Week 4

Ions

4.1 Cations

9/24: • Lecture 5 recap.

- Pericyclic reactions: Concerted reactions with a TS having a cyclic array of atoms and orbitals.
- Three models.
  1. Woodward-Hoffmann rules: Conservation of orbital symmetry.
  2. Dewar-Zimmerman analysis: Aromatic TS theory.
  3. Frontier MO theory: HOMO-LUMO interactions.
- "No mechanism... half in jest, half in desperation... to the thermoreorganization reactions."
  - Essentially, pericyclic reactions really led to a new blossoming of organic chemistry, and a series of successful mergers between theory and experiment.

- Announcements: PSet 1 due tomorrow; if late, we'll lose a lot of points.

- Today: Cations (mostly carbocations).

  - This is the first in a series of lectures on functional groups: Cations, anions, radicals, and carbenes.

- Lecture outline.

  - Overview of cation structure and reactivity.
  - Measuring a cation's (thermodynamic and kinetic) stability.
  - Stabilizing cations to promote reactivity.
  - Cation reactions.
  - Nonclassical carbocations.

- There are three phases in a cation's lifetime: Synthesis, stability, and reactivity.
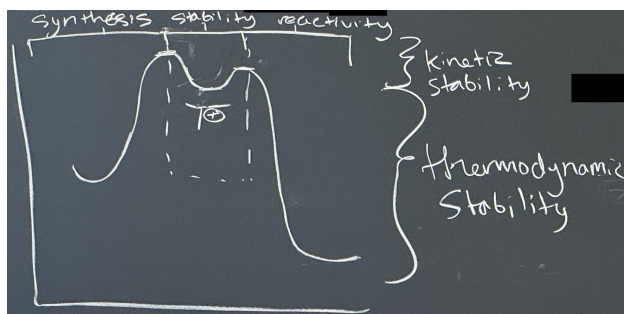

Figure 4.1: Phases in the life of a cation.

- All three phases correspond to specific regions along the reaction coordinate in the energy diagram for a cation-intermediate reaction.
- Stability, in particular, we'll talk about from a kinetic *and* a thermodynamic perspective.
  - ■ Kinetic stability deals with the energy barrier to *form* and to *react* the cation.
  - ■ Thermodynamic stability deals with the energy difference between the cation and the adjacent local ground state structures.
- Cations can have quite "sensitive" energy surfaces, i.e., factors that can stabilize and destabilize cations can have dramatic effects on the synthesis, stability, and reactivity of cations.
- Features that stabilize cations tend to lead to reactions.
  - ■ If you're in the lab, consider stabilizing the cation in order to induce the desired reactivity!
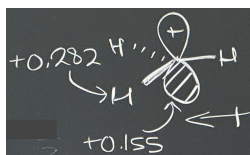
• Cation structure.

Figure 4.2: Cation structure.

- Figure 4.2 depicts a methyl cation ($^{\oplus}CH_3$).
- In general, cations are sp^2-hybridized, trigonal planar species.
  - ■ Recall that Figure 2.5 explains why cations are trigonal planar instead of pyramidal.
- The cationic charge is delocalized across the entire molecule, not localized on the carbon.
  - ■ Indeed, there is a δ^+ on the H's, too.
  - ■ In fact, the dipole qualitatively points *toward* the carbon.
  - ■ Quantitatively, the **Mulliken partial charges** are +0.155 on C and +0.282 on each H. Together, these partial charges sum to the total charge of +1:

$$1 \times 0.155 + 3 \times 0.282 \approx 1$$

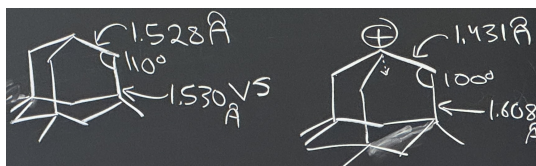• Experimental evidence for cation formation.

Figure 4.3: Evidence that carbocations exist.

