) - 28.4(\pm 0.5) - (-52.23 \pm 0.14) = -2.0 \pm 3.2 \text{ kcal mol}^{-1}$ .

The more the alkyl radical is stable, the least exothermic is its addition to the carbon center of a ketone. This is the case because the oxygen-centered radicals that result from these reactions have the same relative stabilities since they are not affected (Table 1.A.13) by the different tertiary alkyl groups. Indeed, Table 1.A.13 gives  $DH^\circ(\text{MeO}^\cdot/\text{H}^\cdot) = DH^\circ(t\text{-BuO}^\cdot/\text{H}^\cdot) = DH^\circ(\text{Me}_2(\text{Et})\text{CO}^\cdot/\text{H}^\cdot) = 104\text{--}105 \text{ kcal mol}^{-1}$ .

- $\Delta_f H^\circ(\text{Et}^\cdot + \text{Me}_2\text{CO} \rightleftharpoons \text{EtO}-(\text{Me})_2\text{C}^\cdot) = \Delta_f H^\circ(\text{EtO}-(\text{Me})_2\text{C}^\cdot) - \Delta_f H^\circ(\text{Et}^\cdot) - \Delta_f H^\circ(\text{MeCOMe}) = \Delta_f H^\circ(\text{EtO}-(\text{Me})_2\text{C}^\cdot) - 28.4(\pm 0.5) - (52.23 \pm 0.14).$



$\Delta_f H^\circ(\text{EtO}-(\text{Me})_2\text{C}^\cdot)$  is estimated from  $\Delta_f H^\circ(\text{MeOCH}_2^\cdot) = -3 \text{ kcal mol}^{-1}$  (Table 1.A.7) by considering the exchange of a methoxy group for an ethoxy group (contribution X) and by converting the primary alkyl radical into a dimethylalkyl radical: contribution Y.

$X = \Delta_f H^\circ(\text{MeOEt}) - \Delta_f H^\circ(\text{MeOMe}) = -51.73(\pm 0.16) - (-44.0(\pm 0.12)) = -7.7 \pm 0.3 \text{ kcal mol}^{-1}$  (Table 1.A.4).  
 $Y = \Delta_f H^\circ(\text{Et}(\text{Me})_2\text{C}^\cdot) - \Delta_f H^\circ(\text{EtCH}_2^\cdot) = (6.7 \pm 0.7) - (23.5 \pm 0.5) = -16.8 \pm 1.2 \text{ kcal mol}^{-1}$  (Table 1.A.7). One obtains  $\Delta_f H^\circ(\text{EtO}-(\text{Me})_2\text{C}^\cdot) = \Delta_f H^\circ(\text{MeOCH}_2^\cdot) = -3.0 + X + Y = -3.0 - 7.7(\pm 0.3) - 16.8(\pm 1.2) = -27.5 \pm 2.5 \text{ kcal mol}^{-1}$ .

Thus,  $\Delta_f H^\circ(\text{Et}^\cdot + \text{Me}_2\text{CO} \rightleftharpoons \text{EtO}-(\text{Me})_2\text{C}^\cdot) = \Delta_f H^\circ(\text{EtO}-(\text{Me})_2\text{C}^\cdot) - \Delta_f H^\circ(\text{Et}^\cdot) - \Delta_f H^\circ(\text{MeCOMe}) = -27.5(\pm 2.5) - 28.4(\pm 0.5) - (52.23 \pm 0.14) = -3.7 \pm 3.1 \text{ kcal mol}^{-1}$

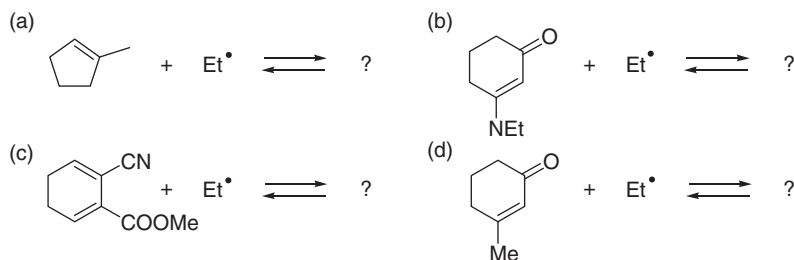
d)  $\Delta_f H^\circ(\text{Et}^\cdot + \text{cyclopentene} \rightleftharpoons 2\text{-ethylcyclopent-1-yl}^\cdot) = \Delta_f H^\circ(2\text{-Et-cyclopentyl}^\cdot) - \Delta_f H^\circ(\text{Et}^\cdot) - \Delta_f H^\circ(\text{cyclopentene}) = \Delta_f H^\circ(2\text{-Et-cyclopentyl}^\cdot) - 28.4(\pm 0.5) - (8.5 \pm ?)$ .

$\Delta_f H^\circ(2\text{-Et-cyclopentyl}^\cdot) = \Delta_f H^\circ(\text{cyclopentyl}^\cdot) + \text{difference } \Delta_f H^\circ(3\text{-Et-pentane}) - \Delta_f H^\circ(\text{pentane}) = 24.3(\pm ?) + W$  (Table 1.A.7).

$W = \Delta_f H^\circ(3\text{-Et-pentane}) - \Delta_f H^\circ(\text{pentane}) = -45.34(\pm 0.28) - (35.0 \pm 0.14) = -10.3 \pm 0.4 \text{ kcal mol}^{-1}$  (Table 1.A.2). One obtains  $\Delta_f H^\circ(2\text{-Et-cyclopentyl}^\cdot) = 24.3 - 10.3 = 14.0 (\pm ?) \text{ kcal mol}^{-1}$ . This leads to  $\Delta_f H^\circ(\text{Et}^\cdot + \text{cyclopentene} \rightleftharpoons 2\text{-ethylcyclopent-1-yl}^\cdot) = 14.0 - 28.4 - 8.5 = -22.9 (\pm ?) \text{ kcal mol}^{-1}$ .

The addition of alkyl radicals to alkenes is much more exothermic than the addition of the same alkyl radicals to ketones. This is due mostly to the greater C=O bond energies than C=C bond energies. The heats of alkyl radical additions to alkenes and carbonyl compounds parallel those of the corresponding hydrocarbocations (Section 1.7.1).

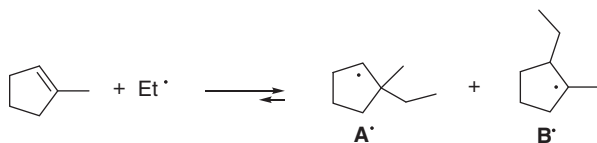
**Problem 1.27** What is the preferred regioisomeric adduct of the following equilibria?



