Chapter 4. Nucleophilic Substitution

- Substitution by the ionization mechanism: S_N1
  - RDS: heterolytic dissociation (k_1); 🕮 391 & Figure 4.1
  - rate = k_1[RX]; independent of conc. or the nature of Y^-
  - the structure of TS resembles that of the intermediate
    - partial carbocation with sp^2 character: planarity of TS
  - faster reactions: stable carbocation & unstable reactants
    - electron donating groups & good leaving group
    - polar solvents for neutral & nonpolar for cationic reactants
    - bulky groups on the starting material: $sp^3 \rightarrow sp^2$; more space
    - stereochemical results: racemization vs partial inversion
      - ion-pair mechanism: mostly inversion but some retention

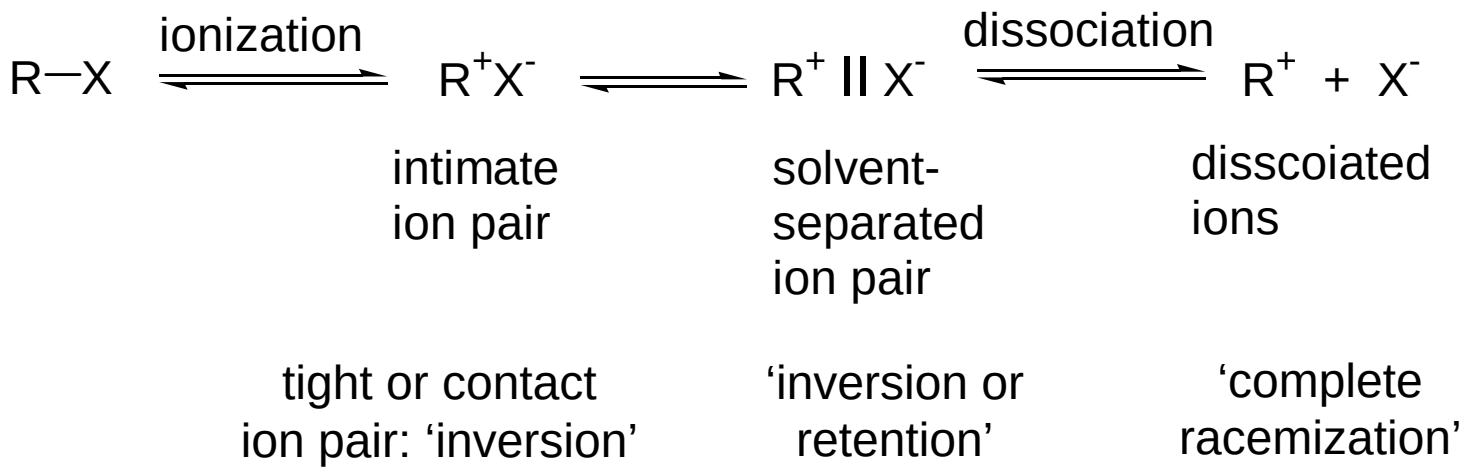
❖ Substitution by the S_N2 Mechanism

- Direct displacement mechanism: 📖 394 Figure 4.2
  - ◆concerted, no intermediate, single rate-determining TS
  - ◆rate = k_1[RX][Y^-]; dependent on conc. or the nature of Y^-
    - ❍better X: rate increase to a less extent than in S_N1
  - ◆a MO approach: HOMO of Y^- & LUMO of C-X; 📖 394 mid.
    - ❍favored back-side vs disfavored front-side attack: inversion
  - ◆trigonal bipyramidal TS: steric congestion & e^--rich
    - ❍the π character carbon: stabilized by vinyl, phenyl, carbonyl
  - ◆the borderline behavior: kinetics & stereochemistry
    - ❍pseudo-1st-order kinetics for S_N2: excess of Y^-; constant [Y^-]
    - ❍partial inversion due to ion-pairs in both S_N1 & S_N2

❖ Borderline Mechanisms in S_N Reactions

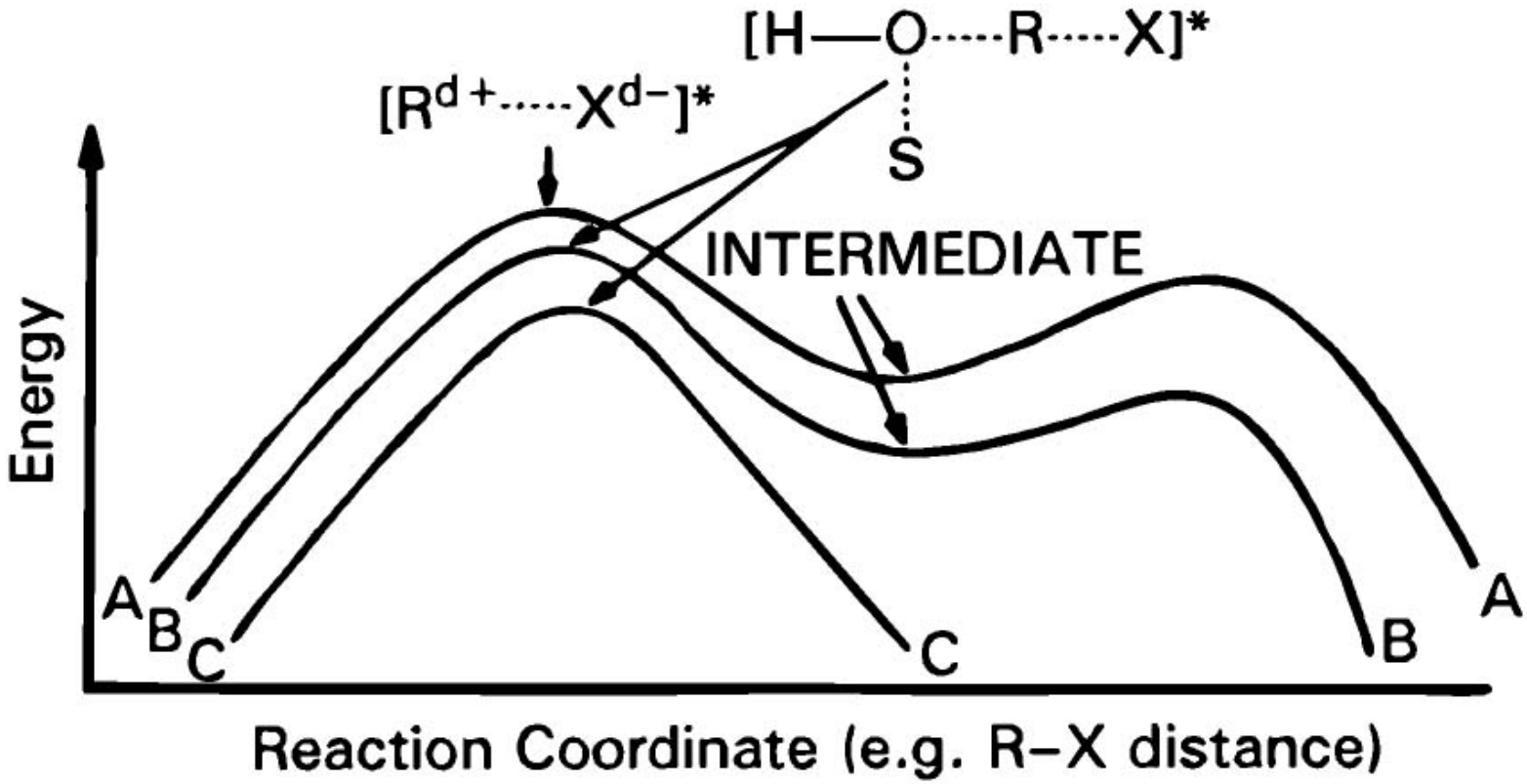
- ❒ Ion pairs: contact & solvent-separated; 🕮 396 top
  - ◆proof for the presence of ion pairs: 🕮 396 middle
    - ❍isotopic scrambling without racemization: 🕮 398 middle
  - ◆small barriers between the ion pairs: 🕮 399 Figure 4.4
    - ❍reaction profiles of the ion-pair mechanism: 🕮 399 Figure 4.5
    - ❍'uncoupled & coupled mechanism': 🕮 400 Figure 4.6
      - – an example of a coupled displacement: 🕮 400 bottom
    - ❍2-D reaction energy diagram: 🕮 401 Figure 4.7
  - ◆minimum solvent participation: less nucleophilic solvents
    - ❍nucleophilicity: $CF_3CO_2H<CF_3CH_2OH<AcOH<H_2O<EtOH$
    - ❍hindrance: ionization with no participation of Nu; 🕮 402 top

