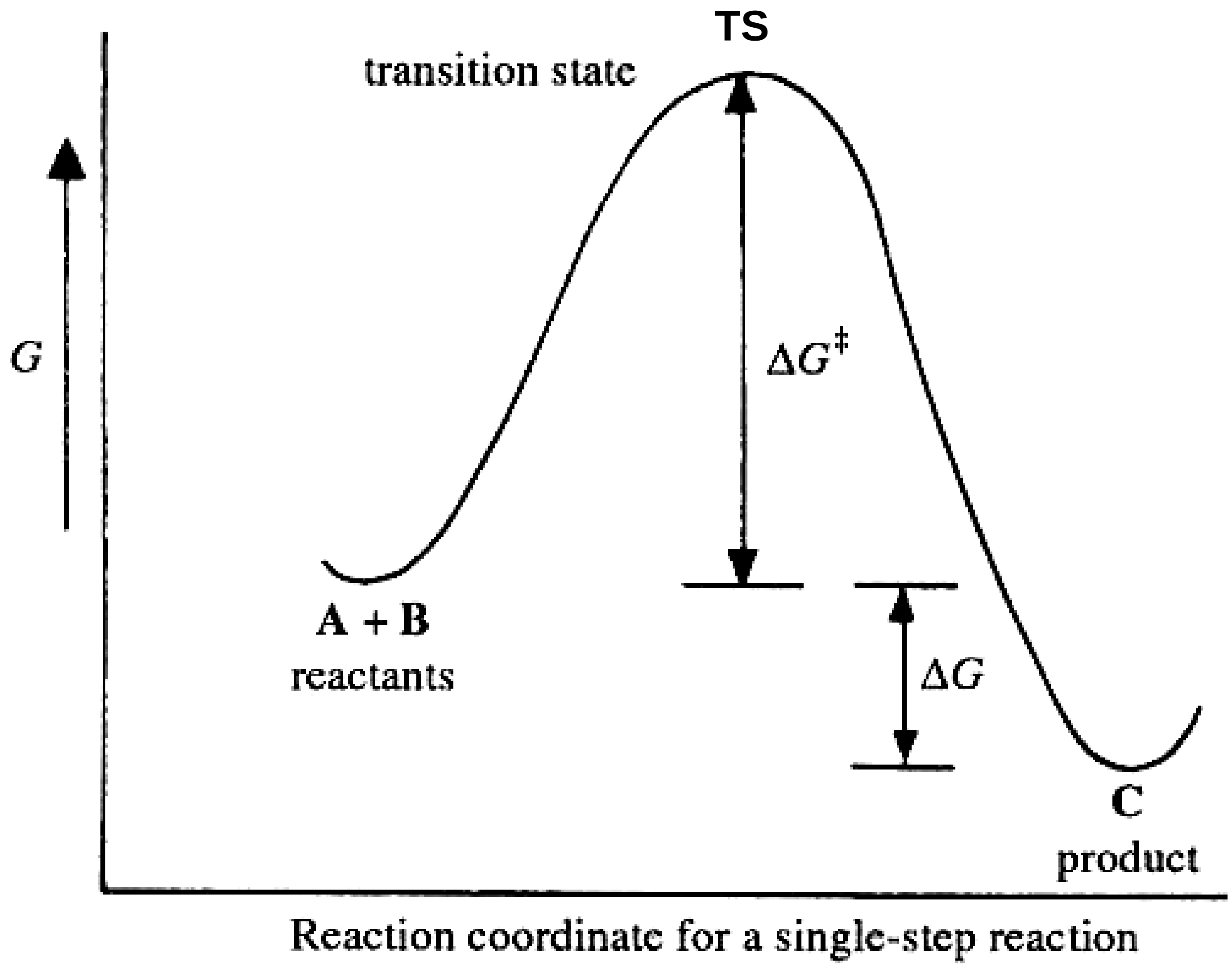
Chapter 3. Stability and Reactivity

- Thermodynamic stability: ΔH; feasibility of reactions
  - stability of hydrocarbons: 🕮 256 Table 3.1 & 🕮 257 top
- How to estimate ΔH: $\Delta H < 0$, exothermic
  - bond dissociation energy (BDE) of the reactants & products
    - $\Delta H = \Delta H_R - \Delta H_P \cong \sum \mathrm{BDE}_{(\mathrm{formed})} - \sum \mathrm{BDE}_{(\mathrm{broken})}$; 🕮 259 top
  - $\mathrm{BDE}_{(\mathrm{product})}$ from electronegativity (χ): L. Pauling; 🕮 259
    - stabilization energy (SE): 🕮 260 Table 3.3
    - CH_3-X < *pri*-C-X < *sec*-C-X < *tert*-C-X: 🕮 261 top
  - group equivalent methods: $\sum \Delta H_{(\mathrm{componet\ group})}$; 🕮 262 top
  - computational methods: MM4, ab initio & DFT; relavance