- Experimental evidence primarily comes from some cool adamantane structures.
- For example, consider trimethyl adamantane and its corresponding cation. The cation has structural characteristics indicative of the "flattening" transformation we would expect. Specifically. . .
  - ■ The adjacent bond angles flatten from 110° to 100°;
  - ■ The bonds immediately surrounding the cation shrink from 1.528 Å to 1.431 Å as the molecular geometry compresses the flattening cation;
  - ■ The bonds α, β to the cation elongate from 1.530 Å to 1.608 Å as electron density is removed from them through hyperconjugation and the no-bond resonance form.
- Reference: Laube (1986).

- Moving on, to measure the thermodynamic stability of a cation, we use the **hydride ion affinity**.

- **Hydride ion affinity**: The extent to which cations want to bind a hydride in solution. *Also known as* **HIA**. *Given by*

$$RH \rightleftharpoons R^+ + H^- \qquad\qquad \Delta H^\circ = HIA$$

  - Always measured in the gas phase.
  - Only tells you the *relative* stability.[1]

- Example HIAs.

(a) The effect of resonance.

(b) The effect of hyperconjugation.

(c) Cyclopropyl stabilization.
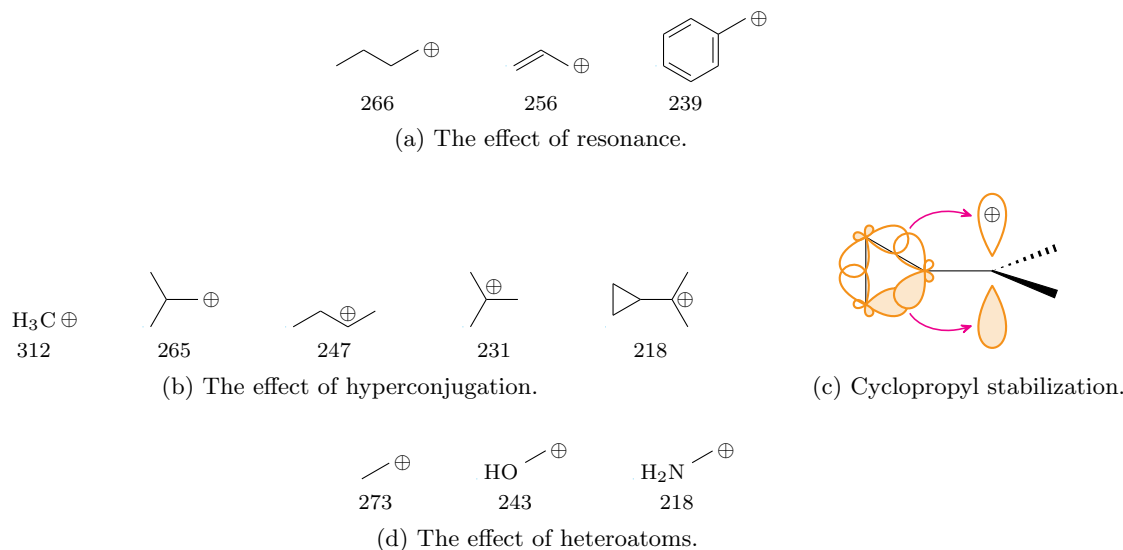

(d) The effect of heteroatoms.

Figure 4.4: Hydride ion affinity examples.

- Alkyl, allylic, and benzylic HIAs (Figure 4.4a).
  - Respectively: 266 kcal/mol, 256 kcal/mol, and 239 kcal/mol.
  - Attributable to resonance delocalization and conjugation.
- Methyl, isobutyl, *sec*-butyl, *tert*-butyl, and dimethylcyclopropyl HIAs (Figure 4.4b).
  - Respectively: 312 kcal/mol, 265 kcal/mol, 247 kcal/mol, 231 kcal/mol, and 218 kcal/mol.
  - Attributable to hyperconjugation.
  - Deeper dive: Hyperconjugation from cyclopropyl rings (Figure 4.4c)
    - This is a follow up to our brief discussion on the same topic in Lecture 3.
    - When this molecule forms, the carbocation's empty p-orbital will align with the σ-plane of the cyclopropyl group.
    - With this alignment, *both* adjacent C–C banana bonds can donate into the carbocation through hyperconjugation.
    - The hyperconjugative interaction is so extreme that the barrier to rotation along the bond between the cation and the cyclopropyl group is 13.7 kcal/mol!
    - We can also picture this interaction through no-bond resonance forms that delocalize the positive charge to the back two carbons in the cyclopropyl group.
    - You can look up the crystal structure of this molecule to see the interaction more.
- Ethyl, hydroxymethyl, and aminomethyl HIAs (Figure 4.4d).
  - Respectively: 273 kcal/mol, 243 kcal/mol, and 218 kcal/mol.
  - Attributable to heteroatom stabilization (aka resonance).