❖ Ion Pairs Mechanism: Borderline Reactions



❖ S_N2(intermediate) Mechanism

carbocation-like TS with 2nd-order kinetics



❖ Stereochemistry and Mechanism

- Substrate & conditions dependent: 🕮 402 Sch. 4.2
  - 1° systems: mostly inversion; concerted mechanism
    - benzylic: partial racemization due to ionization and return
  - 2° systems: complete inversion with moderate Nu (AcO^-)
    - retention product due to solvation by dioxane: 🕮 404 top
    - dioxane not compete for the ion pair with better Nu, N_3^-
    - diminished stereospecificity in benzylic derivatives
  - 3° systems: notable racemization with moderate Nu (benzylic)
    - better Nu (N_3^-): effective inversion; Nu attack on the ion-pair
    - retention: bulky tertiary & H-bonding between water and anion

❖ Nucleophilicity (I)

- Nucleophilicity: effect on rate of S_N reactions; kinetic
  - basicity: effect on the position of the equilibrium with acids
- Factors on nucleophilicity: 🕮 408 middle
  - solvation energy: the higher the solvation, the slower the rate
  - strength of the new Nu-C bond: the stronger, the faster
  - electronegativity: the more electronegative, the slower
  - polarizability: the more easily polarizable, the better Nu
  - size: the smaller the Nu, the faster the rate
- Empirical measures of nucleophilicity: 🕮 409 Table 4.3
  - nucleophilic constant (n): $n_{MeI}=\log[k_{Nu}/k_{MeOH}]$ in MeOH, 25 ^{o}C

❖ Nucleophilicity (II)

- Empirical measures of nucleophilicity (continued)
  - nucleophilic constant (*n*): 🕮 409 Table 4.3
    - no clear correlation with basicity: N_3^- = PhO^- = Br^- & N_3^- > AcO^- & Et_3N < Ph_3P
    - better correlation with basicity when attacking atom is the same: MeO^- > PhO^- > AcO^- > NO_3^-
    - decrease in nucleophilicity with increase in electronegativity: HO^- > F^- & PhS^- > Cl^- (across the periodic table)
    - increase in nucleophilicity with decrease in electronegativity, weaker solvation & increase in polarizability: I^- > Br^- > Cl^- > F^- & $PhSe^-$ > PhS^- > PhO^- (down the periodic table)

❖ Nucleophilicity (III)

- Competition: nucleophile & base; 🕮 410 Scheme 4.3
  - ◆qualitative prediction with the HSAB concept (principle)
    - ❍ *sp*^{3} carbon: soft acid as an E^+ vs H^+: hard acid
    - ❍ soft anions: substitution as a nucleophile (high polarizability & low electronegativity) vs hard anions: elimination as a base (small size & highly electronegative); 🕮 411 Table 4.4
    - ❍ late TS for soft Nu/E^+ (newly forming bond strength) vs early TS for hard Nu/E^+ (electrostatic attraction)
- Better nucleophilicity: better e^--donating ability
  - ◆soft species: low oxidation potential; high-lying HOMO
  - ◆α-effect: $HO\text{-}O^-$ > HO^- & $H_2N\text{-}NH_2$ = $HO\text{-}NH_2$ > NH_3
    - ❍ destabilizing ground state by lone pair-lone pair repulsions: relatively high energy of the nucleophile HOMO
    - ❍ stabilization of the e^--deficient TS (‘exploded TS’)

❖ Solvent Effects on Nucleophilicity

- Solvation affects the nucleophilicity of anions
  - protic solvents: deactivate the hard Nu by strong solvation
    - in MeOH: N_3^- > I^- > ^-CN > Br^- > Cl^- (*cf.*: 📖 409 Table 4.3)
  - aprotic solvents: activate the hard Nu by weak solvation to anion & strong solvation to cation; 📖 412 top
    - in DMSO: ^-CN > N_3^- > Cl^- > Br^- > I^-
  - solvent nucleophilicity in solvolysis: 📖 413 Table 4.5
    - Winstein-Grunwald equation: 2-adamantyl tosylate
      - *Y* values: 📖 362 Table 3.34