  - no information on solvation effects & rate of reactions

❖ Chemical Kinetics

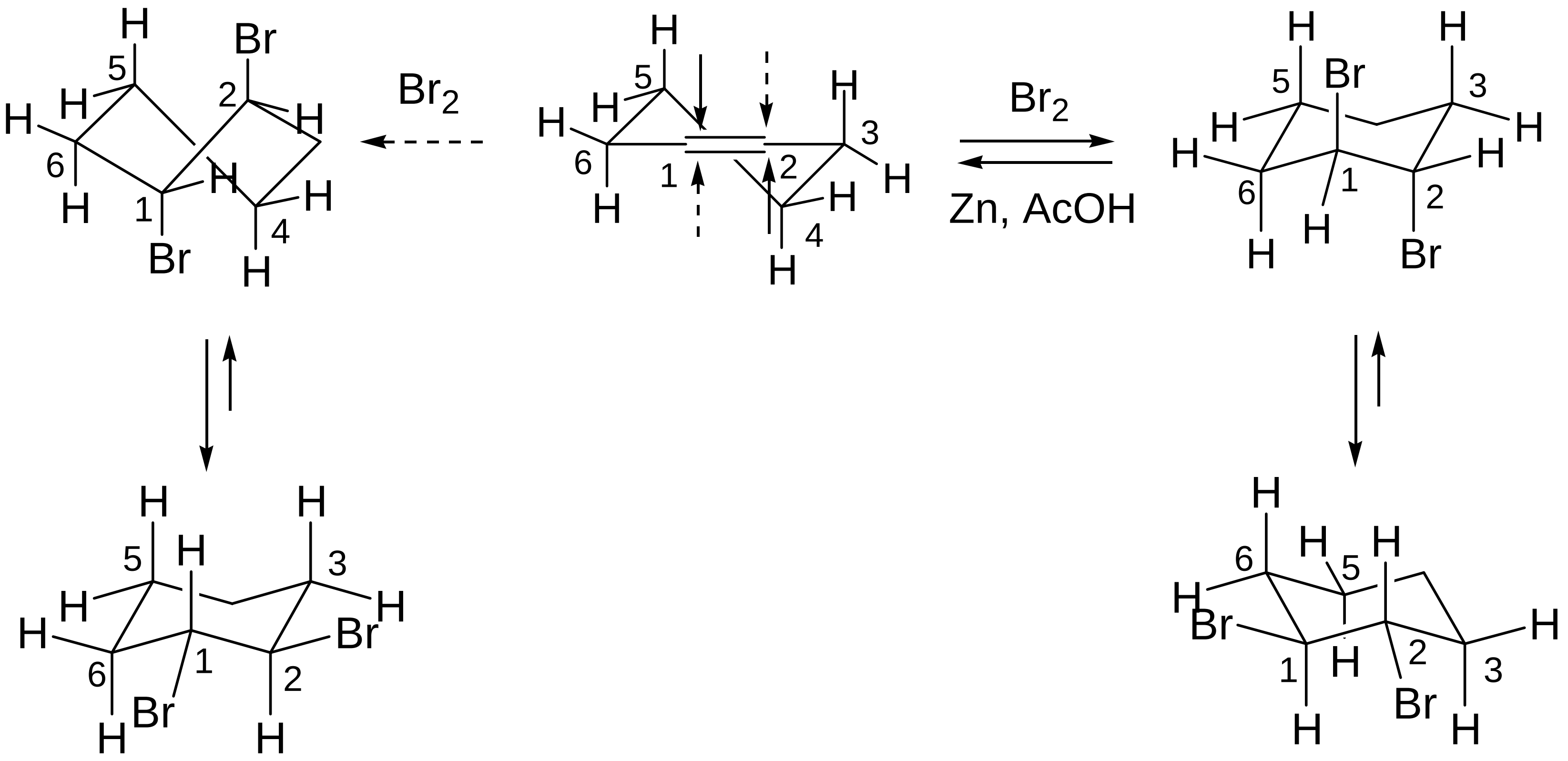
- Quantitative relationship of reactivity & structure
  - rate: detailed insight into the reaction mechanisms
- Transition-state theory: $k_{r(\text{decomp.})} \cong 6\text{-}10^{12}/\text{sec}$
  - an activated complex going to product at very fast rate
  - $A + B \rightleftarrows TS \rightarrow C$: rate = $k_r[A][B]$, $k_r \propto \Delta G^{\ddagger}$; 📖 271 & 272
    - solvent effect for $\Delta S^{\ddagger}$: -6.6 cal/mol·°C for solvolysis of *t*-butyl chloride; greater ordering of solvent
- Potential energy changes in reactions
  - reaction energy profiles: TS vs intermediate with time
    - one/two/three-step reactions: rate-determining step; 📖 275