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[1]Relative to what??

- The stability of the carbocation (as discussed above in terms of HIAs) determines how high the local minimum is in the energy diagram in Figure 4.1.

- We now move onto the kinetic stability/reactivity of cations.

- Two ways of measuring this.

  1. Rates of **solvolysis**.
     - Used all the time.
  2. **Mayr electrophilicity**.
     - More niche, but still good to know.

- **Solvolysis**: A type of nucleophilic substitution (S_N1 or S_N2) wherein the nucleophile is a solvent molecule. *Given by*

$$R_3C-X + H_2O \xrightarrow[\Delta]{k_{rel}} R_3C-OH + XH$$

  - Rates of solvolysis are reported as a relative rate constant k_{rel}.

- Comparing HIAs to rates of solvolysis.

	$\mathbf{Bn-Br}$	$\mathbf{All-Br}$	$\mathbf{^iPr-Br}$
HIA (R^+)	239	256	249
k_{rel}	100	52	0.7

Table 4.1: HIAs and the rate of solvolysis are not correlated.

  - To be clear, we are listing the HIA of the benzyl, allyl, and isopropyl cations.
  - Benzyl bromide affords a cation that is both the most stable and the most reactive in the set.[2]
  - Note that in general, solution-phase measures of stability like solvolysis and gas-phase measures of stability like the HIA *don't* correlate. This means that we do have to measure them independently.

- **Mayr electrophilicity**: The rate of reaction for various electrophilic and nucleophile pairs. *Given by*

$$E^+ + Nuc^- \xrightarrow{k} Nuc-E$$
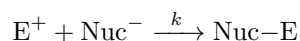
  - By Herbert Mayr from 5.47!
  - Mayr defined three parameters (S, N, and E) via the equation.

$$\log k = s(N + E)$$

    - s is a nucleophile-specific slope parameter.
    - N is a nucleophile parameter.
    - E is an electrophile parameter.
  - Note that "Nuc^-" indicates a nucleophile, just like the more commonly used Nu^-.
  - Mayr has done hundreds of these reactions, measured their rates, had reference nucleophile, etc.
    - His group is still expanding the chart!
    - There's a giant PDF on Mayr's website that we can download if we want.
  - Reference: Mayr and Patz (1994).

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[2]Clarify??
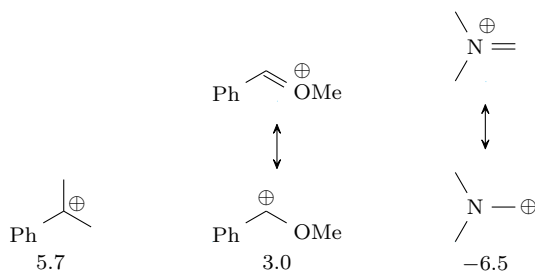
- Example Mayr electrophilicities.

Figure 4.5: Mayr electrophilicity examples.

- To be clear, Figure 4.5 lists the E value for each species.
- Remember that Mayr electrophilicity is reported on a logarithmic scale, so the difference in E between the left two species (approximately 3) corresponds to a difference in reactivity of three *orders of magnitude*.
    - Similarly, the difference in reactivity between the right two species is *nine orders of magnitude*!
- Some of these trends should make sense.
    - For example, it stands to reason that the cation with heteroatom stabilization is the least electrophilic.
- Observe that our most thermodynamically stable carbocation (the 3° one with extensive resonance into the phenyl ring) is also our most Mayr electrophilic one!
    - This is yet another example of thermodynamics being decoupled from the kinetics of reactivity.