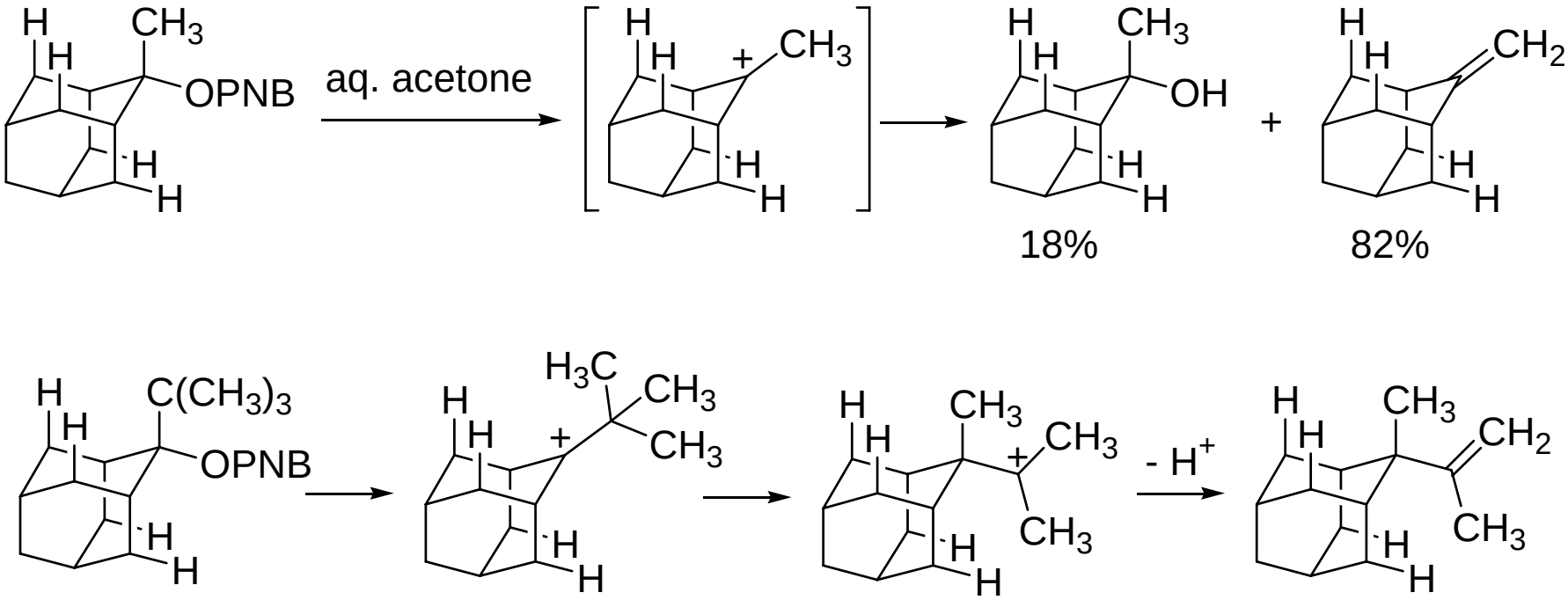
❖ Leaving-Group Effects

- Qualitative correlation of reactivity: 📖 414 Table 4.6
  - acidity of the conjugate acid of the leaving groups
    - high reactivity of triflates (sulfonates)
  - effect by the type of substitution reactions: 📖 414 Table 4.7
    - larger for S_N1 reactions vs smaller for S_N2 reactions
    - diminished leaving-group effect in S_N2: 📖 415 Table 4.8
  - rate enhancement of poor leaving groups
    - alcohols: H^+; amines: diazotization (📖 405), halides: Ag^+

❖ Steric & Strain Effects

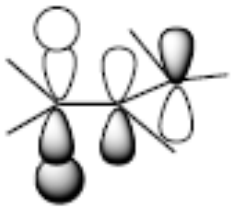
- Good Nu in low *Y*: sensitive to steric hindrance (S_N2)
  - RCl + I^- → RI (acetone), Me:Et:i-Pr = 93:1:0.0076
  - bulkiness & degree of ionization at TS: 🕮 416 Table 4.9
    - RBr → RO_2CH (HCO_2H), Me:Et:i-Pr:*t*-Bu = $0.58:1:26.1:10^8$
    - importance of nucleophilic participation: 🕮 416 middle
  - B-strain effect: k_{rel}[t-Bu/Me] = 4.4; 🕮 417 top
    - [(^{t}Bu)$_3$C-OPNB] : [Me_3C-OPNB] = 13,500:1
    - relief of the steric crowding at trigonal TS from tetravalent C
  - larger B-strain effect in rigid system
    - raised ground-state energy of the starting compound
    - reluctance to form strained substitution products

❖ Rearrangement to Unstrained Products

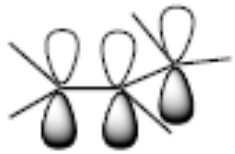


❖ Conjugation Effects on Reactivity

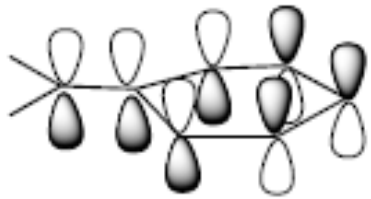
- ❒ vinyl & phenyl: stabilizing effect; 🕮 417 bottom
  - ◆ stabilizing both types of S_N2 reactions: cationic & anionic
  - ◆ α-carbonyl: depends on the nature of S_N reactions
    - ❍ stabilizing anionic S_N2 with strong Nu: 🕮 418 Table 4.10
    - ❍ destabilizing cationic S_N2 reactions with weak Nu



interaction of sp^2 hybridized substitution center with π LUMO



interaction of empty sp^2 orbital with π HOMO

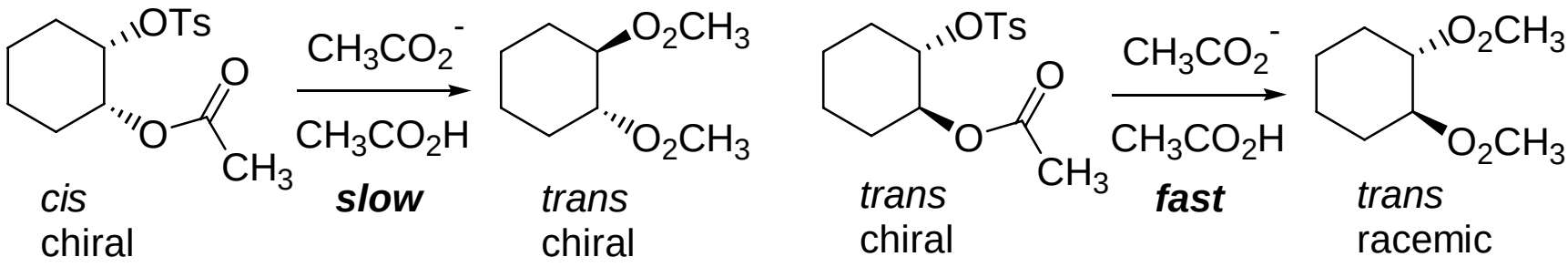


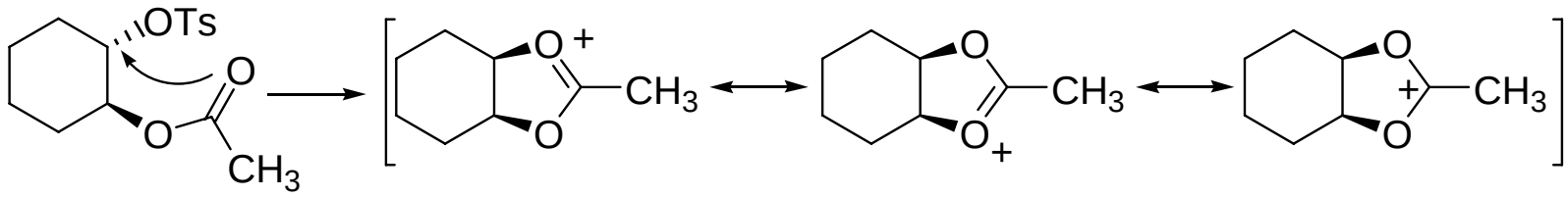
interaction of empty sp^2 orbital of benzyl cation with HOMO aromatic π system