TS
transition state
G
$\Delta G^\ddagger$
ΔG
A + B
reactants
C
product
Reaction coordinate for a single-step reaction

Potential Energy Changes in Reactions

- Principle of microscopic reversibility
  - a reaction follows the lower energy pathway: (de)bromination
    - the same pathway in the forward direction will be followed in the reverse reaction: the lowest energy barrier for either process
- 2/3-D Reaction energy diagrams
  - 2-D: change in two bonds; 📖 276 bot. & 📖 277 Fig. 3.3
    - Albery-More O'Ferrall-Jencks: energy in 3-D: 📖 278 Fig. 3.4
  - reaction cube: changes in 3 bonds; 📖 279 Fig. 3.6
    - more bonding changes: cubes with cubes
- Computation of energy surfaces: E_{TS} = minimum
  - evaluation of energy as a function of structural changes

❖ Microscopic Reversibility: Di(de)bromination



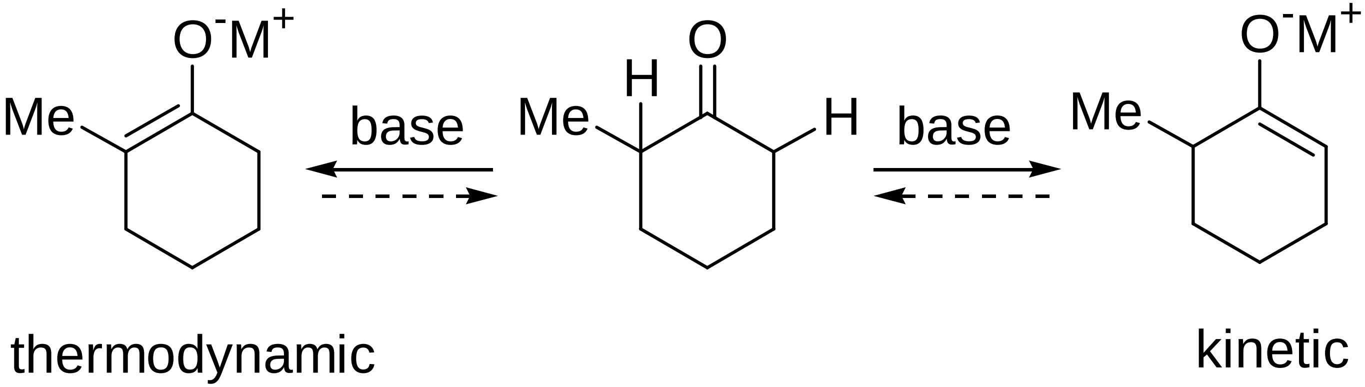
❖ Kinetics and Mechanisms

- ❒ Rate: detailed insight into the reaction mechanisms
- ❒ How to determine the reaction mechanism
    1. Postulate all the plausible mechanisms
    2. Eliminate those mechanisms from the postulated mechanisms incompatible with the observed kinetics