### Answer

Under thermodynamic control (fully reversible reactions) the most stable regioisomeric adduct-radical should be preferred.

a) The two radicals **A** $^\cdot$  and **B** $^\cdot$  can form concurrently:



**A** $^\cdot$  is a secondary alkyl radical with a quaternary carbon center (doubly branched alkane); **B** $^\cdot$  is a tertiary alkyl radical with two monobranchings (branched hydrocarbons are more stable than their unbranched isomers; Section 1.6.4). One needs to consider the difference in standard heats of formation of the corresponding alkanes A–H and B–H and the corresponding homolytic bond dissociation enthalpies  $DH^\circ(\text{A}^\cdot/\text{H}^\cdot)$  and  $DH^\circ(\text{B}^\cdot/\text{H}^\cdot)$ :

$\Delta_f H^\circ(\text{A}^\cdot \rightleftharpoons \text{B}^\cdot) = \Delta_f H^\circ(\text{B}^\cdot) - \Delta_f H^\circ(\text{A}^\cdot) = DH^\circ(\text{B}^\cdot/\text{H}^\cdot) - DH^\circ(\text{A}^\cdot/\text{H}^\cdot) - \Delta_f H^\circ(\text{A} - \text{H}) + \Delta_f H^\circ(\text{B} - \text{H}) = \Delta_f H^\circ(\text{B}^\cdot) + \Delta_f H^\circ(\text{H}^\cdot) - \Delta_f H^\circ(\text{B} - \text{H}) - \Delta_f H^\circ(\text{A}^\cdot) - \Delta_f H^\circ(\text{H}^\cdot) + \Delta_f H^\circ(\text{A} - \text{H}) - \Delta_f H^\circ(\text{A} - \text{H}) + \Delta_f H^\circ(\text{B} - \text{H})$ .

Since  $\Delta_f H^\circ(\text{A} - \text{H})$  and  $\Delta_f H^\circ(\text{B} - \text{H})$  are not available  $\Delta_f H^\circ(\text{A} - \text{H}) - \Delta_f H^\circ(\text{B} - \text{H})$  can be estimated to be similar to the difference  $\Delta_f H^\circ(3,3\text{-dimethylpentane}) - \Delta_f H^\circ(2,3\text{-dimethylpentane}) = -48.17 (\pm 0.22) - (-47.62 \pm 0.30) = -0.55 \pm 0.52 \text{ kcal mol}^{-1}$ .

$DH^\circ(\text{A}^\cdot/\text{H}^\cdot)$  and  $DH^\circ(\text{B}^\cdot/\text{H}^\cdot)$  are not available.  $DH^\circ(\text{cyclopentyl}^\cdot/\text{H}^\cdot) = 94.8 \text{ kcal mol}^{-1}$  (Table 1.A.7) but  $DH^\circ(1\text{-alkylcyclopentyl}^\cdot/\text{H}^\cdot)$  is not available, which is required to estimate the difference in

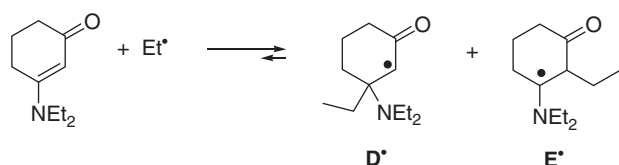
C—H bond energies between secondary and tertiary C—H bonds in alkylcyclopentanes. We thus need to turn to simpler model compounds for which this difference is available. Table 1.A.7 gives  $DH^\circ(2\text{-methylbut-2-yl}/H^\cdot) = 95.3 \text{ kcal mol}^{-1}$  and  $DH^\circ(\text{pent-2-yl}/H^\cdot) = 99.2 \text{ kcal mol}^{-1}$ , a difference of c.  $4 \text{ kcal mol}^{-1}$  in favor of the tertiary C—H bond. The same difference is found with the comparison  $DH^\circ(2\text{-methylprop-2-yl}/H^\cdot) = 95.2 \text{ kcal mol}^{-1}$  and  $DH^\circ(n\text{-but-2-yl}/H^\cdot) = 99.1 \text{ kcal mol}^{-1}$ . Accepting standard deviations of  $\pm 1.0 \text{ kcal mol}^{-1}$  on published  $DH^\circ$  values, one obtains:

$$\Delta_r H^\circ(A^\cdot \rightleftharpoons B^\cdot) = DH^\circ(B^\cdot/H^\cdot) - DH^\circ(A^\cdot/H^\cdot) - \Delta_f H^\circ(A-H) + \Delta_f H^\circ(B-H) = -4(\pm 2.0) + 0.55(\pm 0.52) = -3.5 \pm 2.5 \text{ kcal mol}^{-1}.$$

In this case the greater stability of the tertiary radical **B** $^\cdot$  with respect to isomeric secondary radical **A** $^\cdot$  overwhelms the relative small difference in stability of the alkyl skeletons due to changes in chain branching. Both radical **A** $^\cdot$  and **B** $^\cdot$  do not share any symmetry axis of rotation and have similar conformational flexibility. They are expected to have the same entropy, thus:

$$\Delta_r G^\circ(A^\cdot \rightleftharpoons B^\cdot) = \Delta_r H^\circ(A^\cdot \rightleftharpoons B^\cdot). \text{ Radical } B^\cdot \text{ forms to a greater extent than radical } A^\cdot.$$

- b) Ethyl radical adds to the C=C double bond, not to the C=O double bond (see Problem 1.26). Radicals **D** $^\cdot$  and **E** $^\cdot$  can form concurrently.



$$\Delta_r H^\circ(D^\cdot \rightleftharpoons E^\cdot) = \Delta_f H^\circ(E^\cdot) - \Delta_f H^\circ(D^\cdot) = DH^\circ(E^\cdot/H^\cdot) - DH^\circ(D^\cdot/H^\cdot) - \Delta_f H^\circ(D-H) + \Delta_f H^\circ(E-H).$$

The corresponding hydrocarbons **D**—H and **E**—H are isomers in which **D**—H contains a tertiary alkylamine whereas **E**—H contains a secondary alkylamine. The stability difference  $\Delta_f H^\circ(D-H) - \Delta_f H^\circ(E-H)$  can be taken, to a first approximation, similar to  $\Delta_f H^\circ(\text{Me}_3\text{C}-\text{NH}_2) - \Delta_f H^\circ(\text{MeCH}(\text{NH}_2)\text{CH}_2\text{Me}) = -28.8(\pm 0.2) - (-23.6 \pm 0.13) = -5.2 \pm 0.33 \text{ kcal mol}^{-1}$  (Table 1.A.4).

$DH^\circ(D^\cdot/H^\cdot)$  can be estimated from  $DH^\circ(\text{MeCOCH}_2^\cdot/H^\cdot) = 98 \pm 2 \text{ kcal mol}^{-1}$  (Table 1.A.9) and by considering the fact that **D** $^\cdot$  is a secondary, not a primary alkyl radical. Thus,  $DH^\circ(D^\cdot/H^\cdot) = 98 - 2 = 96 \pm 3 \text{ kcal mol}^{-1}$ .

$DH^\circ(E^\cdot/H^\cdot)$  can be estimated from  $DH^\circ(\text{Me}_2\text{NCH}_2^\cdot/H^\cdot) = 83.8 \pm 1.0 \text{ kcal mol}^{-1}$  (Tables 1.A.7 and 1.A.9) and corrected for the stability difference between a primary and a secondary substituted alkyl radical (c.  $4 \text{ kcal mol}^{-1}$ ). Thus,  $DH^\circ(E^\cdot/H^\cdot) = 83.8 (\pm 1.0) - 4 = 79.8 \pm 1.0 \text{ kcal mol}^{-1}$ .