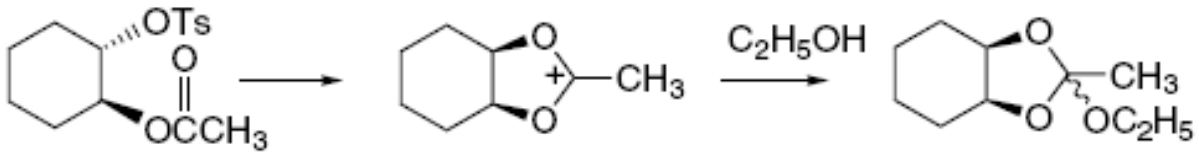
❖ Neighboring-Group Participation

- Involvement of nearby substituents in S_N reactions
  - solvolysis rate: $k_{trans} / k_{cis} \cong 670$; 📖 419 mid.
  - structure dependent: ring size; 📖 421 Table 4.11
    - participation of an alkoxy group: 📖 421 Table 4.12 & middle
  - cyclization of S_N2 reactions: 📖 422 Table 4.13
  - participation of olefinic π-e^-: 📖 423 top
    - formation of a bicyclic byproduct: 📖 423 middle
  - participation of aromatic π-e^-: phenonium ion; 📖 424 top
    - bridged intermediate: *erythro* → retention, *threo* → racemic
    - extent of aryl rearrangement in solvolysis: 📖 425 Table 4.14

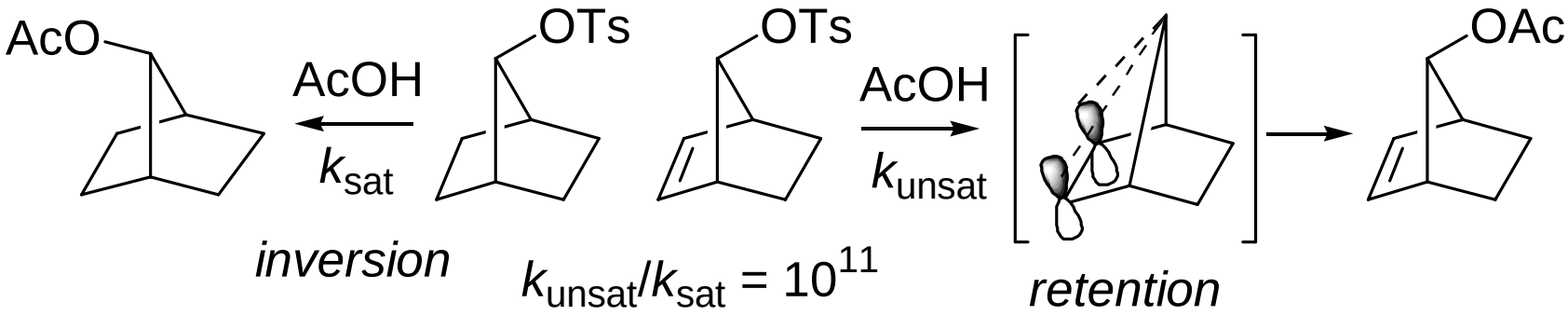
❖ Anchimeric Assistance: Oxygen Atoms

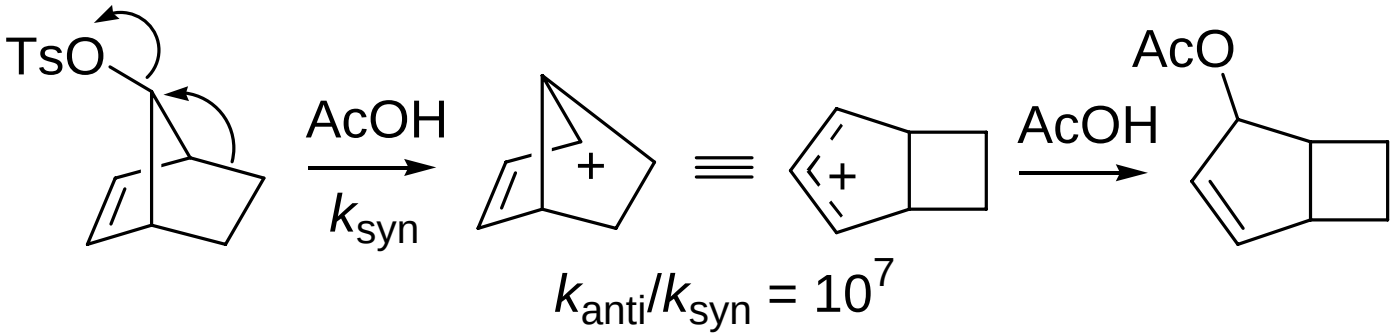






❖ Anchimeric Assitance: *p* Orbitals





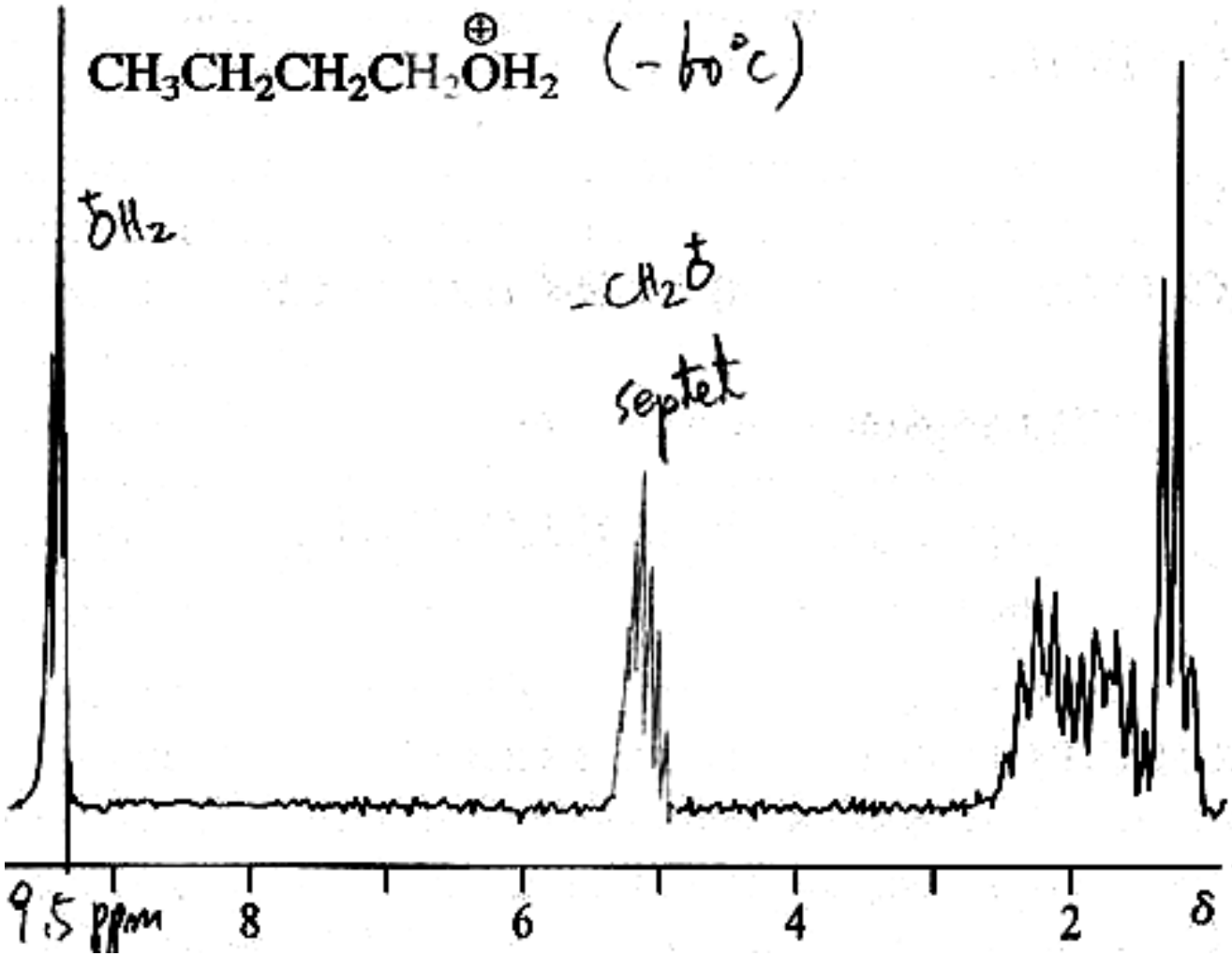
❖ Carbocations (I)