        - ❍ steady-state approximation: reactive intermediates; 🕮 282
            - – the rate of consumption ≅ the rate of formation: 🕮 283
        - ❍ base-catalyzed aldol condensation: 🕮 284
    - ◆ information only about the RDS & the preceding steps
    - ◆ composition but no structure about the transition state

❖ Thermodynamic Stability and Rate (I)

- Kinetic vs thermodynamic control: 📖 286 Fig. 3.8
  - kinetic enolates: bulky strong base, aprotic solvent; 📖 287
    - thermodynamic control: equilibration via an enol form
- Correlations between ΔG^o and $\Delta G^\ddagger$
  - Are more exothermic reactions faster? $\equiv \Delta G^\ddagger \propto \Delta G^o$?
  - Hammond's postulate: 📖 290 Fig. 3.11
    - indirect information about the structure of transition states
      - two states occurring consecutively with nearly the same energy closely resembles each other in structure
      - resemblance of TS structures to reactants or products
    - electrophilic aromatic substitution: bromination; 📖 290-292

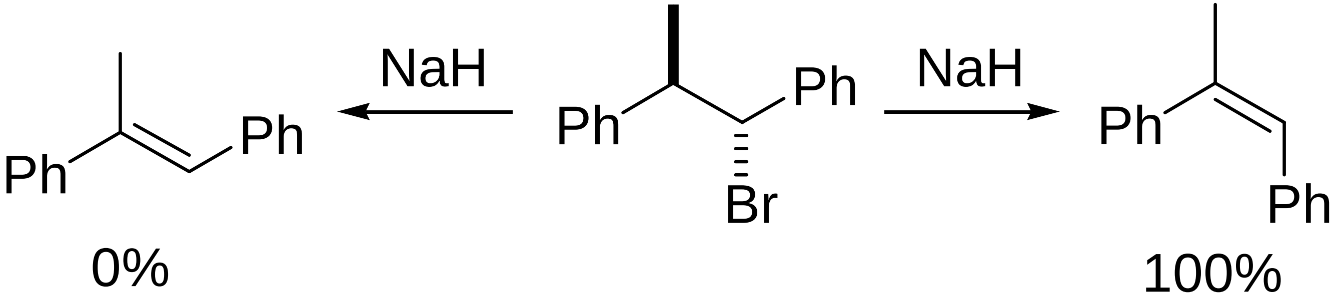
❖ Kinetic vs Thermodynamic Control: Example

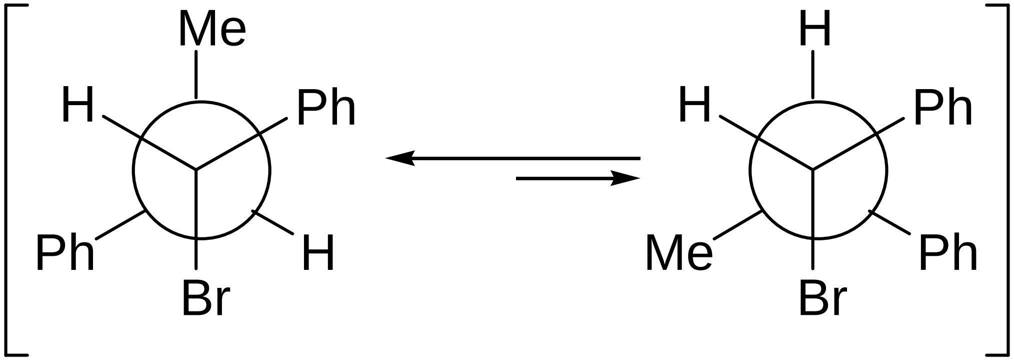


❖ Thermodynamic Stability and Rate (II)