This leads to  $\Delta_r H^\circ(D^\cdot \rightleftharpoons E^\cdot) = \Delta_f H^\circ(E^\cdot) - \Delta_f H^\circ(D^\cdot) = DH^\circ(E^\cdot/H^\cdot) - DH^\circ(D^\cdot/H^\cdot) - \Delta_f H^\circ(D-H) + \Delta_f H^\circ(E-H) = 83.8 - 96 + 5.2 \approx -7 \text{ kcal mol}^{-1}$ . Thus, radical **E** $^\cdot$  is highly preferred over radical **D** $^\cdot$  (two isomers with similar entropies).

- c) Ethyl radical adds to the alkene moieties forming the isomeric tertiary-allylic radicals **F** $^\cdot$  and **G** $^\cdot$ . Isomers **H** $^\cdot$  and **I** $^\cdot$  do not form as they are secondary alkyl radicals, not stabilized by allylic conjugation. Both radicals **F** $^\cdot$  and **G** $^\cdot$  have the same skeleton, the same degree of chain branching. They can be interconverted by exchange of their COOEt and CN groups.

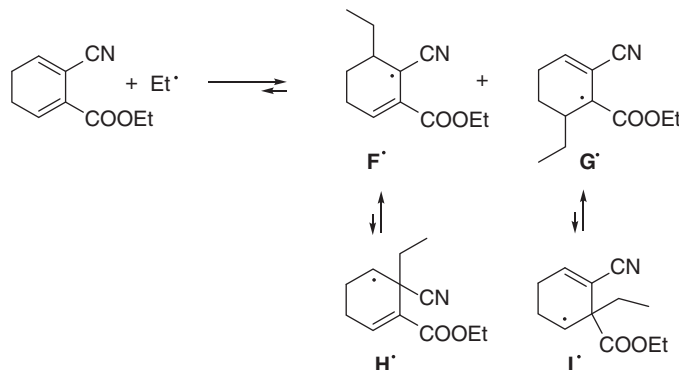
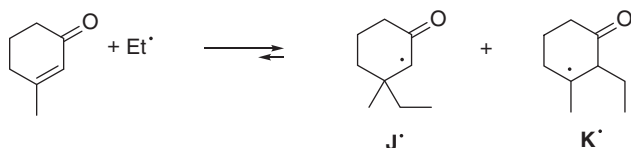


Table 1.A.9 gives the substituent effects on the relative stabilities of primary radicals (MeCOOC stabilizes by  $9.7 \pm 2.0$  kcal mol<sup>-1</sup>, and N≡C by  $12 \pm 2.7$  kcal mol<sup>-1</sup>). Assuming they are similar for tertiary allylic radicals, one predicts that radical **H**• will form to a greater extent than radical **G**•.

- d) Ethyl radical adds to 3-methylcyclohex-2-enone giving the regioisomeric radicals **J**• and **K**•. The former is a secondary alkyl radical stabilized by  $7 \pm 2$  kcal mol<sup>-1</sup> (Table 1.A.9) through conjugation; the latter is a tertiary alkyl radical not stabilized by carbonyl conjugation, but intrinsically 2–4 kcal mol<sup>-1</sup> more stable than a secondary radical. As the difference in stability between an alkane containing a quaternary carbon center and an isomer containing two tertiary carbon centers is very small (see Problem 1.27a), one can predict that radical **J**• will form to a greater extent than radical **K**•.



**Problem 1.28** If you had to propose good radical scavenging agents, which compounds listed in Table 1.A.11 would you choose?

#### Answer

Those compounds with the smallest homolytic bond dissociation enthalpies such as the conjugate base of hydroquinone (O—H bond: 73 kcal mol<sup>-1</sup>) and (*t*-Bu)<sub>2</sub>NO—H (O—H bond: 68.2 kcal mol<sup>-1</sup>).

**Problem 1.29** Compare the gas phase heterolytic bond dissociation energies  $\text{ROH} \rightleftharpoons \text{RO}^- + \text{H}^+$  for methanol, ethanol, isopropanol, and *tert*-butanol. Is the trend the same in solution?

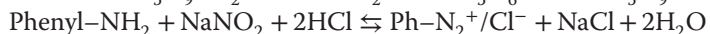
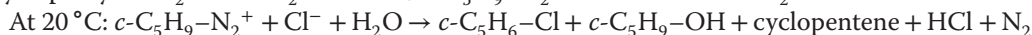
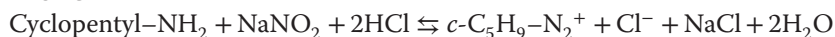
#### Answer

Table 1.A.13 gives  $DH^\circ(\text{MeO}^-/\text{H}^+) = 380.5$ ,  $DH^\circ(\text{EtO}^-/\text{H}^+) = 377.5$ ,  $DH^\circ(i\text{-PrO}^-/\text{H}^+) = 375$ , and  $DH^\circ(t\text{-BuO}^-/\text{H}^+) = 374.5$  kcal mol<sup>-1</sup>. The gas phase acidities of alcohols increases with the size of the alkyl group. The larger the alkyl group, the larger its polarizability, the more it stabilizes the alcoholate anion.

Bordwell's tables give  $pK_a$  values of 16.0, 18.8, and 19.9 for EtOH, *i*-PrOH, and *t*-BuOH in water (Table 1.A.24), and 29.0, 29.8, 30.3, and 32.2 for MeOH, EtOH, *i*-PrOH, and *t*-BuOH in DMSO (Table 1.A.25), respectively. In solution, the acidity of alcohols decreases with the size of the alkyl group. This arises from solvation that overwhelms the intrinsic stability of the alcoholate anions. The smaller the alcoholate anion, the better it is stabilized by interaction with the solvent molecules (charge/dipole interactions depend on the distance separating the charge from the solvent dipoles). In *t*-BuO<sup>-</sup> the solvent molecules cannot get close to the oxide anion as in MeO<sup>-</sup>. There is a steric effect to solvation in large alcoholate anions.

**Problem 1.30** Diazotization of primary alkyl amines with NaNO<sub>2</sub>/HCl/H<sub>2</sub>O at 0 °C leads to mixtures of alcohols, chlorides, and alkenes with the evolution of N<sub>2</sub>. The same reaction with aniline and other aromatic primary amines generates at 0 °C persistent diazonium salts that decompose with N<sub>2</sub> evolution on heating above 60 °C. Why is there this difference in behavior between the diazonium salts resulting from alkyl and aryl primary amines?

#### Answer



At 20 °C, PhN<sub>2</sub><sup>+</sup>/Cl<sup>-</sup> is stable.

Table 1.A.14 gives  $DH^\circ(c\text{-pentyl}^+/\text{H}^-) = 249.8 \ll DH^\circ(\text{Ph}^+/\text{H}^-) = 287$  kcal mol<sup>-1</sup>. Thus, the dissociation of *c*-pentyl-N<sub>2</sub><sup>+</sup> into *c*-pentyl cation and N<sub>2</sub> is much easier than dissociation of Ph-N<sub>2</sub><sup>+</sup> into phenyl cation + N<sub>2</sub>.

**Problem 1.31** Explain the difference in heterolytic bond dissociation enthalpies  $DH^\circ(\text{cyclopent-2-enyl}^+/\text{H}^-)$ ,  $DH^\circ(\text{cyclopentadienyl}^+/\text{H}^-)$  and  $DH^\circ(\text{tropylium}^+/\text{H}^-)$ .