- Relative stability of carbocations: pK_{R+}; 📖 426 middle
  - the larger the pK_{R+}, the more stable: 📖 427 Table 4.15
    - stabilizing: alkyl, aryl, cyclopropenyl, cycloheptatrienyl
  - hydride affinity in solution: 📖 428 Table 4.16
    - ΔH of ionization in SbF_5/SO_2ClF: 📖 429 Table 4.17
- Stabilizing groups: delocalization of cations
  - cyclopropyl: bisected conformation; 📖 427 bottom
  - cyclopropenyl & tropylium: aromaticity
  - alkyl groups: hyperconjugation, C-H vs C-C; 📖 430
    - stabilization by a bridged structure or rearrangements: 📖 432

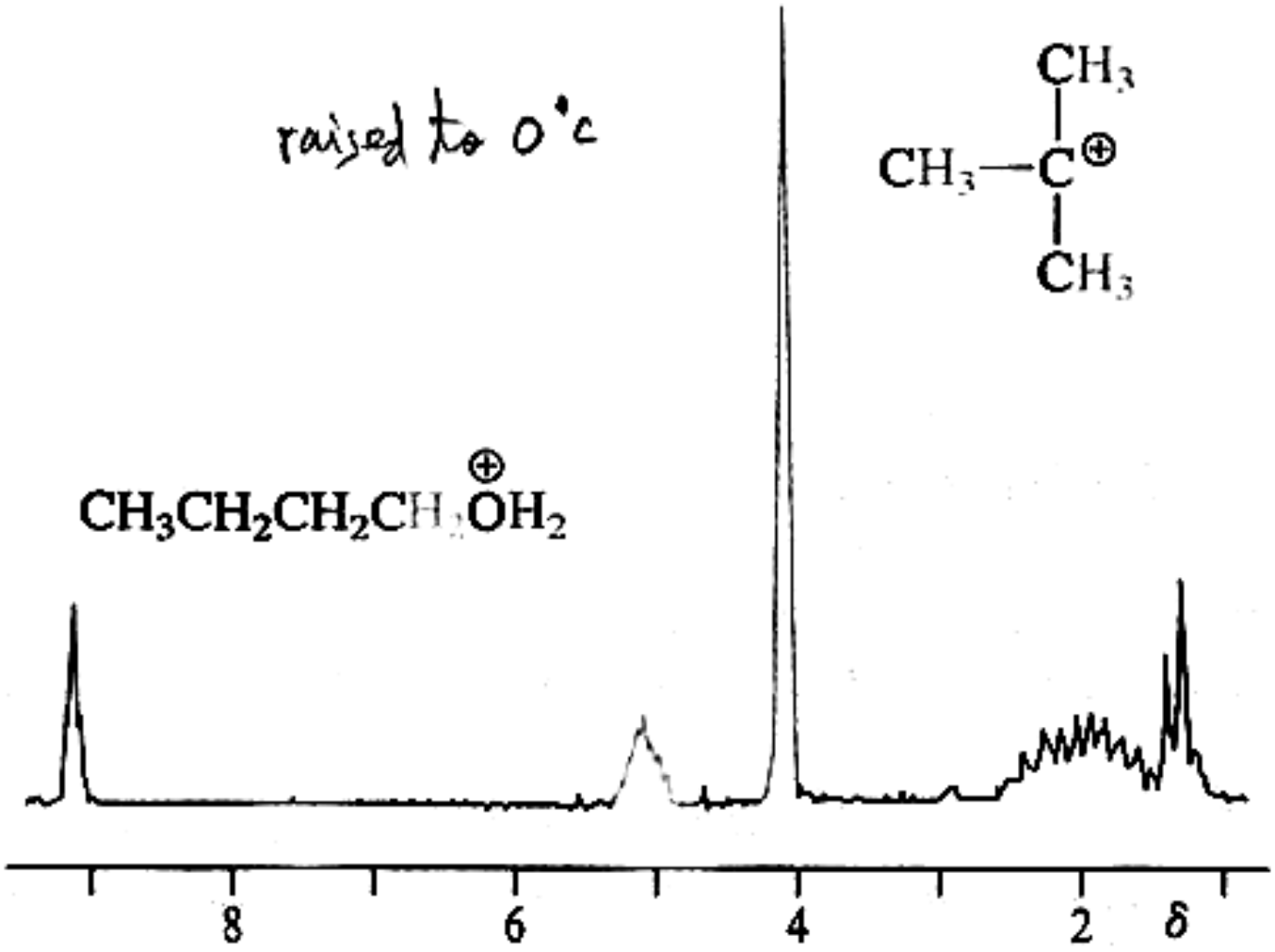
❖ Carbocations (II)

- Stabilizing groups (continued)
  - α-heteroatom: resonance by e^--donation; 📖 433 top
    - barrier to rotation: by NMR; 14 (A) & 19 kcal/mol (B)
  - halogens: resonance by e^--donation; 📖 434 middle
  - nitrile & carbonyl: weak π donors; 📖 434 Table 4.18
  - unstable carbocations: 📖 435-436
- NMR study of carbocations: 📖 437 Scheme 4.4
  - rearrangement to the most stable isomeric cations
    - non-nucleophilic superacid: FSO_3H-SbF_5-SO_2 (magic acid)
  - measurement of butanol: rearranged to the 3° cation at 0 °C
- Substitution vs elimination: 📖 439 Figure 4.10

❖ NMR Study of Carbocations (I)