- Correlations between ΔG^o and $\Delta G^‡$
  - Bell-Evans-Polyani relationship: $Ea \propto \Delta H$; 📖 288-9
  - [Home Study] 3.3.2.3 The Marcus Equation: 📖 293-6
- Curtin-Hammett principle: 📖 296 Fig. 3.17
  - effect of conformational equilibria on a chemical reaction
    - “the product ratio is not determined by relative stability of the products (ΔG_c) but primarily by the relative energy of the two TS ($\Delta\Delta G^‡$)”
    - ‘the ratio of conformers (or tautomers) of reactants can not be deduced from the product ratio’
  - example: elimination reactions; antiperiplanar conformation

❖ An Extreme Case

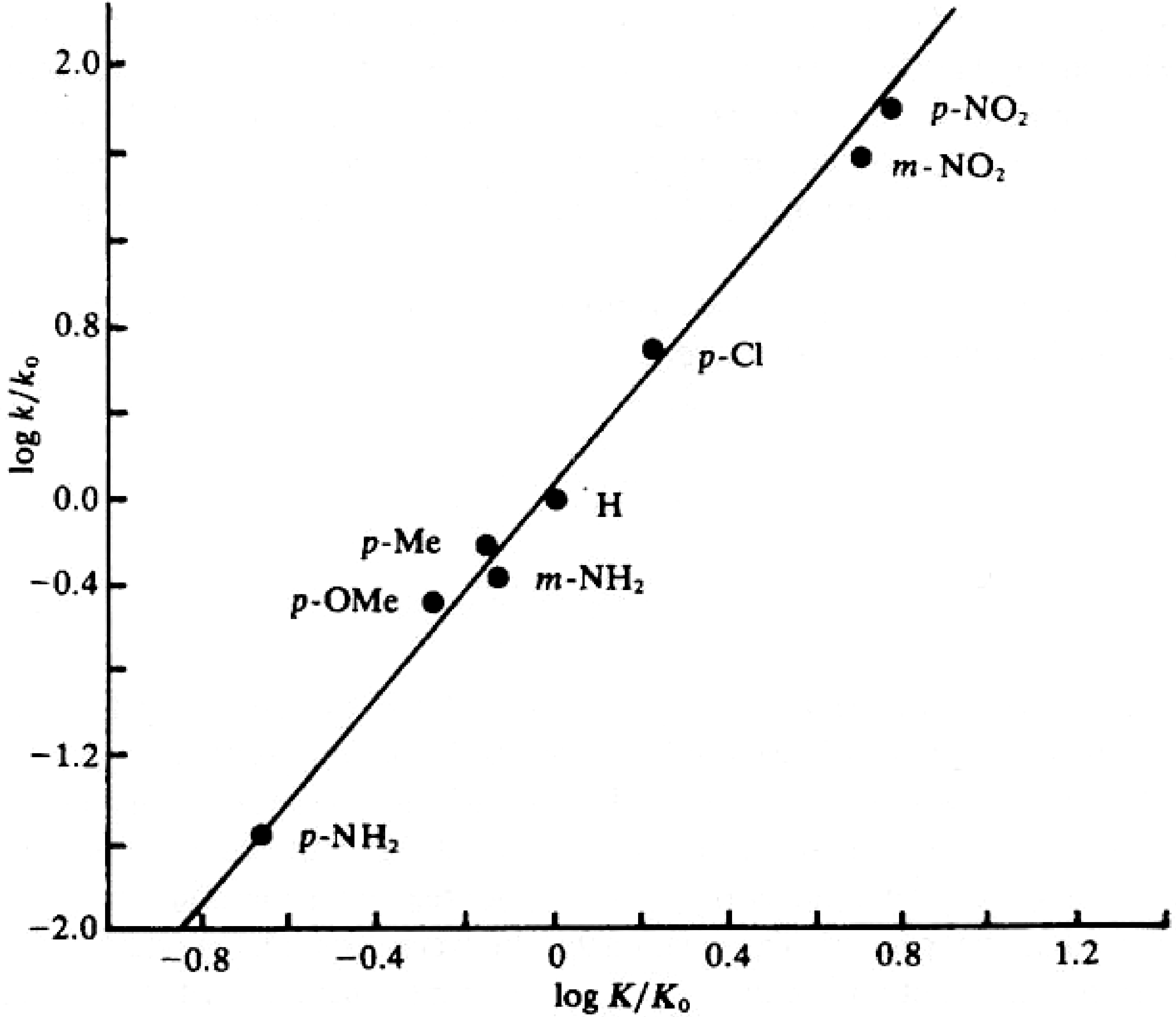




❖ Linear Free-Energy Relationships (I)

- Hammett equation: rates & equilibria; 🕮 336 Fig. 3.25
  - hydrolysis of ethyl benzoates & acidity of benzoic acids
  - $\log k/k_o = m\log K/K_o \rightarrow \Delta(\Delta G^{\ddagger}) = m\Delta(\Delta G)$; 🕮 336-7 (3.42-3)
  - $\log K/K_o = \sigma\rho$, $\log k/k_o = \sigma\rho$: $m = \rho$; 🕮 337 (3.44-5)
    - σ, substituent constant (*m*- or *p*-): ability to donate or withdraw electron density from a reaction site; 🕮 339 Table 3.36