**Answer**

Table 1.A.14 gives  $DH^\circ(\text{cyclopent-2-enyl}^+/\text{H}^-) = 225$ ,  $DH^\circ(\text{cyclopentadienyl}^+/\text{H}^-) = 255.6$  and  $DH^\circ(\text{cycloheptatrienyl}^+/\text{H}^-) = DH^\circ(\text{tropylium cation}/\text{H}^-) = 194 \text{ kcal mol}^{-1}$ . The smaller the hydride affinity, the more stable the carbenium ion. Cyclopent-2-enyl cation is a 1,3-dialkylallyl cation stabilized by allylic conjugation. Cyclopentadienyl cation would be stabilized twice by allylic conjugation, but it realizes a Hückel  $\pi$ -system with four electrons (Section 4.5.8) that is antiaromatic, thus destabilized electronically. In contrast, tropylium cation (Section 4.5.13) is a six electron Hückel system that is stabilized by aromaticity.

**Problem 1.32** Ethyl cation and methylsilicenium ion are both primary cations. Explain the data of Table 1.A.16, in particular  $\Delta_r H^\circ(\text{Et}^+ + \text{MeSiH}_3 \rightleftharpoons \text{MeSiH}_2^+ + \text{EtH}) = -20 \text{ kcal mol}^{-1}$ . Why is this value not closer to zero?

**Answer**

In this equilibrium one exchanges one Si—H bond for a C—H bond. The latter is c.  $14 \text{ kcal mol}^{-1}$  more stable than the former as given by the comparison  $DH^\circ(\text{CH}_3\cdot/\text{H}\cdot) = 104.7 \text{ kcal mol}^{-1}$  with  $DH^\circ(\text{SiH}_3\cdot/\text{H}\cdot) = 90.3 \text{ kcal mol}^{-1}$  [18, 19]. This does not account totally for the  $20 \text{ kcal mol}^{-1}$  of exothermicity in favor of the silenium cation. One needs to consider also the higher polarizability of the Si atom compared with that of the C atom. The Si atom has more electrons circulating about its nucleus than the C atom. The Si atom is thus more polarizable than the C atom. The positive charge in  $\text{MeSiH}_2^+$  is better supported by the Si atom than by the carbon atom in  $\text{MeCH}_2^+$ .

**Problem 1.33** Compare the gas phase hydride affinities of the following primary alkyl cations:  $\text{Et}^+$ ,  $n\text{-Pr}^+$  and  $n\text{-Bu}^+$ . Why are they not the same?

**Answer**

Table 1.A.14 gives  $DH^\circ(\text{Me-CH}_2^+/\text{H}^-) = 270$ ,  $DH^\circ(\text{Me-CH}_2\text{-CH}_2^+/\text{H}^-) = 267$ , and  $DH^\circ(\text{Me-CH}_2\text{-CH}_2\text{-CH}_2^+/\text{H}^-) = 265 \text{ kcal mol}^{-1}$ .

In the absence of solvation, the larger the alkyl substituent, the larger its polarizability, the better it stabilizes the primary carbenium ion.

**Problem 1.34** Calculate the heat of cyclopropanation of ethylene with  $\text{CH}_2\cdot$  (methylene).

**Answer**

$$\Delta_r H^\circ(\text{CH}_2\cdot + \text{CH}_2=\text{CH}_2 \rightleftharpoons c\text{-C}_3\text{H}_6) = 12.74(\pm 0.14) - 62.9(\pm 0.6) - 12.54(\pm 0.1) = -62.7 \pm 0.85 \text{ kcal mol}^{-1}$$

**Problem 1.35** Calculate the heat of the addition of trimethylenemethane to ethylene giving methylenecyclopentane.

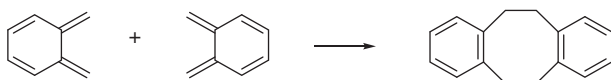
**Answer**

$\Delta_r H^\circ((\text{CH}_2)_3\text{C} + \text{CH}_2=\text{CH}_2 \rightleftharpoons \text{methylenecyclopentane}) = 2.4 - 62 - 12.5 = \text{c. } -72 \text{ kcal mol}^{-1}$ . The standard heat of formation of trimethylenemethane is estimated in the following way:  $\Delta_f H^\circ(\text{trimethylenemethane}) = \Delta_f H^\circ(\text{isobutylene}) + 2DH^\circ(2\text{-methylallyl}\cdot/\text{H}\cdot) - DH^\circ(\text{H}\cdot/\text{H}\cdot) = -4.3 + 2(85.1) - 104.4 \approx 62 \text{ kcal mol}^{-1}$ .

**Problem 1.36** What is the major product of cyclodimerization of *o*-xylylene?

**Answer**

*o*-Xylylene is a highly reactive diene that searches to recover the aromatic stabilization of the benzene system. It can do that by entering into (4+2)- (Diels–Alder reactions) and (4+4)-cycloadditions. The cyclodimerization leading to the highest exothermicity is the [4+4]-cycloaddition forming dibenzocycloocta-1,5-diene.

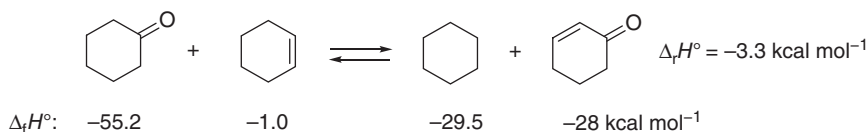


**Problem 1.37** Estimate the equilibrium constant at  $25^\circ\text{C}$  for  $\text{phenol} \rightleftharpoons \text{cyclohex-2,4-dien-1-one}$  [20, 21].

**Answer**

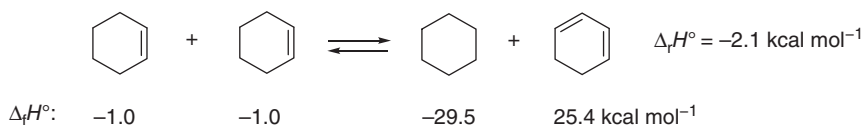
$\Delta_r H^\circ$  (phenol  $\rightleftharpoons$  cyclohex-2,4-dien-1-one) = gain of stability for enol  $\rightleftharpoons$  ketone ( $-11 \text{ kcal mol}^{-1}$ ; Section 1.12.3), plus gain in stability for the  $\pi$ -conjugation in cyclohexa-2,4-dienone ( $-5.4 \text{ kcal mol}^{-1}$ ; see below) and loss of aromaticity of phenol ( $36.2 \text{ kcal mol}^{-1}$ ; see below) =  $19.8 \text{ kcal mol}^{-1}$ .