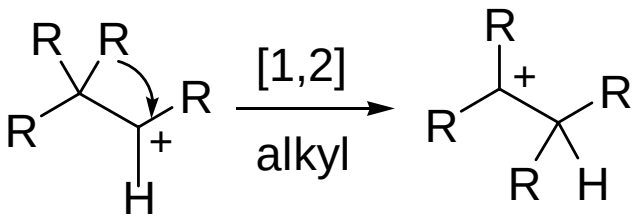


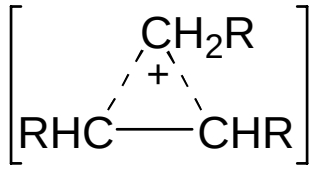
❖ NMR Study of Carbocations (II)



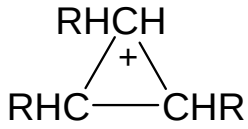
❖ Rearrangement of Carbocations

- Driving force: formation of more stable carbocations
  - 1^o carbocations < 2^o < 3^o ≅ ~ 25 kcal/mol > ~ 10 > 0
  - from 3^o to 3^o: so rapid at -160 ^{o}C, ΔE_a< 5 kcal/mol; 🕮 440
- Mechanism of 1,2-shift: bridged ions; 🕮 440 bottom
  - symmetric 2-butyl cation on NMR: $\Delta E_a \leq 2.5$; 🕮 441 middle
    - H migration via a bridged cyclopropyl ion: 🕮 443 top
    - relative energy & profile: 🕮 441 bottom & 🕮 442 Figure 4.11
    - isotopic labeling: 🕮 443 bottom & 🕮 444 top
  - rearrangement of 2-pentyl cation: 🕮 444-5 Figure 4.12
  - rearrangement of a cyclohexyl cation: 🕮 445-6

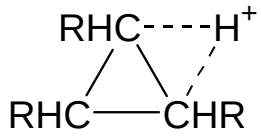




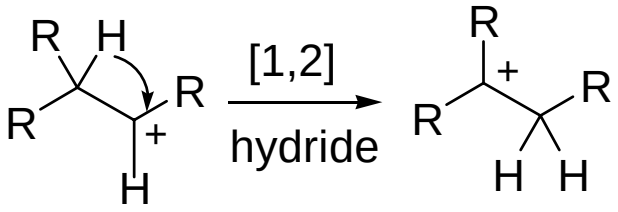
alkyl-bridged

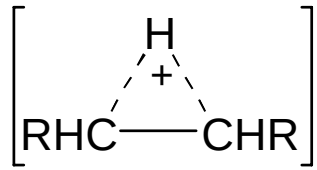


corner-protonated cyclopropane

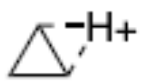
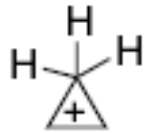