    - ρ, reaction constant (1 for $PhCO_2H$ in water): sensitivity of a particular reaction to the substituent effects; 🕮 340 Table 3.27
  - saponification of $ArCO_2Me$: $\rho = +\ 2.38$; 🕮 339 bottom
    - (+): EWG substituents facilitate the reaction
    - 2.38: more sensitive to substituent effects than those of $PhCO_2H$

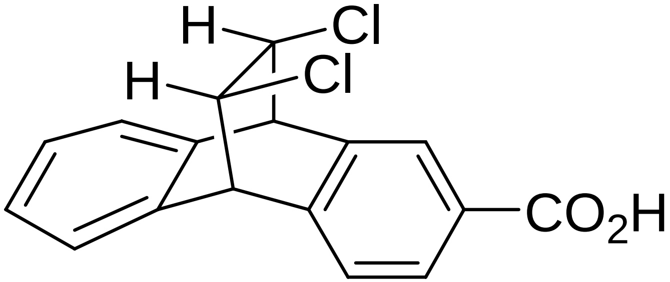
❖ Linear Relationship between Rates & Equilibria



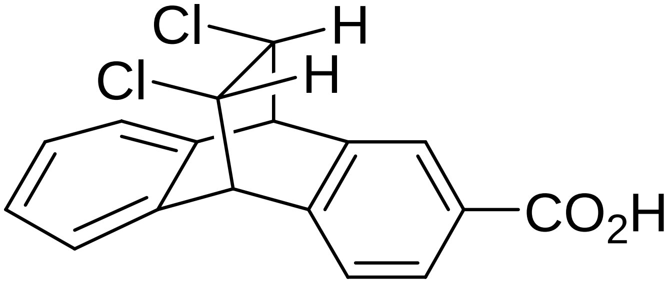
❖ Linear Free-Energy Relationships (II)

- Correlation with the reaction mechanism:
  - solvolysis rates of $ArCH_2Cl$: $\rho = -1.31$; 📖 340 bottom
    - (-): EDG substituents facilitate the reaction
    - 1.31: a bit more sensitive to substituent effects
  - σ from pK_a of the substituted benzoic acid: 📖 339 bottom
- σ: combination of 3 factors; 📖 338 Fig. 3.26
  - resonance effect: π-electron delocalization
  - inductive effect: polarization through σ bonds; polar effects
  - field effect: polarization through space; geometry of molecules

❖ Field Effect: Through-space Electrostatic Interaction



pK_a = 6.07



pK_a = 5.67

❖ Linear Free-Energy Relationships (III)