The following equilibrium gives a first estimate of the  $\pi$ -conjugation stabilization effect in cyclohex-2-enone ( $-3.3 \text{ kcal mol}^{-1}$ ):



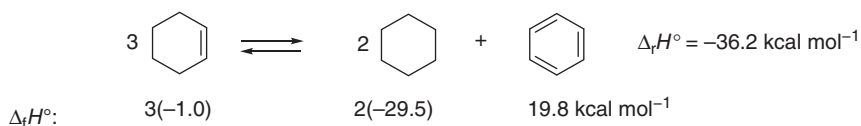
The above equilibrium compares the heats of hydrogenation of cyclohex-2-enone into cyclohexanone with the heat of hydrogenation of cyclohexene into cyclohexane. It ignores the differential hyperconjugation effects ( $\sigma(\text{CH}_2)/\pi(\text{C}=\text{O})$  and  $\sigma(\text{CH}_2)/\pi(\text{C}=\text{C})$  interactions) between products and reactants. In the products one counts two such interactions and four in the reactants. The difference of c.  $2 \text{ kcal mol}^{-1}$  in heat of formation of a terminal olefin (1-alkylethylene) with its 1,2-diakylethylene isomers could be used as the stabilization introduced by one ( $\sigma(\text{CH}_2)/\pi(\text{C}=\text{C})$ ) interaction. With the above equilibrium, one ignores also the differential ring strain effects between products and reactants.

Making the same simplifications (ignoring differential hyperconjugation effects and ring strain effects) the heat of the next equilibrium ( $-2.1 \text{ kcal mol}^{-1}$ ) can be considered as the  $\pi$ -conjugation effect in cyclohexa-1,3-diene.



This leads to an estimate of  $-3.3 - 2.1 = -5.4 \text{ kcal mol}^{-1}$  for the stabilization of cyclohexa-2,4-dien-1-one due to  $\pi$ -conjugation.

Stabilization by aromaticity in phenol is taken to be the same as that in benzene for which the following equilibrium gives a first estimate ( $-36.2 \text{ kcal mol}^{-1}$ , ignores differential hyperconjugation and ring strain effects):



One estimates  $\Delta_r G^\circ$  (phenol  $\rightleftharpoons$  cyclohex-2,4-dien-1-one) =  $\Delta_r H^\circ$  (phenol  $\rightleftharpoons$  cyclohex-2,4-dien-1-one)  $- T\Delta_r S^\circ = 19\,800 - 298(\Delta_r S^\circ) \text{ cal mol}^{-1}$ .

Phenol has one  $C_2$ -axis whereas cyclohexadienone does not have any rotation axis. Thus  $\Delta_r S^\circ$  (phenol  $\rightleftharpoons$  cyclohex-2,4-dien-1-one) =  $R \ln 2 = 1.987 \ln 2 = 1.38 \text{ eu}$ . This gives

$$\Delta_r G^\circ \text{ (phenol } \rightleftharpoons \text{ cyclohex-2,4-dien-1-one)} = 19\,800 - 298(1.38) = 19\,390 \text{ cal mol}^{-1}.$$

This leads to  $\log K = -(\Delta_r G^\circ / RT) \cdot \log e = (-19\,390 / (1.987 \times 298)) \cdot 0.4343 = -14.22$ , and  $K = 0.6 \times 10^{-14}$ .

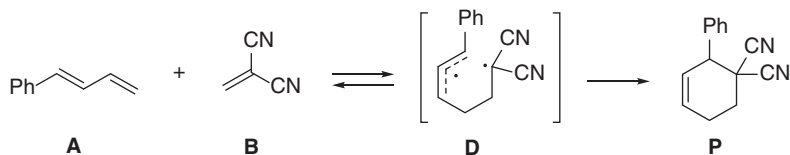
One can also use at  $25^\circ \text{C}$   $\log K = \Delta_r G^\circ \text{ (phenol } \rightleftharpoons \text{ cyclohex-2,4-dien-1-one)} / 1.36 = -14.25$  (see equation (1.8)).

Our estimated value of  $K$  (phenol  $\rightleftharpoons$  cyclohex-2,4-dien-1-one, gas phase) can be compared with the calculated (CBS-QB3) value  $\kappa = 7.15 \times 10^{-14}$  reported by Zhu and Bozzelli, and with the gas phase (flash photolysis) experimental value  $K = 10^{-13 \pm 1}$  [21].

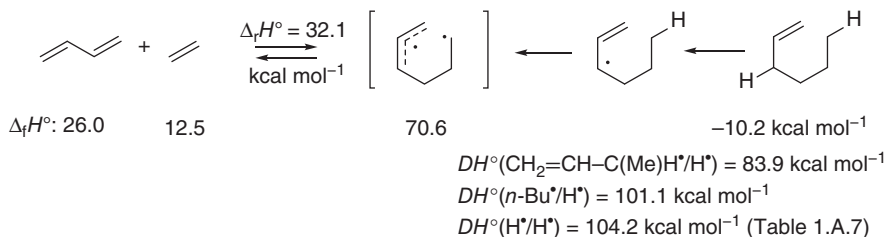
**Problem 1.38** Can the Diels–Alder addition of methylenemalonodinitrile with 1-phenylbutadiene occur through a diradical intermediate? Which one?

### Answer

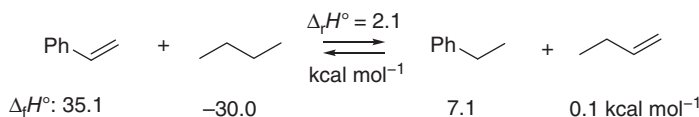
The most stable diradical resulting from the condensation of 1-phenylbutadiene with methylenemalonodinitrile possesses an allyl radical enjoying stabilization by the phenyl substituent and an alkyl radical doubly substituted by the two cyano substituents. Any other diradicals would not be as stable.



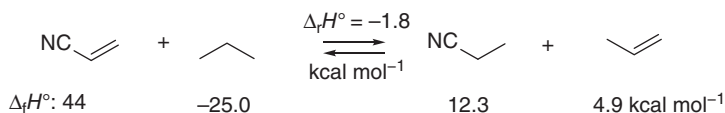
$\Delta_f H^\circ(\text{A} + \text{B} \rightleftharpoons \text{D})$  can be deduced from  $\Delta_f H^\circ(\text{butadiene} + \text{ethylene} \rightleftharpoons \text{hex-2-en-1,6-diyl diradical}) = 32.1 \text{ kcal mol}^{-1}$  by considering  $\pi$ -conjugation stabilization of cycloaddends **A** and **B** introduced by their substituent with respect to butadiene and ethylene, and the phenyl and cyano substituent effect on the relative stability of the radicals they substitute.  $\Delta_f H^\circ(\text{hex-2-en-1,6-diyl diradical}) = \Delta_f H^\circ(\text{hex-1-ene}) + DH^\circ(\text{but-3-en-2-yl}^\bullet/\text{H}^\bullet) + DH^\circ(\text{but-1-yl}^\bullet/\text{H}^\bullet) - DH^\circ(\text{H}^\bullet/\text{H}^\bullet) = -10.2 + 83.9 + 101.1 - 104.2 = 70.6 \text{ kcal mol}^{-1}$ .



The stabilizing  $\pi$ -conjugation effect ( $-2.1 \text{ kcal mol}^{-1}$ ) of the 1-phenyl substituent on butadiene can be evaluated by the standard heat of the following equilibrium, which compares the standard heats of hydrogenation of styrene and of propene.