edge-protonated cyclopropane

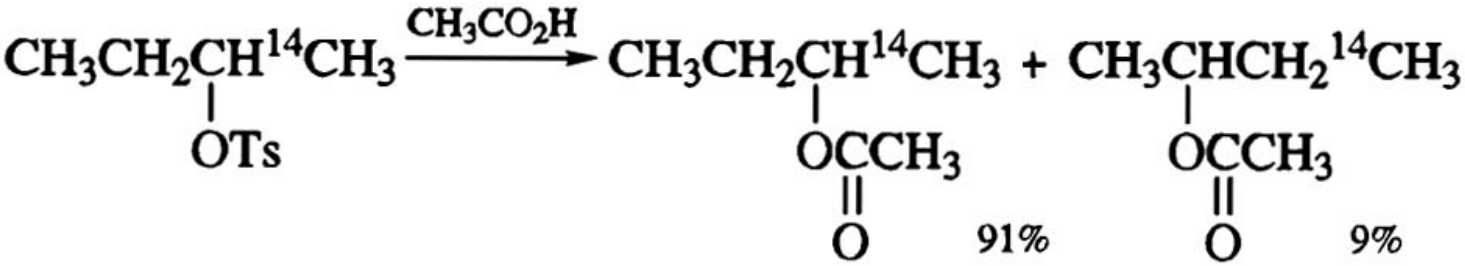


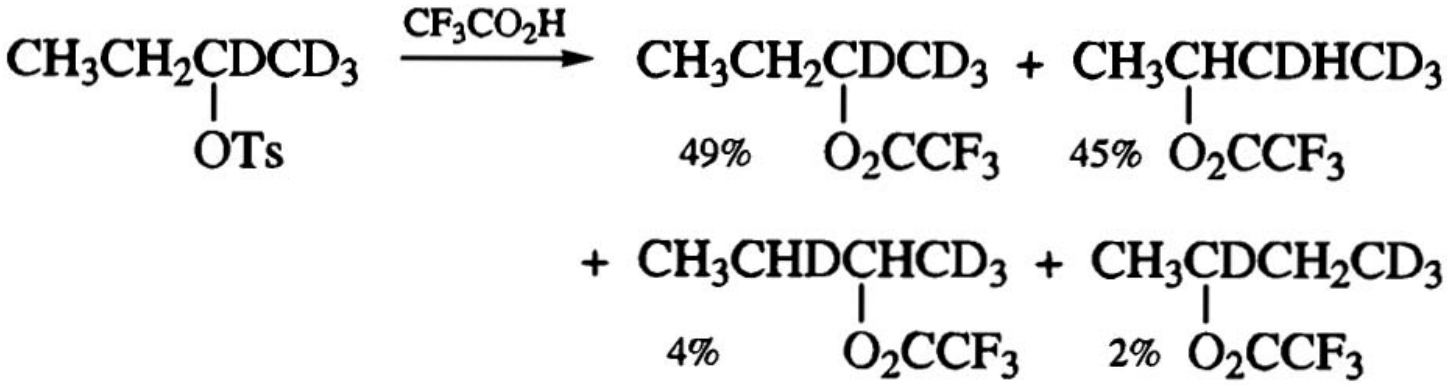


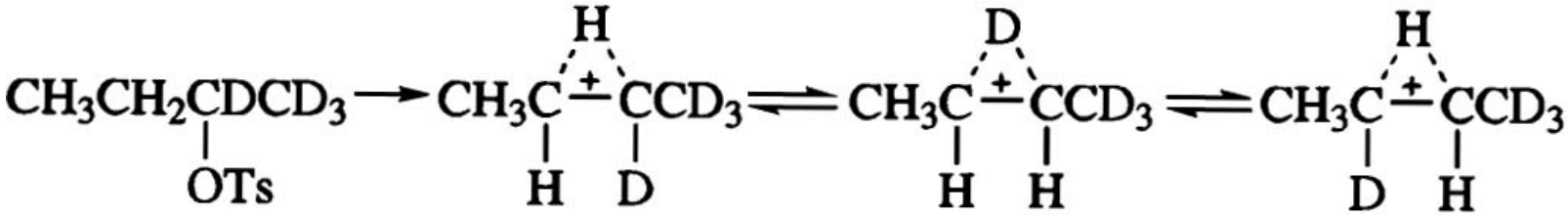
hydride-bridged

	$CH_3CH_2CH_2^+$	$CH_3C^+HCH_3$		
MP4/6-311*	+19.3	0	8.6	7.3
G2		0	8.2	7.2
B3LYP		0	16.0	12.2

❖ Isotopic Labeling Study of Rearrangement



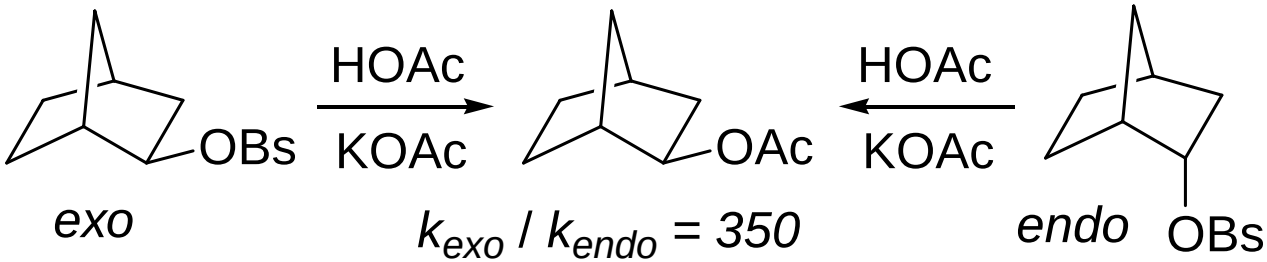




❖ Bridged (Nonclassical) Carbocations (I)

- Evidences for nonclassical carbocations
  - 2-norbornyl brosylate: $k_{exo} : k_{endo} = 350$; 📖 447-8
    - retention for *exo* isomer vs inversion for *endo* isomer
    - 100% racemization for chiral *exo*-brosylate
    - 93% racemization for chiral *endo*-brosylate
  - bicyclo[2.2.2]octyl brosylate: 82 ± 15% retention
    - bicyclo[2.2.2]octyl & bicyclo[3.2.1]octyl acetate: 📖 448 bottom
- Arguments against: rapid equilibrium
  - small difference in rate compared to 5-ring brosylate
  - large difference even for classical 3^o carbocation
- Stable/unstable intermediate? or TS?: 📖 449 Fig. 4.13

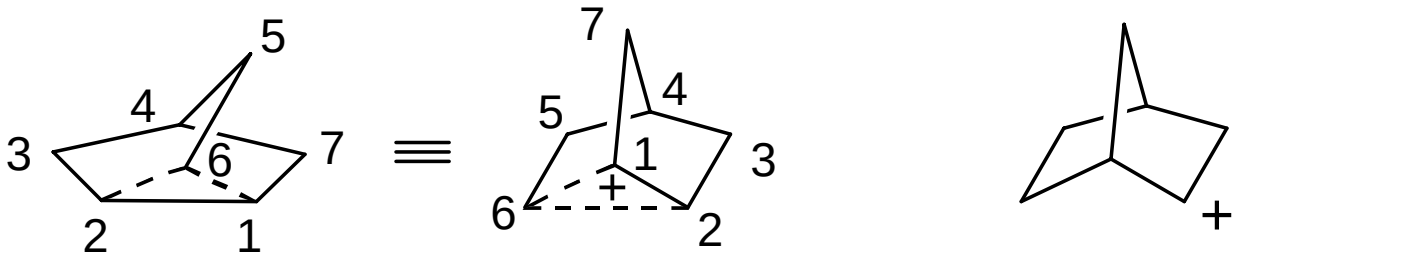
❖ Nonclassical Norbornyl Cations: Achiral



exo

$k_{exo} / k_{endo} = 350$

$k_{endo} \cong k_{\text{cyclohexyl brosylate}}$

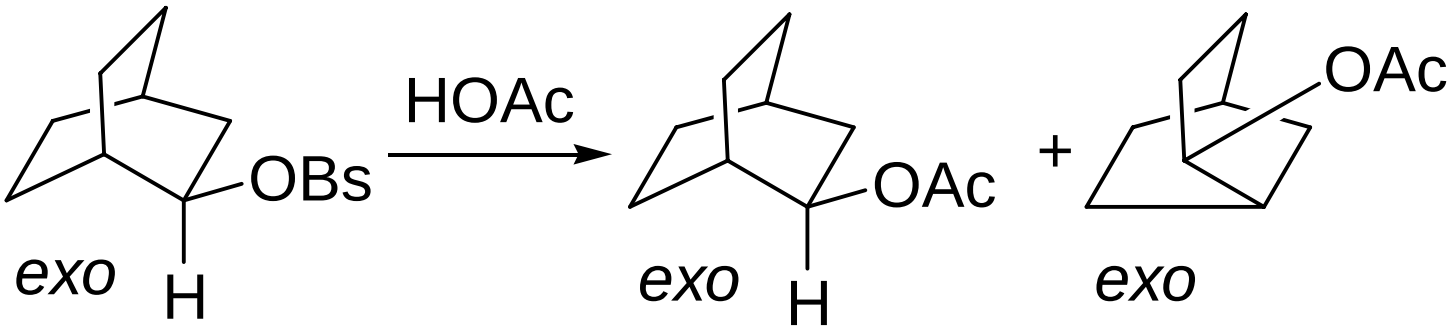


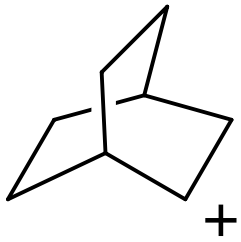
'achiral'

nonclassical

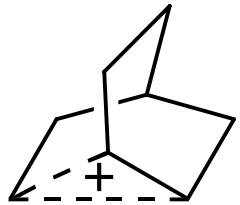
classical: 'chiral'

❖ Nonclassical Bicyclooctyl Cations: Chiral



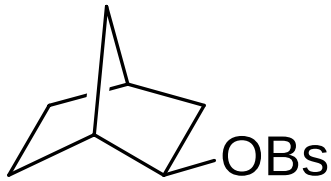


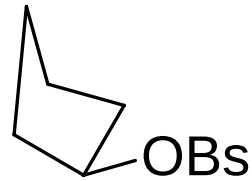
classical: achiral

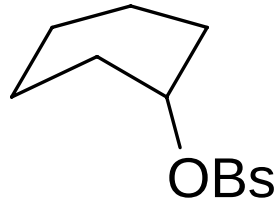


nonclassical: chiral

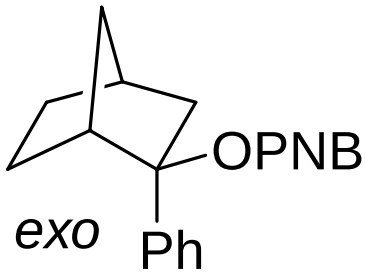
❖ Evidences Against Nonclassical Cations