- This concludes our discussion of *measuring* kinetic and thermodynamic stability. Let's now talk about *enhancing* carbocation stability.

- Four ways of doing this.

    1. **Hyperconjugation**.
    2. Heteroatom stabilization.
    3. The **β-silicon effect**.
    4. The **neighboring group effect**.

- **Hyperconjugation**: The delocalization of electrons through σ-bonds.
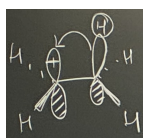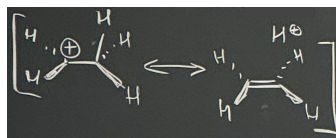
(a) $\sigma_{\mathrm{CH}} \to p_{\mathrm{C}}$ donation.   (b) No-bond resonance.

Figure 4.6: Stabilizing carbocations: Hyperconjugation.

- Hyperconjugation explains why substituted cations are more stable.
- Recall from 5.13[3] that the ethyl cation is stabilized by $\sigma_{\mathrm{CH}} \to p_{\mathrm{C}}$ donation.
- Equivalently, we can say that the ethyl cation is stabilized by **no-bond resonance**.
    - What this really tells us is that the C−C bond is shorter than we'd normally expect, and the C−H bond is longer than we'd normally expect.

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[3]Figure 4.6a is just Figure 2.3a from Labalme (2024).

- Example HIA differences caused by hyperconjugation (Figure 4.4b).

  – Increasing from no adjacent C–C bonds to three adjacent C–C bonds decreases the HIA from 312 kcal/mol to 231 kcal/mol.
  – Essentially, as we add more R groups, the cation's empty p-orbital gets stabilized by additional adjacent σ-orbitals.

- Matthew: Does hyperconjugation induce a barrier to rotation?

  – There's always some barrier.

    ■ In a normal alkyl molecule, it's approx 3 kcal/mol.

  – In a hyperconjugated cation, we will see bigger differences.

    ■ In fact, there's a fascinating example somewhere in the literature of the stereochemistry of a product being determined by geometric constraints caused by hyperconjugation!

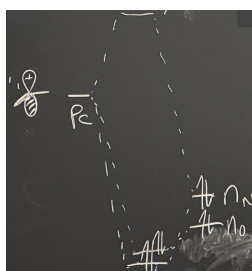 – So all this is to say, yes.

- Heteroatom stabilization.

Figure 4.7: Stabilizing carbocations: Adjacent heteroatoms.

  – The high-energy empty p-orbital on carbon and low-energy heteroatom lone pair interact to form new bonding and antibonding MOs.

    ■ The bonding MO will be lower energy than the lone pair AO, so the electrons in that lone pair will be stabilized.

  – Nitrogen vs. oxygen stabilization: Rationalizing why nitrogen is more stabilizing in Figure 4.4d.

    ■ The n_O AO is lower in energy than the n_N AO.
    ■ This means that there is worse energy overlap between the n_O AO and the p_C AO than between the n_N AO and the p_C AO.
    ■ The worse energy overlap with oxygen leads to a resultant decrease in MO splitting, and hence less stabilization for the oxygen lone pair than the nitrogen lone pair receives.

- **β-silicon effect**: The stabilization of positive charge at the position β to a silicon atom.

  – Caused by hyperconjugation.
  – Specifically, silicon is a better σ-donor, by which we mean that C–Si bonds are better at sharing their electron density via hyperconjugation than C–C or C–H bonds.[4]
  – Silicon is better because. . .

    ■ Silicon is less electronegative than other common σ-donors;
      ➢ Indeed, $\mathrm{EN_C} = 2.55$ and $\mathrm{EN_C} = 2.20$, but $\mathrm{EN_{Si}} = 1.90$.
      ➢ Thus, C–Si bonds hold their electrons less tightly and hence are happier to share.
      ➢ C–Si bonds holding their electrons less tightly also implies the following.

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[4]Note that we do *not* mean that silicon is a better σ-donor ligand, like in inorganic chemistry.