- Modifications of the Hammett equation: σ_m & σ_p
  - correction for the additional resonance contribution
    - Hammet values: a mixture of resonance and polar effects
    - Taft values: direct resonance; σ^+ & σ^+, 📖 341 top
    - Yukawa-Tsuno equation: 📖 341 eqn. 3.48
    - dual-substituent-parameter equation: $\sigma = \sigma_I + \sigma_R$, polar effects ($\sigma_I$) & resonance effect ($\sigma_R$); 📖 341 eqn. 3.49
    - addition of electronegativity & polarizability: 📖 342 eqn. 3.50
  - classification of substituent groups: 📖 343 Scheme 3.5

❖ Linear Free-Energy Relationships (IV)

- Application to the reaction mechanisms
  - basic hydrolysis of aryl esters: $\rho = +2.38$; 📖 339 bottom
    - negatively charged intermediate $\cong$ TS: RDS; 📖 343 bottom
    - the more electrophilic carbonyl of the esters due to EWG
  - solvolysis of diaryl chlorides in EtOH: $\rho = -4.2$; 📖 340 bot.
    - positively charged intermediate $\cong$ TS: RDS; 📖 344 top
- Nonlinear Hammett plots
  - change in the mechanism: TS or RDS; 📖 344 bottom
    - semicarbazone: $\rho = +3.5$ for ERGs & $\rho = -0.25$ for EWGs
  - aliphatics: additional steric and conformational factors

❖ Electronic Substituent Effects (I)

- Substituent effects: classification
  - electronic, steric and structure-specific effects
  - electronic: resonance & polar effects (inductive & field)
    - unrelated resonance and polar effects: 📖 299 Scheme 3.1
- Carbocations: positive empty orbitals; 📖 300 mid.
  - (+)-charge in a less electronegative *p* orbital
  - $CH_3^+ < CH_2^+ < CH^+ < C^+$: polar & delocalization; 📖 301 bot.
  - stabilization of conjugated ions: 📖 302-3 Table 3.9 & 3.10
  - stabilization by substituents: 📖 305 Table 3.12
    - better β-stabilization: Si, Sn, Hg; 📖 307 middle

❖ Electronic Substituent Effects (II)

- Carbanions: negative filled orbitals; 📖 307 bottom
  - (-)-charge in a more electronegative orbital: *sp*^{3} < *sp*^{2} < *sp*
  - stability of *sp*^{3} carbanions: polarizability; 📖 309 Table 3.14
    - much smaller substituent effects than those with carbocations
  - stabilization by substituents: 📖 309 Table 3.15
    - delocalization (BH_2, $CH=CH_2$, NO_2) & polarizability (Cl to SiH_3)
- Radicals: half-filled nonbonding orbital; 📖 311 mid.
  - planar CH_3• (*p*/*sp*^{2}) & trigonal =CH• (*sp*^{2}/*sp*^{2})
  - weak β-C-H: disproportionation of radicals; 📖 311 bottom
  - stability of hydrocarbon C•: BDE of C-H; 📖 258 Table 3.2

❖ Electronic Substituent Effects (III)

- Radicals (continued)
  - stabilized by EWGs or ERGs: 📖 318 Table 3.20
    - delocalization of unpaired e^-: 📖 313 middle & 📖 314 Fig. 3.19
  - captodative radicals: very weak C-H; 📖 316 Table 3.18
- Addition to carbonyls: reactivity; 📖 319 middle
  - reinforcing polar and resonance effects: 📖 319 bottom
    - $C^- < HN^- < O^- < H_2N < RO < F$
  - charge density & bond orders: 📖 321 Fig. 3.20
  - addition and elimination mechanism: 📖 331 Scheme 3.3