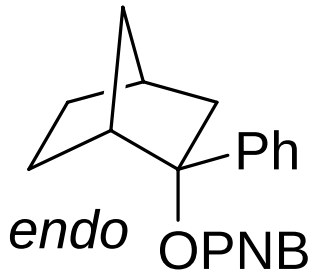


k_{rel} 14 1 0.04



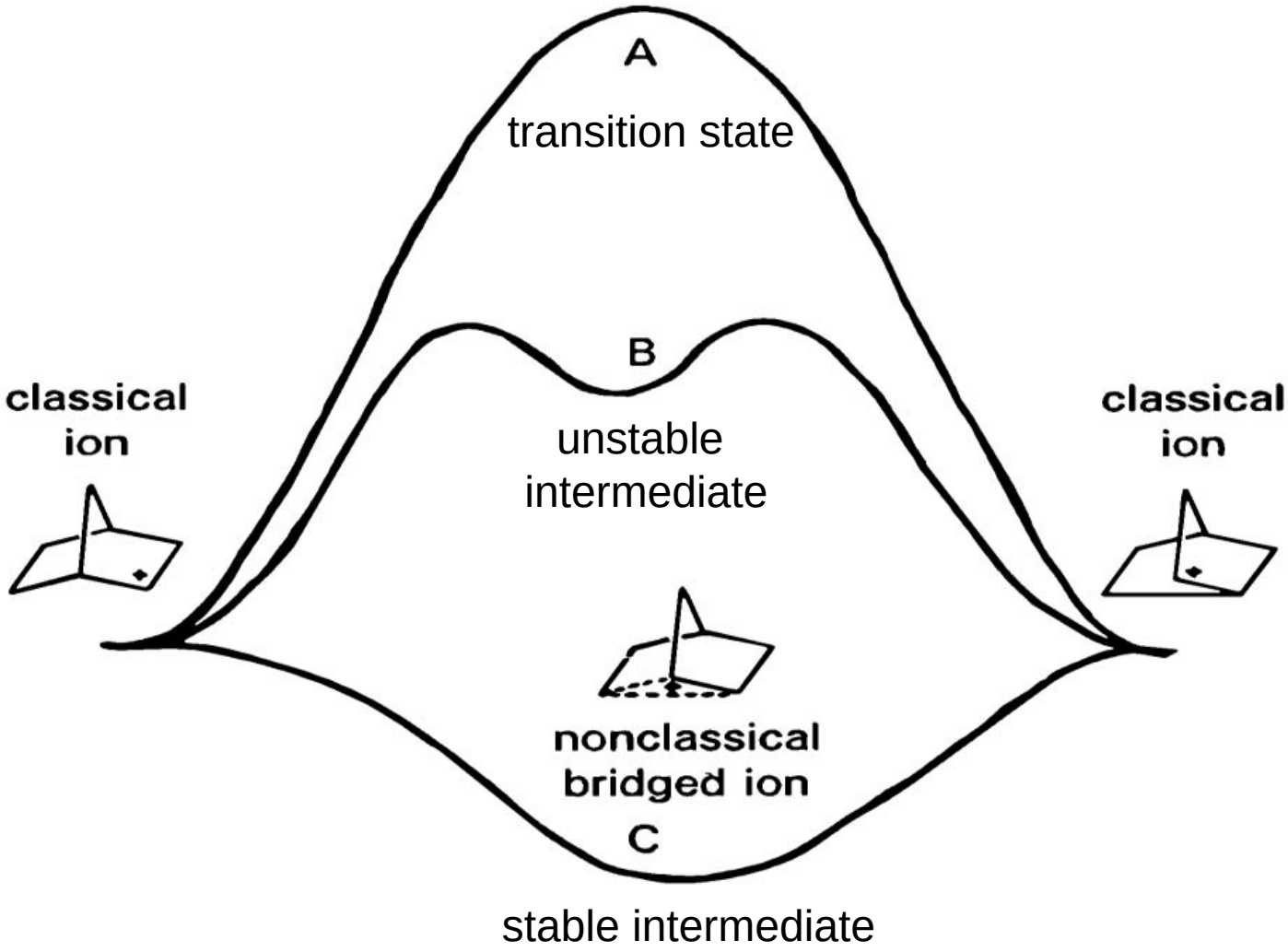
k_{rel}

140 : 1



➢retention of stereochemistry in solvolysis

❖ Question on Nature of Nonclassical Cations

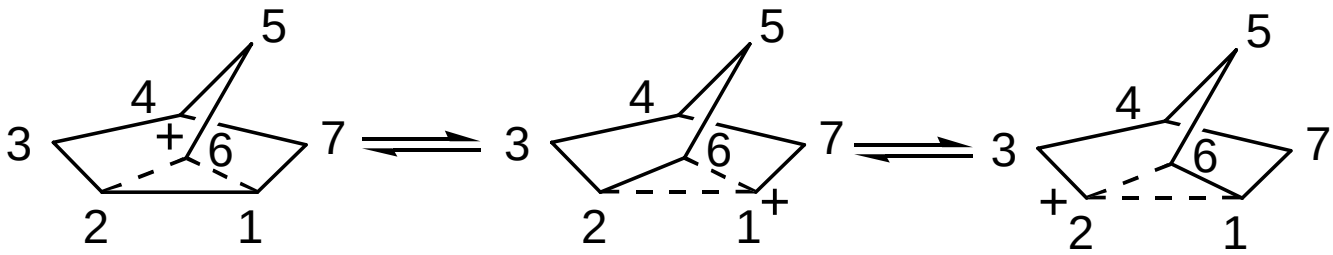


❖ Bridged (Nonclassical) Carbocations (II)

- Direct observation of the norbornyl cation
  - ^{1}H & ^{13}C NMR in super acid (SbF_5-SO_2-SOF_2)
    - upfield ^{13}C δ of the cation than that of classical 2-propyl cation
    - at -100 ^{o}C: 3 types of Hs [H1/H2/H6 & H3/H5/H7 & H4] & Cs
    - at -159 ^{o}C: 5 types of Hs [H1/H2 & H6 & H3/H7 & H5 & H4] & Cs
    - stabilization *E*: 6±1 kcal (MM), 11 (Experimental), 13.6 (MO)

❖ Norbornyl Cation Observation by NMR

- Fast hydride shift between H1, H2 and H6: - 100 ^{o}C
  - 3 types of Hs [H1/H2/H6 & H3/H5/H7 & H4] & Cs



- Slow hydride shift between H1, H2 and H6 : - 159 ^{o}C
  - 5 types of Hs [H1/H2 & H6 & H3/H7 & H5 & H4] & Cs

❖ Bridged (Nonclassical) Carbocations (III)

- Substituent effects at C-4/5/6/7: C1-C6 participation
  - stronger by C-6 substituents & more sensitive *exo* isomer
- Theoretical energy diagram: 📖 452 Fig. 4.14
- Other nonclassical carbocations: 📖 452 Scheme 4.5
  - cyclobutonium ion: equivalent 3 CH_2 on NMR: 📖 453 top
- A rule of thumb: the nature of carbocations
  - 3^o cations: usually classical structure; more stable
  - 2^o cations: bridged where possible; strained & poor solvation
  - 1^o cations: rearrangement to $2^o/3^o$ cations via bridged ions