- ■ C−Si bonds are longer;
  - ➢ 1.86 Å vs. the 1.54 Å typical of a C−C bond.
  - ➢ This allows for greater overlap with the typically lengthy p-orbitals.
- ■ C−Si bonds are more ionic;
  - ➢ Polarization toward carbon (more ionicness) means that there's more electron density on the carbon (i.e., near the carbocation).
- ■ The σ_{CSi} orbital is higher in energy than σ_{CC} orbital.
  - ➢ Thus, like in Figure 4.7, we get closer to the p_C energy level and have more effective overlap.

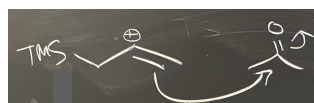- • Example HIA differences caused by the β-silicon effect.

(a) HIA $= 266$ kcal/mol.   (b) HIA $= 228$ kcal/mol.

Figure 4.8: Hydride ion affinities subject to the β-silicon effect.

- – Changing an alkyl cation to the direct silicon analogue alters the HIA by nearly 40 kcal/mol.

- • Examples of how the β-silicon effect alters reactivity.


(a) Accelerating S_N1 and E_1.

(b) Enabling allylations.

Figure 4.9: The β-silicon effect enables cationic reactivity.

- – It can accelerate the departure of a leaving group by orders of magnitude (Figure 4.9a).
  - ■ Suppose we have a trifluoroacetate leaving group on a cyclohexane ring in aqueous solution.
  - ■ Locking $F_3CCO_2^-$ in the axial position with an equatorial *tert*-butyl group aids departure.
    - ➢ Specifically, if R $=$ SiMe$_3$, the anomeric effect will significantly weaken the C−O bond.
  - ■ Once $F_3CCO_2^-$ leaves, the reaction completes through hydration (S_N1) or elimination (E_1).
  - ■ If $k_{rel} = 1$ when R $=$ H, then $k_{rel} = 2.4 \times 10^{12}$ when R $=$ SiMe$_3$.
    - ➢ There's a reason this effect has a name: It's huge!
- – It enables allylations to happen at all (Figure 4.9b).
  - ■ We do allylations with allyl silane because it's the only way this will work.
  - ■ The allyl group attacks the carbonyl as a nucleophile, forming a secondary carbocation that's stabilized by the β-silicon effect at the indicated position.
  - ■ Note that this reaction is *not* an already-formed carbocation somehow engaging in a nucleophilic attack, despite how it's drawn. Here's a helpful reference on this type of reactivity.

- Motivating the neighboring group effect.
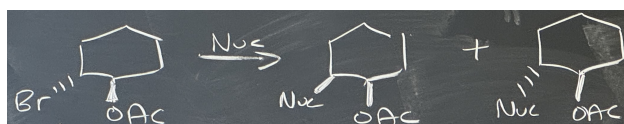
(a) The possible products of a reaction.
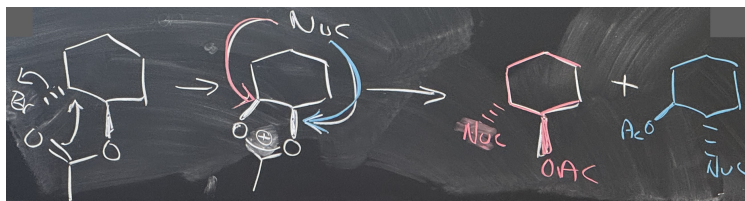
(b) The mechanism of the reaction.

Figure 4.10: The neighboring group effect alters cationic reactivity.

- The reaction in Figure 4.10a is a nucleophilic substitution with an enantiopure starting material, and it has four possible product stereoisomers.
- Through which mechanisms could this reaction proceed?
  - If S_N2: We'll see 100% *syn* and 0% *anti* product because S_N2 is stereospecific.
    - ➤ The syn product will be enantiopure due to the stereoinverting nature of the attack.
  - If S_N1: We'll see 50% *syn* and 50% *anti*, maybe favoring *anti* a bit due to sterics.
    - ➤ Both diastereomers will be enantipure (we're not engaging the acetate's chiral carbon).
  - Observed: We get 0% *syn* and 100% *anti*, and it's a racemic mixture of the *anti* diastereomer.
- What's happening here?!
  - The acyl group is not as innocent as it seems.
  - Per Figure 4.10b, the actual mechanism begins with intramolecular displacement of the bromine to form a resonance-stabilized carbocation. This is followed by a backside attack on *either* carbon, hence selecting the *anti* product and inducing the racemization.
  - Conclusion: The neighboring group effect makes this reaction *trans*-selective and racemizing.