❖ Kinetic Isotope Effect

- Replacement by an isotope: D(T) vs H; 📖 332 Fig. 3.24
  - no effect on chemical reactivity but some effects on rate
  - primary kinetic isotope effect: $BE_{C\text{-}D} > BE_{C\text{-}H}$ at RDS (> 2)
    - maximum effect: H equally bound to at the TS; $k_H/k_D \cong 7$
    - minimum effect: very reactant- or product-like TS; $k_H/k_D \cong 1$
  - information on a reaction mechanism: 📖 334 Scheme 3.4
    - position of the TS: high $k_H/k_D \rightarrow$ close to the midpoint along the reaction pathway
  - secondary kinetic isotope effect: 📖 334 Scheme 3.4
    - when the C-H bond is not directly involved in the reaction
    - α:$k_H/k_D > 1$: normal ($sp^3 \rightarrow sp^2$: C-H loosening); $k_H/k_D < 1$: inverse ($sp^2 \rightarrow sp^3$: C-H tightening); β: 📖 334 bottom (normal)

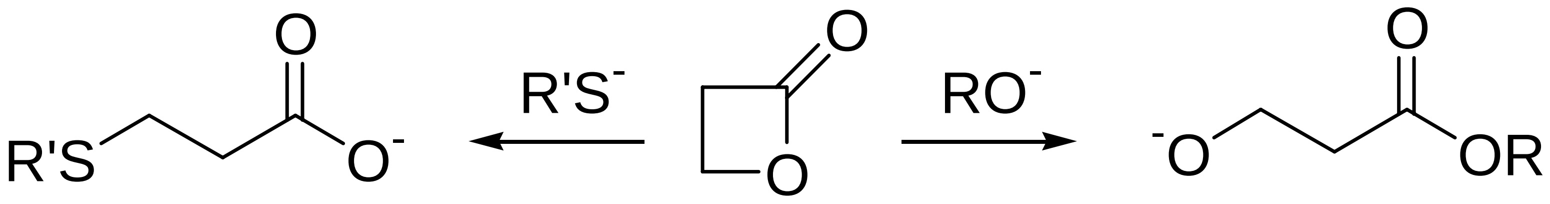
❖ Catalysis by Acids & Bases (I)

- Catalysts: not affect the equilibrium but the rate
  - when the conjugate acid/base is more reactive: 📖 345 bottom
- Quantitative kinetic study
  - specific acid catalysis: depends on equilibrium of protonation of the reactant; independent of conc. & identity of acid
    - formation of hemiacetal of benzaldehyde in MeOH: 📖 347 top; rate = k [H$^+$][PhCHO][MeOH]
  - general acid catalysis: depends on conc. & the nature of acid
    - RDS: H$^+$ transfer; 📖 348 Fig. 3.27 (Brönsted catalysis law)
  - solvent isotope effect: D_2O vs H_2O (acidity: $D_3O^+ > H_3O^+$)
    - inverse kinetic isotope effect: specific acid catalysis
    - normal kinetic isotope effect: general acid catalysis

❖ Catalysis by Acids & Bases (II)

- Acidity functions (H_o): 🕮 350 Table 3.28
  - 'pH' of very concentrated acidic solutions: relative H^+ activity
- Lewis acids: Li^+, Zn^{2+}, BF_3, $La(OR)_3$
  - formation of a donor-acceptor complex: 🕮 355
    - structure: $EtO\text{-}CO\text{-}CH(Me)\text{-}O\text{-}CO\text{-}CH{=}CH_2$ & $TiCl_4$; 🕮 355 bottom
    - donors become more electronegative: carbonyl – more reactive to Nu, ether/sulfide – better leaving group, hydroxyl – more acidic
  - strength of complexation: the HSAB principle
    - the better matched, the stronger: 🕮 356 Scheme 4.3
  - relative acidity: steric & stereoelectronic; 🕮 356 Table 3.29

❖ The Hard-Soft Acid-Base Principle: an example



❖ Solvent Effects

- Classification of solvents: 📖 360 Table 3.33
  - polar vs nonpolar; protic vs aprotic
- Ionization power: *Y* values; 📖 362 Table 3.34
  - polarity & structure: ionization of *t*-BuCl; 📖 361 Fig. 3.33
- Effect on the charged TS: 📖 360 Scheme 3.7 & Fig. 4.12
  - polar & protic: effective for the larger charge separation
  - nonpolar & aprotic: effective for the less charge separation
- Effect on the nucleophilicity of anions
  - reactivity: more reactive in aprotic solvents
  - solubility: loose ion pair; crown ethers