With the next equilibrium one compares the heats of hydrogenation of the C=C double bond of but-1-ene with that of acrylonitrile. One finds that  $\pi$ -conjugation in acrylonitrile does not stabilize the system; in fact, the available data indicate a destabilization of c.  $2 \text{ kcal mol}^{-1}$  in acrylonitrile. This arises from the stabilizing  $\sigma(\text{CH}_2)/\pi(\text{CN})$  hyperconjugative interaction in propionitrile, which is not present in acrylonitrile. This is not compensated by the stabilizing  $\sigma(\text{CH}_3)/\pi(\text{C}=\text{C})$  hyperconjugation in propene, an interaction which is absent in propane.



Thus, it appears that the stabilizing effect introduced on the diene by the 1-phenyl substituent is compensated somewhat by a destabilization effect of the 1-cyano substituent effect in the dienophiles. The 1,1-dicyano substitution introduces an electrostatic repulsion effect due to the two geminal cyano dipoles, a repulsion effect that is probably similar to that in the diradical and cycloadduct. In the above analysis, one ignores the differential  $\sigma(\text{CH}_2)/\pi(\text{C}=\text{C})$  hyperconjugation effects. The stabilization effects introduced by the phenyl group on diradical **D** must be a part of the phenyl substitution stabilizing effect on methyl radical ( $11 \text{ kcal mol}^{-1}$ , Table 1.A.9) as the

diradical **D** is already stabilized by allylic conjugation. One chooses the phenyl stabilization effect on **D** to be c.  $6 \text{ kcal mol}^{-1}$  as the spin is delocalized on two carbon centers in the allyl radical.

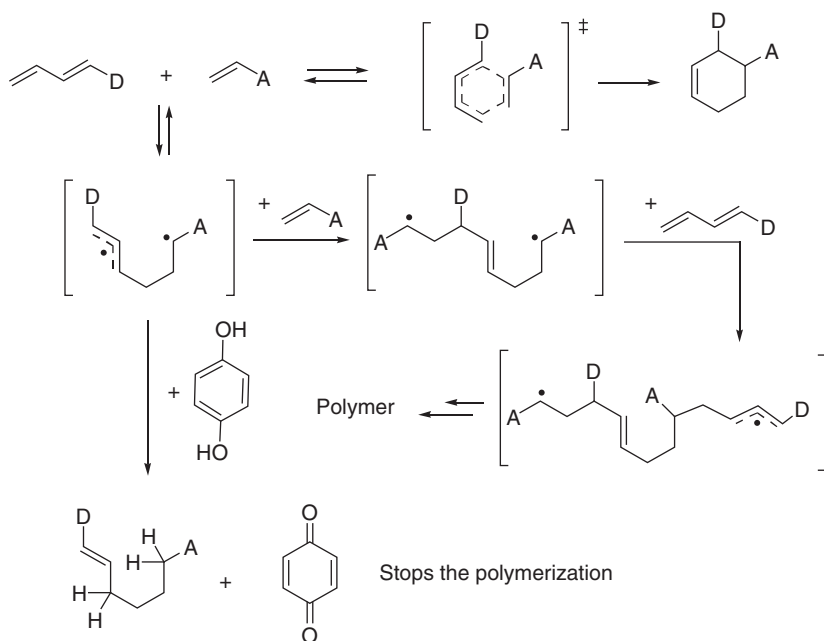
Table 1.A.10 gives  $DH^\circ(\text{Me}(\text{NC})_2\text{C}^\bullet/\text{H}^\bullet) = 84.6 \text{ kcal mol}^{-1}$  for homolysis in DMSO to be compared with  $DH^\circ(t\text{-Bu}^\bullet/\text{H}^\bullet) = 95.7 \text{ kcal mol}^{-1}$  in DMSO and  $95.2 \text{ kcal mol}^{-1}$  in the gas phase. The stabilization effect of methyl radical and in the gas phase by the cyano substituent effect amounts to  $-12 \text{ kcal mol}^{-1}$ . Thus the difference  $DH^\circ/\text{Et}^\bullet/\text{H}^\bullet, (\text{gas}) - DH^\circ(\text{Me}(\text{NC})_2\text{C}^\bullet/\text{H}^\bullet, \text{DMSO}) = 100.7 - 84.6 = 16 \text{ kcal mol}^{-1}$  looks reasonable for the stabilizing effect of the two geminal cyano groups in diradical **D**. Therefore, a first estimate to the reaction heat  $\Delta_r H^\circ(\text{A} + \text{B} \rightleftharpoons \text{D}) = 32.1 - 6 - 16 = 10.1 \text{ kcal mol}^{-1}$  is obtained. If one considers now the reaction entropy,  $\Delta_r S^\circ(\text{A} + \text{B} \rightleftharpoons \text{D}) = \Delta_r S^\circ(\text{butadiene} + \text{ethylene} \rightleftharpoons \text{cyclohexene}) - \text{liberation of the rotation of three } \sigma(\text{C}-\text{C}) \text{ bonds in the diradical } \text{D} \text{ (see Section 2.11)} = S^\circ(\text{cyclohexene}) - S^\circ(\text{butadiene}) - S^\circ(\text{ethylene}) + 15 \text{ eu} = 74.2 - 66.6 - 52.5 + 15 = -30 \text{ eu}$ , which corresponds to an entropy cost of  $-T\Delta_r S^\circ \approx 10 \text{ kcal mol}^{-1}$  at room temperature.

This gives  $\Delta_r G^\circ(\text{A} + \text{B} \rightleftharpoons \text{D}) \approx 20 \text{ kcal mol}^{-1}$ . In Chapter 5, we shall show that **D**, which is only  $20 \text{ kcal mol}^{-1}$  above **A** + **B**, can be an intermediate of the Diels–Alder reaction **A** + **B** at room temperature.

**Problem 1.39** Why are the yields of Diels–Alder additions usually better when adding a small amount of a radical scavenging agent such as 1,4-dihydroxybenzene (parahydroquinone) or 4-methyl-2,6-bis(*tert*-butyl)phenol?

### Answer

Because diradicals resulting from the condensation of two cycloaddends are formed concurrently with the cycloadducts that may or may not follow one-step, concerted mechanisms, addition of radical scavenging agents such as hydroquinone and 4-methyl-2,6-bis(*tert*iobutyl)phenol reduces the diradicals and retards the polymerization of the cycloaddends.



**Problem 1.40** Estimate the heat of formation of naphthalene-1,4-diyl diradical and compare it with the experimental values proposed by Roth and coworkers.