- **Neighboring group effect**: The interaction of a reaction center with either an intramolecular lone pair or an intramolecular pair of π-electrons. *Also known as* **anchimeric assistance**.

  - Note that the intramolecular pair of π-electrons cannot be conjugated with the reaction center; that's just resonance stabilization of the carbocation then.

- **Homoconjugation**: A neighboring group effect in which the neighboring group is a π-system.[5]

- Example of homoconjugation.

Figure 4.11: Homoconjugation.

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[5]This definition is consistent with the definition of homoconjugation as "an overlap of two π-systems separated by a non-conjugating group" because the carbocation counts as a π-system and the carbocation in Figure 4.11 is separated from the π-bond by one methylene group on each side.

- Essentially, the displacement of the tosyl group in Figure 4.11 is much more favorable in the molecule shown than in the saturated analog because a double bond is present nearby (in the unsaturated molecule), and its π-orbitals can donate into the carbocation.
- Something like 5 orders of magnitude faster.[6]

- We're now done with carbocation stability, and we'll begin discussing their synthesis and reactivity.

- Acidity.
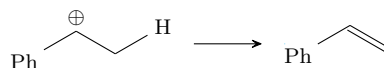
Figure 4.12: Carbocations acidify β-protons.

- Carbocations induce a dramatic acidification of β C−H bonds.
- Indeed, the pK_a of the proton drawn in Figure 4.12 is -14!
- Additionally, this reaction is just the second step in an E$_1$ mechanism: Adjacent deprotonation is just elimination!
  - The reaction is purely downhill thermodynamically, and adjacent deprotonation is actually a great perspective to take on E$_1$.

- Synthesis of carbocations: Two main ways.

(a) Ionization.   (b) π-activation.

Figure 4.13: Synthesis of carbocations.

1. Ionization.
   - This is just the departure of a leaving group.
2. Activation of a π-system.
   - Can be done by an electrophile, such as a proton, metal, etc.
   - Gives the Markovnikov adduct.

- Reactions of cations.

(a) $[1, 2]$-sigmatropic shift.

(b) General form of a rearrangement.

Figure 4.14: Reactions of cations.

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[6]Actually 11 orders of magnitude per Wikipedia.

- Cations most typically appear in elimination (E_1) and capture/substitution (S_N1) mechanisms.
- Once formed, cations can also do rearrangements, shifts, cyclizations, etc.
- An important subcategory of cationic shifts is $[1, 2]$-sigmatropic shifts.
  - These are very common.
  - They are also very fast and very easy to do.
    - ➢ The rate of a $[1, 2]$-sigmatropic hydride shift is $k_{1,2} = 3 \times 10^7\,\mathrm{s}^{-1}$, even at $-139\,^\circ\mathrm{C}$.
    - ➢ The activation energy $\Delta G^\ddagger_{1,2} \approx 3\,\mathrm{kcal/mol}$, which is on the same order of magnitude as bond rotation.
  - If you want these to happen, that's great!
    - ➢ If not, you're going to need to think about explicit ways to prevent it by design because $[1, 2]$-shifts will happen whether or not you want them to — you can't stop it.
  - Migratory aptitude: $s > sp > sp^2 > sp^3$.
    - ➢ The probability that a substituent will shift depends on the extent to which there is s-character in the bonding orbital of the *mobile* group because more s-character leads to better orbital overlap in the transition state (Figure 4.14a).
  - Essentially, the mechanism works by taking hyperconjugation "to the extreme" to move the bond (Figure 4.14a).
  - Two final noteworthy things about shifts.
    - ➢ We have a 2-electron Huckel aromatic transition state, so it will be allowed/favored by the Dewar-Zimmerman analysis.
    - ➢ We retain the stereochemistry of the migrating group (it's a suprafacial shift).
- There are many named rearrangements.
  - Examples include the **Wagner-Meerwein rearrangement**, **pinacol rearrangement**, and **semipinacol rearrangement**.
    - ➢ We are not a named-reactions class, so we will not discuss these much, but you can look them up if you want.
  - These are all variants on a theme, though.
    - ➢ They all follow the general form in Figure 4.14b but with different R and LG groups.
    - ➢ The naming generally depends on the *identity* of the R and LG, based on whichever chemist discovered and popularized the class.
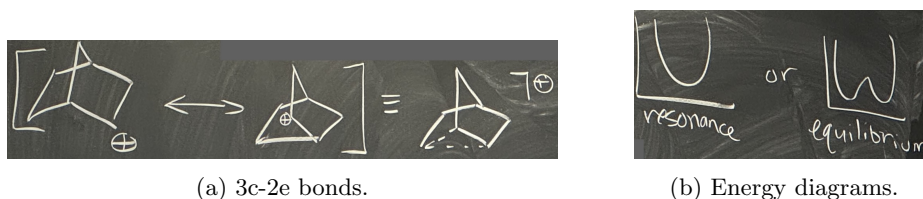
- Nonclassical carbocations.

(a) 3c-2e bonds.   (b) Energy diagrams.

Figure 4.15: Nonclassical cations.

- Consider two cations: The 3° *tert*-butyl cation and a 2° cation on norbornane.
  - Interestingly, HIA = $231\,\mathrm{kcal/mol}$ for *both* of these cations!
  - How can they both be equally stable?
- This question led to the discovery of nonclassical 3c-2e bonds (Figure 4.15a).
  - Essentially, we can draw two no-bond resonance forms for this cation. We move one of the σ-bonds in each of these (which we're not usually supposed to do).
  - Thus, we can draw the real structure with two half bonds.

– Aside (chemis-tea): The debate as to whether the true structure of nonclassical cations was barrierless resonance or an equilibrium between two cations raged in the literature for 70 years (Figure 4.15b).

■ On team resonance: Olah (Nobel prize for this cation work), Wintsein, Schleyer, Saunder.

■ On team equilibrium: H. C. Brown (Nobel prize for unrelated work).

■ Brown just thought this was due to poor techniques.

■ They would go to conferences, sit in the front row, yell at each other; publish snarky papers at each other.

■ Debate era: 1940s-2010s.

■ The debate ended at Science, 2013, 62 with an X-ray structure of the nonclassical cation (which really supported the resonance team). Unfortunately, H.C. Brown died in 2004. Anybody who knew Brown said he wouldn't have accepted this either.

■ "One would have thought that the application of careful experiment and intelligent thought would lead to a rapid solution to the [nonclassical carbocation] problem. This has not been the case" - Brown's book.

■ Until they could prove the structure of one or both, we couldn't know. This really drove the development of spectroscopy, NMR, low-temperature analysis of exotic species, etc. Essentially, people work hard when their ego is at state.

• Takeaway from our discussion of nonclassical cations: Cations exist on a spectrum.
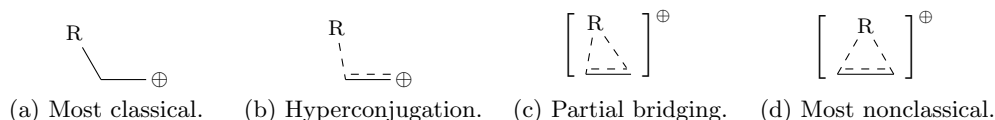

(a) Most classical.   (b) Hyperconjugation.   (c) Partial bridging.   (d) Most nonclassical.

Figure 4.16: A spectrum of cations.

– Most classical: Discrete, trivalent, trigonal carbocations.

■ These rarely exist.

– Next step: Hyperconjugation and resonance.

■ This accounts for most carbocations.

– Next step: Some kind of bridging but asymmetric carbocation.

■ There are some examples.

– Most nonclassical: Bridging, symmetric carbocations (3c-2e).

■ These have to be special cases, such as the norbornane one.