### Answer

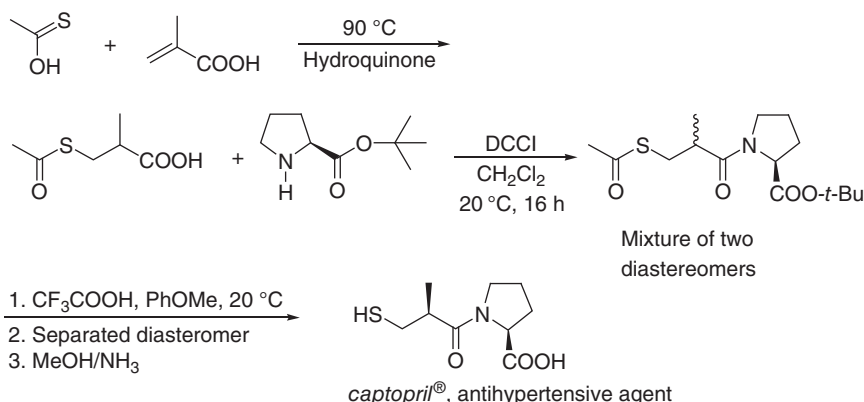
$\Delta_f H^\circ(\text{naphthalene-1,4-diyl diradical, est.}) = \Delta_f H^\circ(\text{naphthalene}) + 2DH^\circ(\text{Ph}^\bullet/\text{H}^\bullet) - DH^\circ(\text{H}^\bullet/\text{H}^\bullet) = 36.0(\pm 2.0) + 2(113.3 \pm 1.0) - 104.2 = 158.4 \pm 4.0 \text{ kcal mol}^{-1}$ . Squires and coworkers have measured  $DH^\circ(\text{naphth-1-yl}^\bullet/\text{H}^\bullet) = 113.4 \pm 5.2 \text{ kcal mol}^{-1}$  similar to the C–H bond energy of benzene [22].

Roth and coworkers measured  $\Delta_f H^\circ(\text{naphthalene-1,4-diyl diradical, exp.}) = 152.9 \pm 1.4 \text{ kcal mol}^{-1}$  [23].



**Problem 1.41** Captopril® is one of the early discovered inhibitors of angiotensin converting enzymes and is an antihypertensive agent. It can be prepared according to the method presented below [25].

- Why is the sulfur moiety of  $\text{CH}_3\text{C}(\text{S})\text{OH}$  adding to methacrylic acid and not the oxygen moiety?
- Why does one add hydroquinone to this reaction mixture?
- The second step of the procedure is an amidification. What is the role of dicyclohexylcarbodiimide (DCCI) added to this reaction mixture?
- The third step implies the acidic hydrolysis of the *t*-butyl ester. What is the mechanism of this reaction?

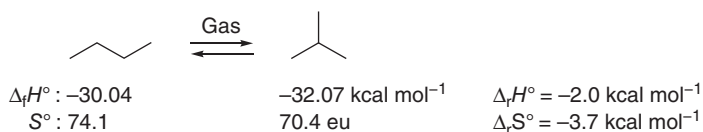


### Answer

- As per Newman–Kwart rearrangement, which converts phenols to thiophenols via their O- and S-thiocarbamates (Problem 1.9), thionocarboxylic esters ( $\text{R}-(\text{C}=\text{S})-\text{OR}'$ ) are less stable than their isomeric thioesters ( $\text{R}-(\text{C}=\text{O})-\text{SR}'$ ). Furthermore, the addition of an alcohol to an alkene and the addition of a carboxylic acid to an alkene are less exothermic than the addition of a thiol to the same alkene (Section 1.6.1, equilibria (1.48)).
- One adds hydroquinone to trap radicals and diradicals that could be formed concurrently with the nucleophilic conjugate addition of the thionoacetic acid to methacrylic acid. In the absence of radical scavenger (hydroquinone) radical-induced polymerization of methacrylic acid could compete and this would lower the yield of the desired reaction.
- DCCI is a carbodiimide (dicyclohexylcarbodiimide) that reacts with water, coproduct of the amidification, forming a highly stable urea derivative (*N,N'*-dicyclohexylurea). One thus shifts the equilibrium amine + carboxylic acid  $\rightleftharpoons$  carboxamide + water in favor of the amide, the desired product.
- The acid-catalyzed hydrolyses of *tert*-butyl esters are usually  $\text{E}_1$ -eliminations or  $\text{S}_{\text{N}}1$ -substitutions. The conjugate acid of the ester ( $\text{RCOO}-t\text{-Bu} + \text{HX} \rightleftharpoons \text{RC}^{(+)}(\text{OH})-\text{O}-t\text{-Bu} + \text{X}^-$ ) undergoes heterolysis into  $t\text{-Bu}^+ + \text{X}^- + \text{RCOOH}$  (first order rate law, depends on the concentration of the ester and the acidic catalyst HX, not on the concentration of base or nucleophile). Then  $t\text{-Bu}^+$  combines with  $\text{X}^-$  or the solvent to give isobutylene + HX ( $\text{E}_1$ -elimination) or eventually, at low temperature,  $t\text{-Bu}-\text{X}$  ( $\text{S}_{\text{N}}1$  substitution).

**Problem 1.42** Estimate the equilibrium constant of the isomerization butane  $\rightleftharpoons$  isobutane (2-methylpropane) at 300 K, at 600 K.

### Answer



The branched hydrocarbon, 2-methylpropane (isobutane), is more stable than the linear hydrocarbon, butane, and its entropy is smaller than that of butane. With one methyl group more than butane, it thus has more local symmetry (for a freely rotating  $\text{CH}_3$  group, the entropy is reduced by  $-\text{Rln } 3$ ; see Eq. (1.35)). Furthermore, isobutane has a  $C_3$  axis, whereas butane has a  $C_2$  axis. Thus the entropy of isobutane is further reduced by  $\text{Rln } 3 + \text{Rln } 2$ . Therefore,  $\Delta_r S^\circ(\text{butane} \rightleftharpoons \text{isobutane}) \cong -2.18 - 2.18 + 1.38 = -2.98 \text{ eu}$ . Experimentally,  $\Delta_r S^\circ(\text{butane} \rightleftharpoons \text{isobutane}) = -3.7 \text{ eu}$ ; this is in fact more negative than the estimate based on variation on symmetry and local symmetry between product and reactant. Isobutane is more compact than butane, thus its three moments of inertia must be smaller than those of butane. From Eq. (1.35) one predicts that entropy decreases as the inertia moments diminish. This explains the experimental value  $\Delta_r S^\circ(\text{butane} \rightleftharpoons \text{isobutane}) = -3.7 \text{ eu}$  vs. the estimated value of  $-2.98 \text{ eu}$ . At  $T = 300 \text{ K}$ , one calculates  $\Delta_r G^{300\text{K}} \cong \Delta_r H^\circ - 300(\Delta_r S^\circ) = -2000 - 300(-3.7) = -2000 + 1110 = -890 \text{ cal mol}^{-1}$ . This gives  $\ln K^{300\text{K}} = -\Delta_r G^{300\text{K}}/1.99 \times 300 = 1.490$ , or  $K^{300\text{K}} = e^{1.490} = 4.4371$ , which corresponds to 81.5% isobutane and 18.5% butane in equilibrium at 300 K. For the reaction at  $T = 600 \text{ K}$ , one can use the standard heats of formation and entropies. This is reasonable as the error that will be made on  $\Delta_r H^{600\text{K}}$  will be compensated more or less by the error made on  $T\Delta_r S^{600\text{K}}$ . Thus  $\Delta_r G^{600\text{K}} \cong -2000 - 600(-3.7) = -2000 + 2220 = +220 \text{ cal mol}^{-1}$ . This gives  $\ln K^{600\text{K}} = -220/1.99 \times 600 = -0.184$ , or  $K^{600\text{K}} = e^{-0.184} = 0.832$ , which corresponds to 45.4% of isobutane and 54.6% of butane at equilibrium at 600 K.

**Problem 1.43** Methyl isopropyl ketone (MIPK: 3-methylbutan-2-one) is an efficient high-octane ( $>100$ ) oxygenate gasoline additive, without many of the undesirable effects of the widely used methyl *tert*-butyl ether. One of the methods of preparation of MIPK involves the rearrangement of pivalaldehyde (2,2-dimethylpropanal) catalyzed by strong acids [26]. Evaluate the equilibrium constant for this rearrangement at  $25^\circ\text{C}$  using gas phase standard heats of formation for MIPK and *t*-BuCHO.

#### Answer

Table 1.A.4 gives  $\Delta_f H^\circ(3\text{-methylbutan-2-one}) = -62.76 \pm 0.21 \text{ kcal mol}^{-1}$ . It does not give

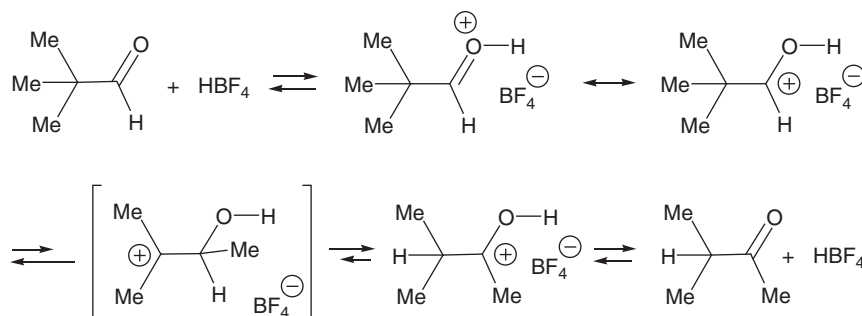
$\Delta_f H^\circ(2,2\text{-dimethylpropanal})$ , but gives  $\Delta_f H^\circ(2\text{-methylpropanal}) = -51.57 \pm 0.37 \text{ kcal mol}^{-1}$  and  $\Delta_f H^\circ(3,3\text{-dimethylbutan-2-one}) = -69.47 \pm 0.21 \text{ kcal mol}^{-1}$ . Thus, 3-methyl substitution of 3-methylbutan-2-one amounts to  $-69.47 - (-62.76) \approx -6.7 \text{ kcal mol}^{-1}$ . If one admits that the same substitution effect can be retained for the 2-methyl substitution of 2-methylpropanal, one estimates  $\Delta_f H^\circ(2,2\text{-dimethylpropanal, est.}) = -51.57 - 6.7 \approx -58.3 \text{ kcal mol}^{-1}$ . This gives  $\Delta_r H^\circ(2,2\text{-dimethylpropanal} \rightleftharpoons 3\text{-methylbutan-2-one}) = -62.76 - (-58.3) \approx -4.5 \text{ kcal mol}^{-1}$ .

To a first approximation, the entropy variation of this reaction must be close to zero as it is an isomerization with no blockage of liberalization of single bond rotation. There are three methyl groups in both the reactant and product. *t*-BuCHO has a local  $C_3$  axis (*t*-Bu group), which is not present in MIPK. Thus, the overall symmetry of MIPK is lower than that of *t*-BuCHO, which contributes  $\text{Rln } 3 = 2.18 \text{ eu}$  to the entropy of reaction (reaction entropy increases because the product is less symmetrical than the reactant):

$$\Delta_r S^\circ(2,2\text{-dimethylpropanal} \rightleftharpoons 3\text{-methylbutan-2-one}) = 2.18 \text{ cal mol}^{-1} \text{ K}^{-1}$$

Accordingly,  $\Delta_r G^\circ(2,2\text{-dimethylpropanal} \rightleftharpoons 3\text{-methylbutan-2-one}) = -4500 - 298(2.18) = 5156 \text{ cal mol}^{-1}$ . This gives  $K = \exp(-\Delta_r G^\circ/RT) = \exp.(5156/1.987 \times 298) \approx 6050$  at  $25^\circ\text{C}$ .

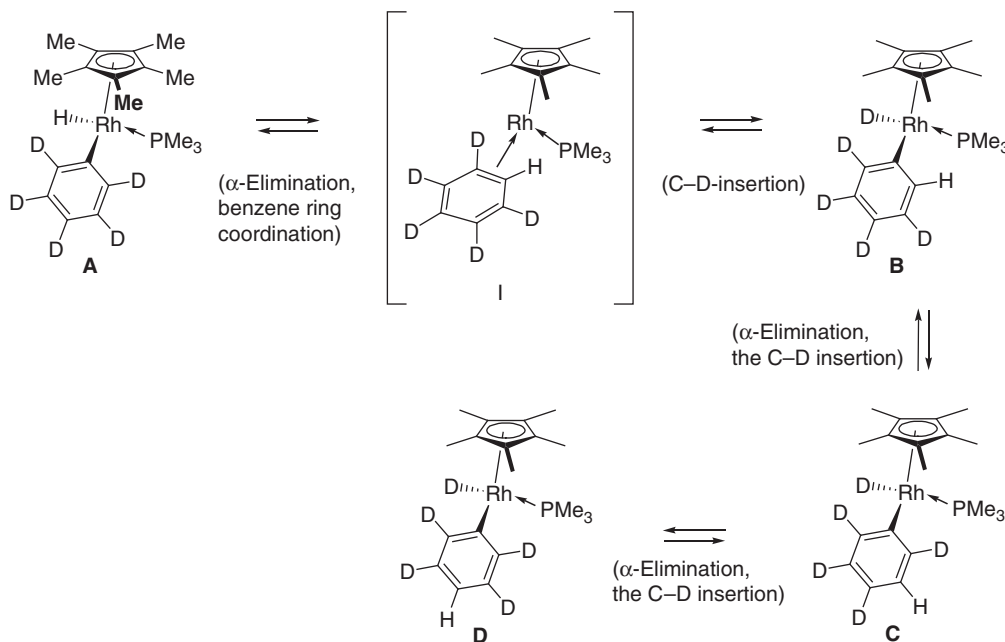
A possible mechanism for the acid-catalyzed isomerization of *t*-BuCHO into MIPK is given below. It involves protonation of the aldehyde followed by two successive Wagner–Meerwein rearrangements (Section 5.5.1) that are the 1,2-migrations ((1,2)-sigmatropic shifts) of a methyl group and of an hydride.



**Problem 1.44** Complex **A** equilibrates with complexes **B**, **C**, and **D** via intermediate **I**. At equilibrium the relative proportions of **A/B/C/D** are 2.7 : 2 : 2 : 1. What are **B**, **C**, **D**, and **I**? Why are the relative proportions not 1 : 2 : 2 : 1?

**Answer**

In the absence of equilibrium isotopic effect (EIE) the proportion of **A/B/C/D** should be 1.0 : 2.0 : 2.0 : 1.0 (statistical distribution of the H atom between one Rh—H bond, two *ortho* C—H, two *meta* C—H, and one *para* C—H bonds of the phenyl group. At 25 °C in THF- $d_6$  the measured proportion are 2.7 : 2.0 : 2.0 : 1.0, which demonstrates that the heavy (deuterium) isotope prefers the stronger C—H bonds of the phenyl group to the weaker metal—H bond [26].



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